BOLK'S COMPANIONS

FOR THE STUDY OF MEDICINE

PHARMACOLOGY

Selected Topics from a Phenomenological Point of View

Christa van Tellingen MD

LOUIS BOLK INSTITUUT

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For further information:
Louis Bolk Institute
Hoofdstraat 24
NL 3972 LA Driebergen, Netherlands
Tel: (++31) (0) 343 - 523860
Fax: (++31) (0) 343 - 515611
www.louisbolk.nl
c.vantellingen@kingfishergroup.eu

Colofon:

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About the author

Christa van Tellingen MD (1949) has been a family physician in California since 1982 and currently practices medicine in the Netherlands. From the beginning of her medical studies she recognized the importance of a new approach to science for understanding the human being in health and disease. In her practice she has found the goethean phenomenological method of observation of great value in understanding and treating patients. She has taught medical students and physicians in the United States, Canada, and Europe, and since 2004 teaches anthroposophical medicine at the Medical School of Herdecke University (Germany). She is a member of the Medical Section of the School of Spiritual Science at the Goetheanum, Dornach, Switzerland. In 1998 she was one of the originators of "Renewal of Medical Education", a project at the Louis Bolk Instituut to offer a complement to the current biomedical scientific approach to the human being.

About the project

The project *Renewal of Medical Education* aim to produce Companions that demonstrate how the insights of current biomedical science can be broadened by using the Goethean phenomenological method. This method innovates current concepts and expands the understanding of biochemical, physiological, psychological, and morphological factors in living organisms and their development in time and space, and in health, illness, and therapy. The project is commissioned by the Kingfisher Foundation, which aspires the development, application, and publication of the Goethean phenomenological research method in the widest sense, to complement and innovate the accepted scientific view and research method.

BOLK'S COMPANIONS FOR THE STUDY OF MEDICINE complement current medical education, specifically disclosing human qualities in the fundamental biomedical sciences of today.

BOLK'S COMPANIONS FOR THE PRACTICE OF MEDICINE contribute to a scientific phenomenological basis for integrative medicine and integral psychiatry.

Contents

Preface

This module of BOLK'S COMPANIONS FOR THE STUDY OF MEDICINE is presented in an effort to aid medical and other science students in their study of pharmacology and to help them remember it better in later study and work.

It is meant as a supplementary text in pharmacology and aims to provide an overview by using the Goethean method*, an innovative study and research method, in which the known facts are first gathered and evaluated. The next step is to demonstrate where a certain process accompanying the use of a pharmacological compound is typical in the living world and to characterize it. Then we may compare typical processes with others within the organism or living nature, which enables us finally to draw conclusions as to its role or meaning in the whole of the organism. Therefore, alongside studying the details in pharmacology texts, this Companion will show the coherence of these details by finding relations between the effects of pharmacological compounds and organs, organisms, and living nature. At the Louis Bolk Instituut, Holland, where this work was written, this method is used extensively in research in agriculture, nutrition, and medicine, since it brings details in connection with one another.

I dedicate this work to all students who need to learn the facts of pharmacology and who also want to gain a greater understanding. I want to emphasize that this Companion does not replace studying a pharmacology textbook. The information contained in this Companion is compact and presupposes the knowledge contained in such textbooks. But it hopes to make studying and remembering the texts (ever) more interesting.

The illustrations in this Companion are paintings by Lyonel Feininger (1871-1956). While writing this Companion, I was also studying his paintings, and it was a pleasure to find paintings in his work that could be used to illustrate the motives of this Companion. They were taken from Luckhardt, 1998.

*The originator of this approach to science is the author and scientist Wolfgang von Goethe. For further information on this method we recommend the book by Henri Bartoft, 1986, and the Companion Phenomenology by Guus van der Bie.

Acknowledgments

This Companion in the series BOLK'S COMPANIONS FOR THE STUDY OF MEDICINE was written at the Louis Bolk Instituut in Driebergen, the Netherlands. It is the result of a stimulating exchange with my colleagues and would not have been possible without their help. I want to thank Judi Klahre-Parker, Els Hupkes, and Theo van Oort, all pharmacists, and Tom Scheffers, Diederik Houwert, Arie Bos, Marko van Gerven, Edmond Schoorel, Machteld Huber, Erik Baars, and Guus van der Bie, all physicians, for their valuable comments and constructive criticism.

We received financial help in the period I wrote the Pharmacology Companion from the Stichting Phoenix, the Iona Stichting, Stichting ter Bevordering van de Heilpedagogie, and the Software Stiftung.

Christa van Tellingen MD
Driebergen, June 2006

1. Introduction

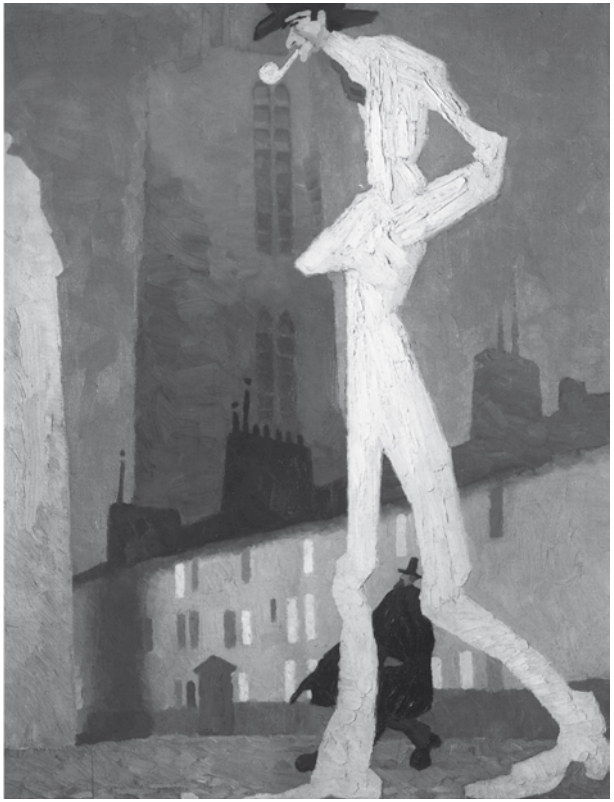
This **BOLK'S COMPANION FOR-THE STUDY OF MEDICINE** will promote a coherent overview in the study of pharmacology. In earlier **BOLK'S COMPANIONS**, dealing with the study of the healthy organism (Anatomy, Embryology, Physiology, Immunology, and Biochemistry), we were able to find an overview of the subject by studying the subject matter in question. However, diseased organisms are by definition not coherent. Consequently, in describing pharmacological substances we will not find a self-evident coherence in the study material itself. Since pharmacology as a subject does not have the same inner coherence, we will have to find an overview with the help of our knowledge of the functioning healthy organism. As a consequence, we shall have to assume some knowledge of the content of other **BOLK'S COMPANIONS** in this Pharmacology Companion, in contradistinction to what was done in previous Companions. There will be notes in the text referring to the content of earlier booklets so that this content can be easily found and (re) read.

The Pharmacology Companion consists of a general section and a special section. In the general section (chapter 2) we will describe some subjects related to the biochemistry and physiology of the human organism and discuss them in a pharmacological context. From this discussion we will formulate a framework for our pharmacological study, which is then used and worked out further in the special section (chapters 3 till 6).

This leaves one more item to be discussed before we turn to the above mentioned subjects. Pharmacological compounds are usually described as having an effect and side effects. The effects are desirable, the side effects usually undesirable. However, occasionally a compound side effect may change to become the desired effect, as with the "erection pill" sildenafil (Viagra), which started out as a coronary vessel dilator with erection as a side effect. And presently, sildenafil is found useful in altitude sickness and pulmonary hypertension due, for instance, to pulmonary embolism, because of its dilatory effect on the pulmonary arteries, which in turn is a side-effect of sildenafil as both a coronary artery dilator and as an erection pill. It is somewhat a matter of choice and therapeutic indication which action we describe as desired effect and which as side effects. Compounds usually have many effects on the organism, and as we try to get a coherent picture of their activity we will consider the array of effects of a compound as a whole rather than dividing the

array into (desirable or important) effects and (less desirable and important) side effects.

Pharmacology is a changeable subject, dependent as it is on the emergence of new disease and on new discoveries in the field of pharmaceutics. The emergence of diseases such as AIDS or post-traumatic stress syndrome, or the near disappearance of certain diseases such as scarlet fever in the last century, even before the advent of antibiotics, change the spectrum of available pharmacological substances. Pharmacological treatment also changes as new medications or new groups of medications are discovered, such as the antimicrobial ketolides or the antidepressant group of the Selective Serotonin Reuptake Inhibitors (SSRIs). The discussion of the relative effectiveness of SSRIs compared to the tricyclic antidepressants is ongoing, and whereas at first this discussion almost took the tricyclics off the market, it may now put them back on. Newly discovered side-effects may render new or old medications obsolete, as is evidenced by the disappearance from the market of the Cox-2 inhibitor Vioxx after the discovery of its cardiovascular toxicity. The emergence of bacterial resistance in antibiotics may make them less used in clinical practice. **The study of pharmacology is conditioned by the needs and knowledge of the time rather than by the coherence found in organic processes**.



The white Man (Der Weisse Man), 1907.
Oil on canvas, 68 x 53 cm.

2. General Pharmacology

This section will discuss a possible framework for the study of pharmacology (section 2.1.). It will also discuss the relation of substance size to function (section 2.2.) and the impact of anabolic and catabolic reactions on consciousness in relation to pharmacology (section 2.3.).

2.1. A framework for the study of pharmacology

2.1.1. Introduction

In the *Biochemistry Companion*, we looked for a coherent picture of known biochemical compounds and their properties. We found three distinct qualities for the three main biochemical families: the carbohydrates, proteins, and lipids. We named these qualities vegetative, interactive, and integrative and described specific attributes to these qualities. These qualities and their attributes helped us characterize the biochemical families and put them in relation to each other. This contributed to a more coherent picture of biochemistry.

In the *Physiology Companion*, we found the same above mentioned three specific qualities plus one more for the functions of four main organ systems: the respiratory system, digestive system, urogenital system, and circulatory system. We named their qualities to be of physical character, vegetative character, interactive character, and integrative character. These qualities and the attributes connected to them helped us characterize the organ systems and put them in relation to each other, thus contributing to a more coherent picture of the physiology of these four organ systems.

The four (three plus one) qualities and their attributes found in the above mentioned Companions overlap and complement each other. Since pharmacological compounds are (bio)chemical compounds that are used to affect the organism's physiology, it would seem plausible to use the qualities found in the study of biochemistry and physiology to describe their molecular structures, biochemical and pharmacological properties, and physiological activities, and compare them. The four mentioned qualities will be our reference and provide

a framework to understand activities of pharmacological compounds. As we set out to explain in the Introduction, this could help the student remember detailed information on pharmacological compounds more easily.

First, we will reiterate briefly the attributes for the qualities found in the two previously mentioned Companions.

2.1.2. Qualities in biochemistry

We found the following three qualities to be related to the three main biochemical families of substances. For details see the *Biochemistry Companion*, chapters 3, 4, and 5 respectively.

2.1.2.1. The vegetative quality

We found vegetative or plant-like functions principally linked to carbohydrates.

The attributes of the vegetative quality of carbohydrates follow (*Biochemistry*, chapter 3).

1. They *provide energy* for organism functions, a characteristic function of carbohydrates.
2. They are involved in anabolic metabolism such as *growth* and *regeneration*, also a characteristic function of the carbohydrates.
3. They have a relation to *water*, which plays an important role in all carbohydrate structures and in processes such as the photosynthesis of the plant, a characteristic metabolic process for carbohydrates (*Biochemistry*, section 3.1.).

Characteristic of carbohydrates are their vegetative functions. Vegetative functions provide the basis for life.

> *Carbohydrates have a structural role in plants in the cellulose of plant walls. Having ransformed light energy into plant substance in photosynthesis, plants then function as nutrients and provide energy in nature (Biochemistry, section 3.4.).*

2.1.2.2. The interactive quality

We found the interactive or animal-like quality primarily linked to **proteins**.

The attributes of the interactive quality of proteins follow.

1. They *connect* functions, tissues, or the whole organism to their surroundings. Examples are connective tissue proteins, which connect different types of tissue, the mono-amine neurotransmitters, or muscle proteins, allowing the organism to be effective in its environment.
2. They are both *diverse and specific*. We can see this in protein conformation, which is very specific and results in specific functions, and protein bonding, which is also diverse as well as specific. Functions of amino acids and proteins are as specific as they are diverse (*Biochemistry*, section 4.4.).
3. They have a relation to the *air* through *nitrogen*. Nitrogen distinguishes proteins and amino acids from carbohydrates and lipids and originally comes from the atmosphere.

> *Characteristic of proteins are their interactive functions. Interactive functions are related to diversification and specialization in organisms.*

Protein metabolism and structural principles further refine carbohydrate metabolism and structure. Proteins have a structural role in animals and humans in connective tissue and muscles. The interactive quality refines vegetative functions.

2.1.2.3. The integrative quality

We found the integrative principle primarily linked to lipids in biochemistry.

The attributes of the integrative principle of lipids follow.

1. They enable *differentiated* functions to exist together in one organism. Integration akes differentiation possible without the organism falling apart; there can be no differentiation without integration. On the one hand, lipids support differentiation in organisms through the formation of membranes, which allows the existence of differentiated multi-cellular organisms. This separates cells and cell organelles from

their surroundings. On the other hand, the membranes are interrelated and support the integration of the differentiated tissues. Membranes may form integrated functional entities, such as the endothelium of blood vessels. Proteins in the membranes provide connections between the intra- and extracellular compartments (an interactive quality).

2. They have *inhibiting* qualities, which are instrumental for the emergence of higher functional levels, such as the existence of integrated multicellular organisms. The *hydrophobic* linkage is characteristic for lipids and it is characteristic for hydrophobic bonds that they inhibit the relation with the watery milieu in organisms. This *inhibition* creates the possibility for the formation of interrelated lipid membranes, and subsequently a greater integration of the organism on a higher level. Compounds with many hydrophobic bonds are lipid soluble rather than water soluble (hydrophilic).
3. *Warmth* enhances the integration of functions in organisms. Lipids play an important role in regulating and providing warmth (Biochemistry, section 5.5.).
4. Integration of functions in organisms is enhanced by a *rapid spread of electrical impulses*. The formation of myelin sheaths around nerve axons promotes the velocity of electrical impulses throughout the organism. Myelin sheaths are rolled up phospholipid membranes and are particularly abundant in the white matter of the brain. The white brain matter derives its name from its high lipid content and it is essential in integrating the brain's functions. The amount of white brain matter is largest in humans. The lipidbased white matter also plays a structural role in the human brain.

> *Characteristic of lipids are their integrative functions. Integrative functions provide the necessary counterpart for more differentiation and individualization. Integrative qualities make functions on a "higher" level possible.*

The structure and metabolism of lipids further enhances carbohydrate and protein structural and metabolic functions. Lipids have an essential structural role in the human brain. The integrative principle enhances both vegetative functions and interactive qualities.

2.1.3. Qualities of four main organ systems

For four main organ systems we found four different qualities. Three are similar to the ones we found in biochemistry, the fourth (section 2.1.3.1.) would relate to inorganic chemistry and we had called it the physical quality (*Physiology*, section 6.1.). For more detailed information see the *Physiology Companion*, chapters 2, 3, 4, and 5 respectively.

2.1.3.1. The physical quality

Physical qualities dominate the physiology of **lungs and respiratory tract**.

1. *Cartilage* occurs in this organ system, which, together with surrounding bony structures, keeps the respiratory tract and lungs functioning and open.
2. Their function depends on *physical laws*, such as the law of elasticity.
3. The lung is physiologically *passive*. This includes the passivity of the process of diffusion along pressure gradients, which is the driving principle behind the gas exchange, and its rhythmical movement being affected by the surrounding structures (*Physiology*, section 2.4.1.).
4. The physiology of this organ system is regulated *from without*. Ventilation and perfusion are regulated through the pH of the blood, the nervous system, and cardiac output.

2.1.3.2. The vegetative quality

Vegetative qualities or plant-like qualities dominate the physiology of **liver and digestive tract**.

1. The liver and intestine play an important role in the *energy supply* of organisms.
2. The liver and digestive tract have strong *growth and regenerating* forces, supporting anabolic processes, such as growth and regeneration in the organism.
3. Liver and intestines play a central role in *metabolism*, specifically carbohydrate metabolism.
4. The physiological processes and external form of the liver *adapt* to the environment, just like any body of water.
5. The physiological processes of liver and intestines have *autonomous and local* regulation.

2.1.3.3. The interactive quality

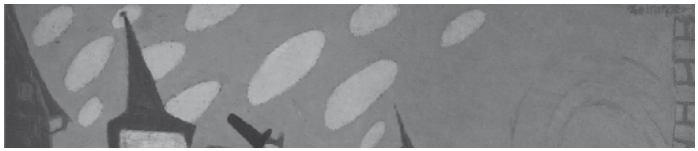
Interactive qualities dominate the physiology of **kidneys and urogenital system**.

1. The physiology of the kidneys is both *diverse and specific*, comprising many different but specific functions, such as volume regulation, blood pressure regulation, pH regulation, hormonal function (erythropoietin), and excretion.
2. The kidneys *carry opposite qualities* in the same organ, for instance in the anatomy and physiology of the cortex and the marrow. This results of necessity in interactive processes between the opposites. Another demonstration of opposites in the physiology of the kidneys is that they excrete large amounts of ultrafiltrate in the glomerulus (180L/day) and then resorb most of that (179L/day) back in the tubuli (*Physiology*, section 4.2.2.).
3. *Regulating* is an important aspect of interactive qualities. Organs of perception are needed for regulating, which the kidneys have in the form of the juxtaglomerular apparatus. The kidneys regulate the internal milieu of the organism. Internal feedback mechanisms regulate the kidney function itself, for instance in the regulation of urine output.
4. Nitrogen plays an important role in kidney regulation.

2.1.3.4. The integrative quality

Integrative qualities dominate the physiology of **heart and circulation**.

1. The heart and circulation are instrumental in making the organism into a *unity* through the flow of the blood. The blood, with its warmth, nutrients, and rhythm flows *throughout the body*, and waste products such as carbon dioxide are carried back to the central heart.
2. The heart is an *active, autonomous* organ; its activity is moderated principally by the venous return. Being regulated by the metabolic needs of its periphery strengthens the integrative function of the heart.
3. The heart and circulation carry *warmth* throughout the organism.



2.1.4. Conclusion: Four Qualities in Pharmacology, a Pharmacological Framework

The four (three plus one) qualities that emerged from studying biochemistry and physiology in the healthy human organism can be of use for our study of pharmacology. Summarized, the attributes of the four qualities we will use for our framework are:

The physical quality *represents mineralizing tendencies, passivity, dependence on physical laws and external support, being regulated from without. Biochemically, this would refer to inorganic processes and substances, such as acids and salts. It is related to the physiology of the lungs.*

The vegetative quality *represents growth, regeneration, a relation to metabolism and energy production, water, and adaptation to the environment. Biochemically, it is related tothe carbohydrates, and physiologically, to the liver.*

The interactive quality *represents connections and connecting opposing qualities, a relation to nitrogen and air, diversity and specificity, perception and regulation. Biochemically, it is related to the proteins, and physiologically, to the kidneys.*

The integrative quality *enables differentiation, inhibits, and, with the occurrence of warmth, autonomy, and rhythm, it makes organisms into a unity. It is biochemically related to the lipids, and physiologically, to the heart.*

We will use this framework in chapters 3, 4, 5, and 6 and give examples of how to work with it. But first we will look at the molecular size of compounds in relation to their function and to the impact anabolic and catabolic processes have on consciousness in relation to pharmacology.

2.2. Molecular size of compounds in relation to their area of activity

The size of compounds in relation to their area of activity is an important question in harmacology, and its influence can be studied by looking at the functions of monomers and polymers. In the *Biochemistry Companion*, chapter 2, we looked at the metabolism and structure of carbohydrates, proteins, and lipids. We described how each of these groups or "families" of substances consists of small singular molecules (monomers, such as glucose, amino acids, or fatty acids) and is subject to polymerization to larger molecules (such as glycogen or protein) or composition of molecules (such as lipid membranes). We found that monomers and polymers in general serve different types of functions in organisms.

Monomers are physiologically active compounds. Monomers of the **carbohydrate** family are sugars, such as glucose. Sugars eventually undergo further metabolism on a cellular level. In this process, energy is released and becomes available for the organism's functions in the form of adenosine triphosphate. The monomers of **proteins** are amino acids. Amino acids and their derivatives can be active as neurotransmitters or hormones, which have messenger functions (see also *Biochemistry*, section 2.1.1.). The smallest **lipid** molecules are the fatty acids and their derivatives, and ketone bodies. The ketone bodies play an exclusive role in the energy requirements of the human heart and can be active as neurotransmitters.

> *The smaller monomers are metabolically active compounds. In pharmacology we mainly use smaller compounds because of their activity in the organism.*

The function of **polymers** is to serve as important ***structural compounds***. They are not found in the constantly changing biochemically active group of substances, but as glycogen deposits, collagen, or muscle proteins. Enzymes are proteins that have a function in the metabolism of organisms by providing the structural *matrix* for biochemical reactions to

occur up to 10^{14} faster. They may change structurally to facilitate a metabolic reaction, but are themselves not part of the reaction. Thus their catalyzing function has a structural character. Cell membranes consist of a composition of lipids, which we will also put into this group since they are important structural entities, as are the lipid myelin sheaths in the brain (*Biochemistry*, section 2.1.2.3.).

Larger compounds, such as the polymers, usually serve structural functions.

2.3. Anabolic and catabolic processes and their impact on consciousness

We discuss the impact of anabolic and catabolic processes on consciousness here to provide an insight into the impact of pharmacological substances on consciousness. Much of the information in this section was taken from Elsas, 1994.

Anabolic reactions result in the formation of polymers and other complex compounds from smaller molecules. Anabolic reactions are endothermic, meaning they need added warmth. Free warmth or energy is used and bound into the larger compounds. Conversely, the breakdown of these compounds in catabolic reactions is exothermic, and warmth or energy is released as the smaller compounds are formed. The released warmth or energy can be used for other functions of the organism. We will see that consciousness increases when compounds (especially in the central nervous system) undergo catabolic degradation and energy is freed, and that consciousness decreases as energy is caught in the chemical bonds that build the organism's (structural) compounds.

2.3.1. Protein metabolism and consciousness

2.3.1.1. Peripheral protein metabolism

A characteristic catabolic process in the human organism can be observed when the injury of a peripheral nerve results in the breakdown of neurofilament proteins. Neurofilament proteins are part of the internal structure of the nerve cell, including the neuronal axon, and are not normally metabolically active. In nerve injury, the neurofilament proteins break down, which results in the formation of at least two metabolites. Both are metabolically active compounds:

1. adrenocorticotropic hormone (*ACTH*) and
2. melanocyte stimulating hormone (*MSH*).

These two substances have a stimulating effect on local anabolic processes and enhance new growth and regeneration of the neuronal axons in the peripheral nervous system. Sometimes we are aware of this peripheral activity when we feel the tingling of a healing wound.

Neurofilament ⟶ injury, protein breakdown ⟶ ACTH + MSH
(inactive, structural) *(active, growth and regeneration)*

> *In peripheral nerve injury, a catabolic process frees energy for growth and regeneration. There may be a slight raise in our awareness of the area through the tingling of the wound.*

2.3.1.2. Protein metabolism in the central nervous system

In the central nervous system (CNS), ACTH and MSH are cleavage products of the polypeptide proopiomelanocortin (*POMC*, about 400 amino acid residues) (fig.2.1.). POMC, a keratin-like polymer peptide, is a *structural compound* of the anterior lobe of the pituitary gland. It is inactive metabolically, and we are ***not aware*** of its existence, nor do we experience its functioning directly or specifically.

The breakdown of POMC and other neuropeptides occurs in stages (fig.2.1.). At each stage, active metabolites are formed with specific actions. The metabolites become smaller with every step of degradation. At the same time, the metabolites and further smaller compounds have an increasing effect on awareness.

First step: At first, the degradation of POMC results in the formation of the peptides β-**lipotropin** (91 amino acid residues) and **ACTH** (39 amino acid residues). These compounds are metabolically active and, when released from the CNS, have a *growth stimulating* effect in the organism, for instance by acting as hormonal stimulators of glandular function. We are not normally directly aware of these growth stimulating processes. Even though we may be conscious of their effect, for instance through the increase in size of the body, we are ***asleep*** to the growth processes themselves. ACTH and the lipotropins have *anabolic and vegetative activity.*

Second step: In a next step, β-lipotropin can be broken down to the peptide β-**endorphin** (31 amino acid residues) and ACTH is broken down to the peptide **MSH** (13 amino acid

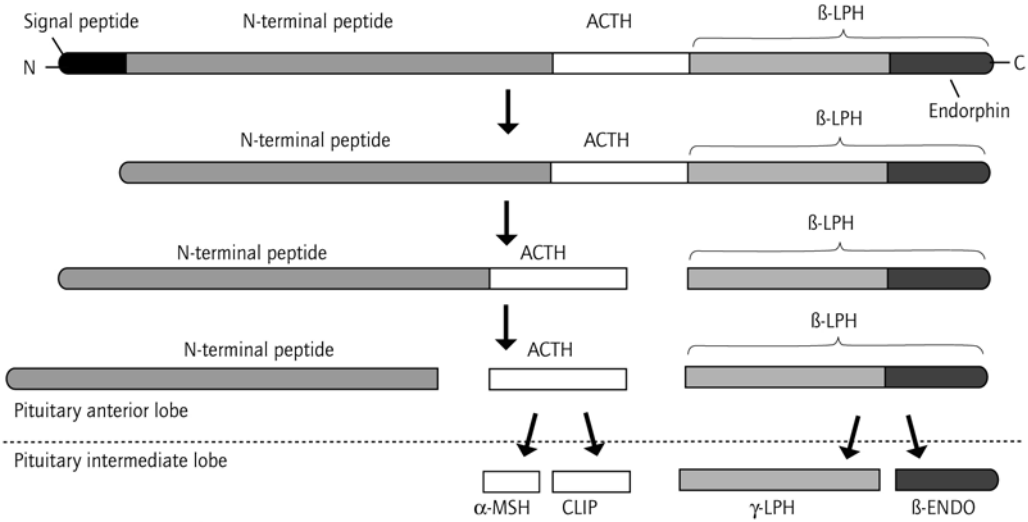


Fig.2.1. Degradation of proopiomelanocortin in the hypophysis (from Elsas, 1994)

residues), among others. The endorphins ***reduce the experience of pain***. MSH functions as the hormonal *stimulator of melanocyte growth* and it ***increases our tendency to sleep***. These are two experiences that we can be more readily aware of than the mere regenerative action of the larger compounds they have derived from. The emergence of these smaller compounds goes along with more consciousness.
This sequence is shown in figure 2.2.

This sequence is shown in figure 2.2.

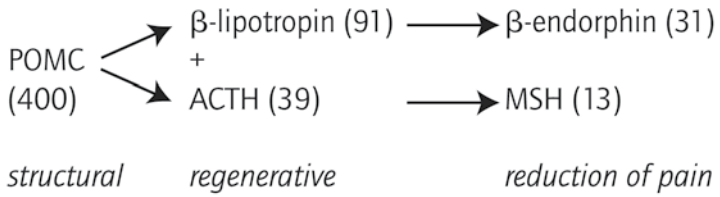


Fig.2.2. Breakdown of POMC yields compounds that accompany greater awareness

Third step: amino acid derivatives. If we look at even smaller protein metabolites in the CNS and their relation to consciousness, we see a continuation of this sequence. Compounds such as **histamine, serotonin**, and **adrenaline** are amino acid derivatives, which are in size smaller again than the peptides discussed above. Increased serotonin and catecholamine levels lead to an increase in awareness. We can learn this from illnesses like schizophrenia and from the serotonin-like effect of LSD, which are accompanied by symptoms such as *fear, hallucinations, increased perceptions, and ideation*. On the other hand, when serotonin and catecholamine levels are relatively low, as we see in people with endogenous depression, then *perception and thinking have slowed down.*

Thus, the occurrence of excess of these amino acid derivatives is accompanied by excess wareness, and their absence seems to take away from being awake and aware. The consciousness accompanying an excess or depletion of these compounds is not our normal waking consciousness; it has a ***picture-like, dream-like*** character.

The amino acid derivatives are also known to have peripheral action. In excess, they

produce *local pain and inflammation* and *increase blood pressure.*

Fourth step: endmetabolites. In certain areas of the brain, amino acids, such as arginine, may split off **nitrogen monoxide** (NO). NO is a gas and lipid soluble, and is a CNS modulator. Other modulators include CO_2 and NH_4, arising from active neurons or glia, but not active as neurotransmitters. We know that NO degradation occurs in the hippocampus of the CNS, in the endothelium of blood vessels, and in macrophages. NO is a very toxic gas that is accompanied by strong vasodilatation during systole. In excess, it causes *cell death.* In physiologically normal amounts, it probably plays an important role in the *capacity for memory* (the so called "long term potentiation" in the hippocampus area). Memory is vital to human waking consciousness and may be what distinguishes being ***fully awake*** from dreaming.

The degradation of proteins leads to compounds that accompany increasing awareness.

2.3.2. Lipid metabolism and consciousness

Arachidonic acid is a fatty acid that is a ***structural*** part of phospholipid membranes. In injury it is released, and its subsequent metabolism results in the formation of the **prostaglandins, leukotrienes, and thromboxane**. Important known effects of these compounds on consciousness include ***enhancing the pain reaction.***

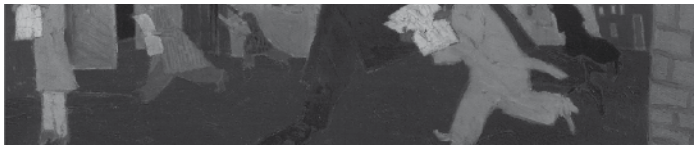
The degradation of phospholipid membranes leads to compounds that have effects that heighten conscious awareness.

2.3.3. Carbohydrates and consciousness

When we eat the large, structural carbohydrates such as **cellulose and starch**, they hardly produce a taste sensation at all. When we eat the smaller **sugars**, they have an outspoken sweet taste, which ***wakes us up.***

Catabolic processes resulting in the degradation of carbohydrates are accompanied by increasing awareness as the degradation products become smaller in size.

The smaller the compound the more effect it has on waking consciousness: structural compounds have no perceivable effect; anabolically active compounds are accompanied by deep sleep consciousness; catabolically active compounds affect dream consciousness; endmetabolites that are almost inorganic affect fully awake consciousness.



2.3.4. Levels of awareness: Addition to our Pharmacological Framework

We distinguished four levels of awareness.

1. On **a structural physical level**, in relation to substances such as POMC, starch, or arachidonic acid, there seems to be ***no perceptible awareness.***

2. We may have some awareness in relation to **growth and regeneratio**n, which is the awareness we also have of our metabolism. We can sometimes be aware of it, usually as a feeling of being satisfied or hungry, awareness that is strongly related to our organism. It is like a ***deep sleep consciousnes***s, that can be refreshing. We could describe this as having a ***vegetative or regenerative consciousness.***

3. The **awareness of pain (or pleasure)** has characteristics that are ***reflex-like, not fully awake***. It includes alertness as a reflex to pain or pleasure and is often limited to the area or the cause of the pain or pleasure. This consciousness is interwoven with pictures. It is characteristic for animal life, but is also the way we humans usually function in life. Everything that we do as a reflex action, without thinking twice about it, such as breathing, walking, eating, typing, driving, playing a musical instrument, has this reflex-like quality. We are more aware than in our metabolic processes, but are not creative. We could describe this type of consciousness as an ***interactive consciousness***, since it is

there in interaction with what happens around us or in our organism.

4. The consciousness in which we are acutely aware and awake is when we learn something new, solve a riddle or a problem, or are creative. The reflex-like, interactive awareness with which we normally function is held up, *inhibited for a momen*t by the question we had put and the answer we are looking for. A new awareness ensues that helps us solve the question: a light goes on! Then the piece of music can become a masterpiece and a new invention is discovered. It is characterized by finding a new integration of the insights and ideas we already had. It is an ***integrative consciousness***, which brings us and the world around us to a new level. It helps us integrate past experiences with our present question to answer it. Our memory, rather than a learned reflex, is essential for this type of awareness. It is this consciousness that has helped us humans to build up our cultural, social, and economic life. This is when we have a ***fully awake awareness, self-consciousness***, a level of functioning that is essential in human culture.

The central role of the CNS is epitomized by the ability to integrate information from a variety of external and internal sources. The inhibition that is characteristic for integrative functions also plays a role in the central motor system. The *inhibition* of reflex movements through the pyramidal system, which innervates the motor neurons to our musculature, determines the normal resting state of our muscular system. Movement comes about by temporarily terminating the pyramidal inhibition.

> *We distinguished four levels of awareness: no perceptible consciousness of structural or physical processes; sleep consciousness accompanying vegetative processes; reflex consciousness accompanying interactive processes; and fully awake self-consciousness accompanying integrative processes in the CNS.*

This concludes the formulation of the framework for our pharmacological study. Next comes the special section with four groups of compounds.

For the attentive readers:
At the end of each chapter a print of one of Lyonel Feininger's paintings is added that

fits the contents. You will find parts of this same painting within the chapter, and can try to guess while reading what the whole painting will look like at the end. This is how I experienced the study of pharmacology.

Newspaper Readers (Zeitungsleser), 1909.
Oil on canvas, 50,2 x 63,2 cm.

3. Sedative and hypnotic drugs

The first group of compounds in this special section of this Pharmacology Companion deals with sedative and hypnotic drugs.

3.1. Introduction

Drugs that aid sedation and sleeping depress the functions of the central nervous system. The main transmitter involved in sedation is gamma-aminobutyric acid (GABA) (fig.3.1.). GABA is the *principle inhibitory* neurotransmitter of the CNS, especially the hypothalamus. It has both fatty acid and amine qualities, and is formed by the breakdown (decarboxylation) of glutamate, the *principle excitatory* neurotransmitter in the brain. GABA formation is an example of how the breakdown of an excitatory neurotransmitter (with interactive qualities) results in a metabolite with inhibitory action that affects an enhanced integrative awareness (compare sections 2.2., 2.3.1.2., and 2.3.4.). I will briefly describe glutamate and GABA function so you can understand the role of the sedatives and hypnotics in the organism.

- **Glutamate** is an amino acid precursor and a neurotransmitter. This would indicate that it functions on an interactive level. Glutamate's excitatory activity in the CNS is accompanied by interactive awareness (section 2.3.4).
- **GABA** (fig.3.1.) is also a neurotransmitter, which suggests interactive qualities. However, its function as an inhibitory substance and its lipid connection would indicate that it may also affect integrative qualities. Integrative qualities are accompanied by a fully awake consciousness (section 2.3.4.). In excess, however, GABA dampens the capacity to be fully awake and to have a functioning memory. Research is under way to investigate the role of GABA in the pathogenesis of anxiety disorders (see for instance Lydiard, 2001). GABA, and gamma hydroxybutyric acid (GHB), which can be derived from GABA, are used as so-called date-rape or drug-rape drugs that may be added to drinks to make people more relaxed, detached and uninhibited, and less aware. GHB strongly causes amnesia for what happened during the time the drug was used (Frankenheim, 2000).

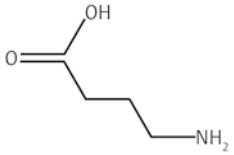


Fig.3.1. Gamma-aminobutyric acid (G. Peters, after Wikipedia)

We will discuss three main groups of sedative and hypnotic drugs. We will compare he *barbiturates* with the *benzodiazepines*. The barbiturates and the benzodiazepines affect GABA neurotransmission. We will set their action next to the sedative action of *antihistamines* such as diphenhydramine and hydroxyzine. They will serve as examples of how drugs fit into the pharmacological framework of sections 2.1.4. and 2.3.4.

Sedation and sleeping are states in which integrative functions and interactive qualities are diminished.

3.2. Benzodiazepines

3.2.1. Molecular structure

The benzodiazepines have been available since 1961. Benzodiazepine derivatives are now used for most sedative and hypnotic purposes. Benzodiazepines consist of a benzene ring coupled to the diazepine ring in their basic structure (fig.3.2.). Almost all available drugs have an additional two rings as well, which makes these compounds very lipid soluble. They cross the intestinal barrier as well as the blood-brain barrier easily.

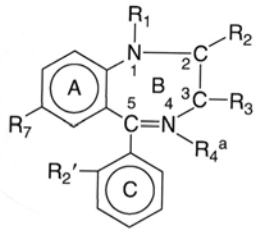


Fig.3.2. Benzodiazepine structure (from Goodman & Gilman's, 2001)

As strongly lipid soluble compounds, benzodiazepines would be structurally related to integrative functions.

3.2.2. Biochemical and pharmacological properties

The sit e of action of benzodiazepines is almost exclusively at the $GABA_A$ receptor in the CNS. The GABA receptor is in fact a voltage-gated chloride channel that opens in the presence of GABA, allowing the influx of negative Cl^- ions into the cell. Benzodiazepine binding sites on GABA receptors only exist in the CNS, which limits the activity of these typical sedatives and hypnotics to the CNS, pointing again to their effect on integrative qualities. The benzodiazepine effect is that the channel opens more frequently. Benzodiazepines are not themselves active at the receptor site; they require GABA to be present. Through an allosteric change in both GABA and the benzodiazepine compound, GABA remains longer at the receptor site than if it had been there alone. This causes a hyperpolarization of the neuronal cell, and subsequently it is harder to transmit the next electrical impulse. The final effect is an *excessive inhibition*.

The benzodiazepines also decrease the reuptake of adenosine, a purine derivative of ATP, from synaptic spaces. This compound is an endogenous neuronal depressant, and its increased presence in the synaptic space would mean that its inhibiting effect on neuronal function is potentiated.

Benzodiazepines potentiate inhibitory biochemical functions in the CNS, which would indicate that these compounds affect integrative functions. The inhibition they produce is

prolonged and in excess. Benzodiazepines pharmacologically affect neurotransmission, an interactive function.

3.2.3. Physiological activity

Benzodiazepines cause sedation, in larger quantities sleep (hypnosis), and additionally an nterograde amnesia, so that experiences during sedation are forgotten afterwards. These effects are based on a prolonged inhibition of neuronal activity in the CNS and affect integrative functions. This inhibition is not the type that creates moments of creative awareness as described in section 2.3.4. It rather stops fully awake and creative functioning, indicating that for integrative awareness just the right amount of inhibition may be essential. The general neuronal depression caused by the benzodiazepines is less pronounced than that with for instance the barbiturates, so that reflex-like interactive awareness is maintained to a certain extent in sedation. Therefore, in general benzodiazepines are not good anesthetics. However, there is amnesia for the period during which they were used! This would indicate that they have less of an effect on interactive awareness than on integrative awareness.

The benzodiazepines have specific CNS activity and depress respiration through depression of the respiration center in the medulla oblongata and cause muscle relaxation. They also have an anticonvulsant effect and are used in anxiety disorders such as panic disorder, all affecting interactive qualities.

Benzodiazepines mostly have only two peripheral effects.

1. Some cause vasodilation of the coronary vessels in large doses (diazepam causes increased coronary flow by increasing the interstitial concentration of adenosine, also a cardio depressant).
2. Some cause neuromuscular blockade in high doses.

The site of action being mainly the CNS, and the amnesia that typically accompanies their use would indicate that, physiologically, the benzodiazepines mainly suppress integrative functioning in the human organism. General reflex-like awareness is less impaired, thus interactive functions would be involved to a lesser extent.

The benzodiazepines affect foremost the integrative functions of the central nervous system in humans, and to a lesser extent interactive functions.

3.3. Barbiturates

3.3.1. Molecular structure

The original barbiturates were discovered in 1903 (barbital) and 1912 (phenobarbital). Their action, though strong, is also *general* and has little selectivity. They have no effect on memory. Their therapeutic index (the relation between therapeutic dose and toxic dose) is small. The basic structure of the barbiturates has one ring (fig.3.3.). Phenobarbital is one of the few barbiturates that has an additional (phenol) ring. Barbiturates are generally smaller than benzodiazepines and somewhat more water soluble, indicating less integrative quality than the benzodiazepines. Structural changes that increase lipid solubility will increase the hypnotic strength of the barbiturates and make their onset of action faster, as well as decrease their duration of action, since the compound's metabolic breakdown is faster when it is more lipophilic.

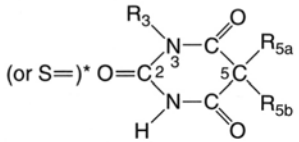


Fig.3.3. Barbiturate general structure (from Goodman & Gilman's, 2001)

Barbiturate structure has integrative qualities, but less so than benzodiazepine structure.

3.3.2. Biochemical and pharmacological properties

In sedative concentrations, barbiturates can *activate the chloride channel* of the $GABA_A$ receptor, regardless of the presence of GABA. It causes a longer duration of influx of chloride ions (compared to more frequent opening of the channel through benzodiazepines). Barbiturates also *block Na^+ receptors*, which are present throughout the organism. This gives them many peripheral effects as well. Na^+ receptors are usually involved in excitatory action, and have interactive quality.

Barbiturates also inhibit excitatory receptors for glutamate. Glutamate is the most potent excitatory neurotransmitter (see also section 3.1.).

The inhibitory biochemical activity of barbiturates in the CNS is based on prolonged stimulation of GABA receptors as well as inhibition of the excitatory neurotransmitter glutamate. This indicates an effect on interactive awareness as well as on integrative awareness.

3.3.3. Physiological activity

Barbiturates reversibly depress the activity of all excitable tissues. They have a strong sedative and hypnotic effect. Barbiturates have anticonvulsant properties. They depress respiration, but they have not much of an effect on anxiety, nor do they depress pain perception. There is no amnesia. Barbiturate anesthesia may cause laryngo-spasm. After the sedative effect, which impairs integrative awareness, there can be a residual depression of the CNS as well as problems with fine motor skills, mood changes, and impaired judgment, all interactive functions. Barbiturates decrease the tone of the gastrointestinal tract, which may be accompanied by nausea and vomiting. They cross the placental barrier. In higher doses, barbiturates may depress the electrical transmission in autonomic ganglia peripherally, and can be accompanied by a fall in blood pressure and heart rate.
Physiologically, barbiturates have an effect on the integrative functions of the CNS. They also strongly affect central interactive physiology and peripheral interactive qualities and peripheral interactive functions of the muscular, cardiovascular, and gastrointestinal systems.

Barbiturates affect integrative qualities of CNS activity. In addition they have a strong effect on interactive functioning. Their area of activity is larger than that of the benzodiazepines.

3.4. Antihistamines

Histamine is a derivative of the amino acid histidine. Histamine has a single aromatic ring in its structure and a primary amino group. It acts on at least two receptors with differentiated functions in the organism. *H_1 receptor* activity causes allergic symptoms, such as redness through local vasodilation, wheal formation through increased capillary permeability, and flare and itch, related to the effect of histamine on local nerve endings. These are all interactive functions, since allergy is itself a re-action, a response to external stimuli. The *H_2 receptor* mediates gastric secretion, which is also an interactive quality, a response to the food that enters the stomach.

Histamine may also be a central neurotransmitter, with evidence that most of the histamine secreting neurons are located in the hypothalamus, with tracts covering the whole of the CNS. There are histamine receptors in the CNS that may mobilize Ca^{++} ions. In section 6.5. we will see that Ca^{++} metabolism affects integrative functions in the cardiovascular system.

3.4.1. Molecular structure

The H_1 receptor antagonists, commonly called the antihistamines, mostly have two rings and a tertiary amino group (fig.3.4.). Antihistamines are structurally related to the protein family through their amino group. They are larger than histamine, and somewhat less water soluble. They would influence CNS functions more readily than histamine, affecting integrative qualities in addition to interactive qualities.

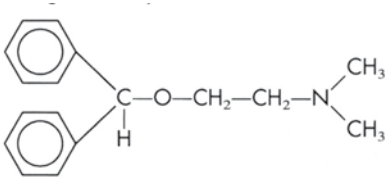


Fig.3.4. Structure of diphenhydramine (from Goodman & Gilman's, 2001)

Antihistamine structure primarily has interactive qualities and some affinity to integrative qualities.

3.4.2. Biochemical and pharmacological properties

Antihistamines act as competitive inhibitors to histamine through the similarity in structure. In competitive inhibition the usual connection between ligand and receptor is impeded. This implies that competitive inhibition impedes interactive processes are impeded. The binding of antihistamines to the receptor is reversible.

The biochemical and pharmacological competitive inhibition of antihistamines would affect interactive qualities.

3.4.3. Physiological activities

Most antihistamines in use today depress CNS activity, especially the so-called first generation antihistamines. Those with the greatest CNS effect that are also used as sedatives or hypnotics are diphenhydramine, hydroxyzine, and doxepin. With these antihistamines, alertness is diminished and reaction time is prolonged, both effects related to interactive awareness. There is somnolence, indicating an effect on integrative consciousness. Doxepin has the most potent antihistamine activity, and is also in use as an antidepressant (see also chapter 5).

Peripheral effects are smooth muscle relaxation, blocked capillary permeability, diminished

itch and flare, blocked glandular excretion of several exocrine glands, such as salivary and lacrimal glands. The peripheral effect seems to block mostly interactive functions.

Physiologically, antihistamines depress interactive awareness in the CNS. The peripheral effects of antihistamines block interactive functions.

> *Antihistamines influence interactive and some integrative qualities of CNS activity. Peripherally, they mainly affect interactive qualities.*

3.5. Profile of the sedative and hypnotic drugs

Characteristic of the typical sedative and hypnotic drugs, the benzodiazepines and the barbiturates, is that they enhance inhibitory $GABA_A$ activity, which appears to be related to integrative function. Integrative qualities give us acute awareness and awakeness to answer to new questions, as well as the capacity to use our memory to find these new ideas. *Benzodiazepines* are most specific in their effect on the GABA receptor and they affect integrative awareness most strongly. The effect of the *barbiturates* is not limited to GABA receptors but also biochemically includes inhibition of interactive Na^+ receptors and some vegetative actions. The *antihistamines* were developed as drugs with their main point of action outside the CNS. Subsequently, histamine was found to play a role as CNS neurotransmitter. Antihistamines appear to affect integrative qualities through their biochemical effect on Ca^{++} metabolism. Antihistamines are an example of how peripheral drugs influence CNS functions. In fact, most peripheral drugs will have additional CNS effects, and it is important to be aware of these.

Trumpeters I (Trompetenbläser I), 1912.
Oil on canvas, 94 x 80,3 cm.

4. Antiseizure drugs

4.1. Introduction

Epilepsy is characterized by a transient, more or less generalized depolarization of neurons in the CNS. Action potentials that normally allow activation of certain pathways in waking consciousness, are fired at a higher frequency for a relatively long duration of time over a more generalized area of the brain. However, the repetitive firing of the many axons in an epileptic seizure is synchronized and seems to originate in a reciprocal firing between thalamus and cerebral cortex. Under physiological circumstances, there are rhythmic oscillations between thalamus and neocortex, which could indicate that the repetitive firing may signify the intensification of an underlying pattern rather than a random process. The potential for this reflexive and interactive pattern is then always present, but is normally held back by inhibitory activity, such as we know, for instance, from inhibitory GABA receptor functions that support integrative qualities. There is evidence to suggest that GABA receptors dysfunction plays a role in the development of chronic epilepsy in childhood, implying that the inhibiting effect on the excess interactive quality is not functioning properly (Ben-Ari, et al, 2005).

When the brain is injured or irritated, for instance by edema, infection, a hematoma, a tumor, or other space-occupying processes, this inhibitory action falls away and seizures may occur, mostly as partial complex seizures (60% of all seizures are partial complex). Generalized seizures, such as absences and generalized tonic-clonic seizures, often occur in familial clusters and mostly have a genetic predisposition, although no one gene has been found to explain this seizure activity. Where specific mutant genes have been found, they encode for voltage gated ion channels or neurotransmitters. In absences, the loss of waking consciousness is most prominent, indicating that integrative qualities are disturbed. In tonic-clonic seizures, the motor activity that gives these seizures their name is most prominent, suggesting that interactive qualities are characteristically impaired. Antiseizure drugs modify Na^+-voltage-gated channels, which occur in the whole organism. Apart from in the CNS, they are also markedly present in the heart, musculature, vasculature, and gastro-intestinal tract, and antiseizure drugs affect these structures to a greater or

lesser degree. Cardiac arrhythmias, ataxia, nausea and vomiting, and migraine herefore often accompany the CNS effects. These indicate that antiseizure drugs may also have interactive qualities peripherally. CNS effects should ideally only increase the threshold for repetitive firing and not affect waking consciousness. The preferred antiseizure drugs have little effect on waking consciousness and have few effects in the rest of the organism.

The action of *benzodiazepines* and *barbiturates* was already mentioned in the previous hapter on sedatives and hypnotics (section 3.2.). Since the members of these drug families have sedative action as well as seizure modifying action, they are no longer the preferred treatment for epilepsy. However, diazepam and lorazepam have an important role in treating status epilepticus, and clonazepam and clorazepate are used as seizure medications. Phenobarbital, in use for epilepsy since 1912, and derivatives of phenobarbital such as primidone are still used when other medications fail to reduce seizure activity sufficiently. In this chapter we will discuss some of the other typical antiseizure drugs: valproic acid, phenytoin, carbamazepine, and topiramate. All of these also have GABAergic effects.

It is probable that the older antiseizure drugs cause fetal deformation such as congenital heart defects and neural tube defects. There is as yet not enough experience with the newer agents to definitely say whether they cause fetal deformations. However, the interference with signal transmission in the CNS and peripherally, which is a property that all antiseizure drugs have in common, is likely to have deleterious effects on growing organisms. This property of the antiseizure drugs indicates that vegetative functions in growing organisms are impaired by the interactive qualities of antiseizure drugs.

4.2. Valproic acid

4.2.1. Molecular structure

Valproic acid has been in use as an antiseizure medication since 1978. It is a simple ranched-chain carboxylic acid with eight C-atoms, three each on two branched chains, and two on the carboxylic acid moiety (fig.4.1.). A lengthening of the C-atom chain with one more C-atom produces a compound with marked sedative qualities. Valproic acid has limited water-solubility. It has no N-atoms in its structure and resembles small fatty acids.

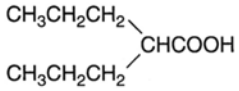


Fig.4.1. Structure of valproic acid (from Goodman & Gilman's, 2001)

Valproic acid is a relatively small, lipid-like molecule, which would indicate that it has integrative qualities structurally.

4.2.2. Biochemical and pharmacological properties

Valproic acid inhibits and thus prolongs the recovery of activating Na^{+}-channels, and ffects the metabolism of GABA, the chief inhibiting neurotransmitter in the CNS. It inhibits degradative enzymes that break down GABA, which prolongs the action time of GABA, and stimulates the activity of glutamic acid decarboxylase, an enzyme in GABA synthesis (see section 3.1.). It also reduces some of the activity of Ca^{2+}-ion currents (compare sections 3.4. and 6.5.). Valproic acid is 90% protein bound in plasma, and displaces many other drugs from their protein binding, including many other antiseizure drugs, thereby increasing their plasma levels and making them more effective. This is an interactive quality. It has at least one active metabolite.

Valproic acid's inhibitory biochemical effect on the catabolism of the main inhibitory neurotransmitter GABA, and its stimulation of the synthesis of GABA from glutamate would affect integrative activity. Prolonging the recovery of Na^+-channels relates to its integrative effect on interactive qualities.

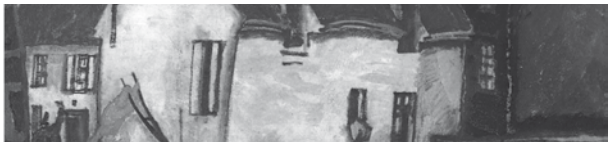
4.2.3. Physiological activities

Valproic acid has seizure modifying action on all types of seizures. This can be accompanied by some sedation, indicating integrative impairment, and intestinal problems such as nausea, vomiting, and anorexia, and ataxia and tremor, all due to interactive impairment. Valproic acid is also in use for migraine headaches.

Outside the CNS, valproic acid also affects liver functions, with a resultant increase in liver enzymes in 40% of patients. This would indicate an effect on vegetative functions. It also may cause a fulminant hepatitis with microvesicular steatosis. The fatty degeneration of the liver could indicate that integrative qualities inadvertently have taken the place of normal liver (mostly vegetative) function. We had described the liver as having predominantly vegetative qualities.

Physiologically, valproic acid affects integrative functions in the CNS, and it has an inhibiting effect on interactive qualities both inside and outside the CNS. It appears to inhibit vegetative qualities of the liver.

Valproic acid affects integrative qualities, and, possibly by imposing these on interactive and vegetative functions, inhibits neuronal and peripheral interactive and vegetative activity.



4.3. Phenytoin

4.3.1. Molecular structure

Phenytoin came into use as an antiseizure drug in 1938. Its structure is closely related to phenobarbital. It has two phenol rings connected to a ring of five atoms (including two nitrogen atoms), this is a so-called imidazole ring (fig.4.2.). The nitrogen atoms would indicate that it has interactive effects. It has low aqueous solubility, which would point to an integrative effect.

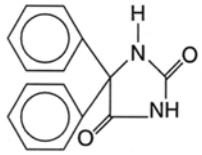


Fig.4.2. Structure of phenytoin (from Goodman & Gilman's, 2001)

Phenytoin's structure suggests a relation to interactive and integrative qualities.

4.3.2. Biochemical and pharmacological properties

Phenytoin affects the voltage-gated Na^+-channels and slows their recovery from inactivation. At toxic concentrations it will enhance GABA- response. 80-90% is proteinbound in plasma. It is displaced by valproic acid from its protein binding site.

Phenytoin's chief biochemical and pharmacological influence is on interactive qualities; it has integrative activity at toxic levels.

4.3.3. Physiological activities

Phenytoin does not cause general CNS depression. It causes some drowsiness, but has no

hypnotic qualities. It also does not affect absences, which are characterized by a decreased integrative awareness (section 4.1.). At therapeutic drug levels, seizure modification has no effect on spontaneous CNS activity. Phenytoin causes nausea, vomiting, cardiac arrhythmia, and ataxia due to the blockage of Na^+-channels peripherally. Overdose results in symptoms of the cerebellar and vestibular tracts. This demonstrates that phenytoin has mainly interactive effects and only in high doses lowers integrative functions.

Other effects of phenytoin outside the CNS include the inhibition of insulin secretion carbohydrate metabolism), inhibition of the release of antidiuretic hormone (ADH, increases the amount of water in the organism), and altered vitamin D and K metabolism, which is probably responsible for the osteomalacia sometimes seen with phenytoin. It also depresses immune function by reducing IgA production, and causes a peripheral neuropathy. In children, phenytoin will cause a coarsening of facial features, hirsutism, and gingival hyperplasia. Fetal deformations include cleft lip and palate, congenital heart disease, general slowed growth, and mental deficiency. These effects demonstrate an unwanted increase of vegetative and morphological functions.

Physiologically, phenytoin mainly affects interactive and also vegetative and physical functions, in high doses also integrative qualities.

Since the qualities of phenytoin are mainly interactive, its effect on vegetative functions may be related to the fact that interactive qualities and vegetative qualities no longer work together properly. At the appropriate moment, the tissues that are subject to vegetative growth do not interact sufficiently with their surroundings to stop the growth qualities, and the result is that they grow too much. From this we can understand the importance of the integration of interactive qualities into the general vegetative function. Interactive qualities prevent vegetative function from becoming too plant-like; they curtail overabundant growth. On the other hand, there can be no catabolic (interactive and integrative) processes without first having anabolic (vegetative) growth. This can be compared to what we found in section 2.3.4. There we stated that the progressive breakdown of compounds in the human organism promotes greater awareness. Here we find that vegetative activity, when it is not stopped at the appropriate moment, will result in too much growth. There is a delicate balance in the human organism between anabolic and catabolic processes (see also chapter 7.).

Phenytoin is a compound with interactive and some integrative qualities. It may affect vegetative qualities through a failed integration of interactive qualities into vegetative functions, which causes the vegetative qualities to proliferate.

4.4. Carbamazepine

4.4.1. Molecular structure

Chemically, carbamazepine resembles the tricyclic antidepressants. It has two phenol rings connected by a third ring of carbon and nitrogen atoms, and a carbamyl group, consisting of a carbon with an amide moiety, connected to the nitrogen atom (fig.4.3.). The latter seems to be the active group for antiseizure activity. It has limited aqueous solubility.

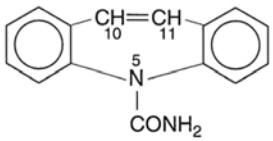


Fig.4.3. Structure of carbamazepine (from Goodman & Gilman's, 2001)

Carbamazepine has a structure suggesting interactive qualities with some integrative properties.

4.4.2. Biochemical and pharmacological properties

Carbamazepine limits repetitive firing by slowing the rate of recovery of voltage-activated Na^+-channels from inactivation. It has no effect on spontaneous activity at therapeutic levels. It is oxidized by liver enzymes and affects liver metabolism (compare section 4.3.3.). Carbamazepine has an active metabolite and is 75% bound to plasma proteins.

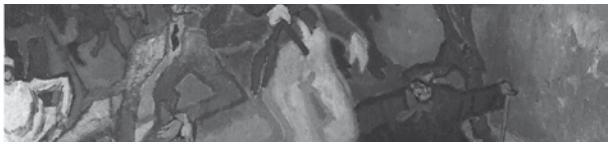
Biochemically, carbamazepine affects interactive functions. Its interactive qualities also affect vegetative functions.

4.4.3. Physiological activities

Carbamazepine has been in use as an antiseizure compound since 1974. Before, it was in use for the treatment of trigeminal neuralgias. In addition to its seizure modifying effect, its central effects include drowsiness, which affects integrative quality. It is also accompanied by nausea, vomiting, ataxia, and blurred vision, all interactive qualities. In overdose, it may cause stupor and respiratory depression. Carbamazepine is used also for the treatment of acute mania (The Medical Letter, 2005). Outside the CNS it causes a rise in liver enzymes, hepatic and pancreatic toxicity, hematological toxicity (aplastic anemia, agranulocytosis), and hypersensitivity reactions. It also has antidiuretic effects with a resultant retention of water and decrease of the level of ADH. These are vegetative effects.

Physiologically, carbamazepine has interactive qualities that affect a wider variety of vegetative functions. It has some integrative qualities.

> *Carbamazepine affects interactive functions and some integrative activity. It also causes an increase of vegetative qualities.*



4.5. Topiramate

4.5.1. Molecular structure

Topiramate has been in use since 1996. It is a sulfamate substituted monosaccharide. Sulfamate is a sulphate with an amide moiety at the end (fig.4.4.). Its structure consists of three rings, and it has many (8) oxygen molecules and one nitrogen in its formula.

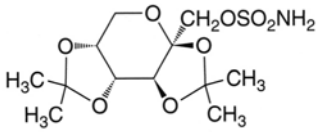


Fig.4.4. Structure of topiramate (from Goodman & Gilman's, 2001)

Topiramate as a monosaccharide structurally has vegetative qualities in addition to interactive and integrative qualities.

4.5.2. Biochemical and pharmacological properties

Topiramate affects the rate of recovery from inactivation of voltage-gated Na^+-channels n the cerebellum and decreases glutamate receptor currents. This indicates an influence on interactive qualities. It also enhances currents of the $GABA_A$ receptor post-synaptically, thereby inhibiting transmission in the cerebrum and cerebellum, and thus affects integrative functions. It is a weak carbonic anhydrase inhibitor, thereby affecting vegetative qualities, and is excreted unchanged in the urine.

Topiramate influences vegetative, interactive, and integrative biochemical functions.

4.5.3. Physiological activities

Topiramate has seizure modifying qualities, affecting interactive functions. Topiramate is also in use for migraine headaches. In general it is well tolerated. It can cause some somnolence, an integrative quality, and fatigue and weight loss, both vegetative functions.

Physiologically, topiramate affects vegetative qualities, as well as interactive and some integrative qualities.

The fact that topiramate is basically a monosaccharide would suggest that its primary action is on vegetative qualities. The increase in vegetative qualities then would also affect interactive and integrative qualities, slowing them down (see also section 4.3.3.).

> *Topiramate probably affects interactive and integrative functions by influencing vegetative qualities.*

4.6. Profile of the antiseizure drugs

The characteristic action of antiseizure drugs is to suppress excitation by suppressing the positively charged sodium channels which exist in the CNS, but also in other regions of the organism. The inhibition of excitation by these drugs makes it harder for the cell to become depolarized. This is in contrast to the action of the sedatives and hypnotics, which enhance inhibition to suppress depolarization of these neurons. The interference with the positively charged sodium channels by the antiseizure drugs rather than the negatively charged GABA channels by the sedatives is accompanied by little to no sedation. Antiseizure drugs that have more general sedative action, such as valproic acid, also influence the negatively charged GABA channel transmission more, this time by interfering with the metabolism of GABA, rather than with the voltage-gated receptor itself. When GABA transmission is enhanced

this is accompanied by more sedation. When sodium transmission is suppressed this is accompanied by less excitation. The action of antiseizure drugs can originate

a. on an integrative level (valproic acid), inhibiting interaction by enhancing inhibition
b. on an interactive level (phenytoin and carbamazepine), directly inhibiting interactions
c. on a vegetative level (topiramate), inhibiting interaction by increasing vegetative function.

Most antiseizure drugs also have vegetative and physical effects, such as increased and deformed growth and anti-diuretic effects. This indicates that the four different qualities of our framework are related and influence each other.

The antiseizure drugs characteristically interfere with excitatory Na^+ channels. This interference with interactive qualities is initiated by some drugs from the interactive level, by others from an integrative or vegetative level.

Uprising (Grosse Revolution), 1910.
Oil on canvas, 104,4 x 95,4 cm.

5. Antidepressant drugs

5.1. Introduction

Depression is one of the most widespread chronic diseases in our culture, and can be found in all age groups. There are different forms of depression. We will only discuss general characteristics of depression here. In depression, people often have a sleep disorder, a change in appetite and weight, fatigue, loss of libido and a slowed metabolism, as well as slowed psychomotor activity and thinking (See also **Bolk**'s Companion Depressive Disorders). This indicates a preponderance of vegetative qualities and a lack of sufficient interactive and integrative qualities in depression. The major antidepressant drugs that are available today have been in use since the 1950s-1970s. The monoamine oxidase inhibitors (MAOIs) became available in the mid 1950s, the tricyclic antidepressants (TCAs) in the early 1960s, and the selective serotonin-reuptake inhibitors (SSRIs) in the 1970s.

The antidepressants have in general either a secondary or tertiary amine moiety. They interfere with the reuptake or metabolism of different excitatory neurotransmitters, prolonging and potentiating their action. These properties put the antidepressants in the category of drugs that increase interactive functions in the human organism. They principally potentiate the activity of the neurotransmitters serotonin and norepinephrine, which both derive from tyrosine.

Serotonin (5-hydroxytryptamine or 5-HT) has many receptor subtypes that may relate to the different functions of serotonin. Serotonin is a mono-amine, an interactive compound (section 2.1.2.2.) that is synthesized in the enterochromaffin cells in the gastrointestinal tract and in certain areas of the CNS. Platelets have the ability for uptake, storage and endocytic release of serotonin. It occurs in the plant and animal kingdoms, for instance in the hairs of the common stinging nettle and in venoms of wasps and scorpions, causing inflammatory reactions. This shows its interactive character. It also occurs in fruits and nuts. In the CNS, serotonin functions as a neurotransmitter that is involved in neuronal excitation as well as inhibition. In addition to its release in synapses, it is also found in nonsynaptic varicosities of axons, which suggests that, in addition to its actions as

a neurotransmitter, it can also act as a neuromodulator for areas of the CNS. The main serotonin secreting neurons are situated in the raphe nuclei of the pons and upper brainstem and from there they project throughout the brain and spinal cord. Its effects are multiple and varied, influencing cognition, sleep, sensory perception, motor activity, temperature regulation, appetite, sexual behavior, and hormone secretion. From this it becomes clear that serotonin is a phylogenetically "old" compound with CNS functions that form the general basis for CNS activity. This also becomes evident from the fact that in many human studies an increase in violent and aggressive behavior is found when there is a low turnover rate of serotonin. At the same time, this violent suicidal behavior is not accompanied by increased suicidal ideation, so that cognitively higher functions are not activated. Peripherally, serotonin release is accompanied by contraction of smooth musculature and platelet aggregation.
Electrophysiologically, different serotonin receptor types will either increase or decrease **K^+ conductance**. The increase in conductance first hyperpolarizes the neuron. Then follows a slow depolarization with a decreased K^+ conductance. These effects influence the repolarization or regeneration of the neuron, a vegetative quality. Certain serotonin receptor subtypes may activate GABA-mediated inhibition. In the same area of the brain the increase and the decrease of K^+ conductance may both be present, as in the hippocampus.

Norepinephrine, or noradrenalin, is also a mono-amine neurotransmitter in the CNS, which has different receptor subtypes both in the CNS and peripherally, and is a compound with interactive quality. In the CNS, larger amounts are found in the hypothalamus and in the limbic system, more specifically in the amygdala and the hippocampus, but norepinephrine is found almost everywhere in the brain. The neuron bodies of norepinephrine secreting axons are situated in the locus ceruleus of the pons and/or in the reticular formation of the brainstem. Electrophysiologically, norepinephrine release results in hyperpolarization or depolarization of target neurons secondary to a change in K^+ conductance, thus influencing the vegetative, regenerative qualities of the cell (see above). In the CNS, its effects are often described as "enabling" or "state-dependent". This means that it has a general tonifying effect, giving the CNS electrophysiologically a higher tonus. Norepinephrine has a marked effect on the cardiovascular system: blood pressure and smooth muscle tone in the vessels is increased. These are interactive qualities.

Antidepressants that potentiate these neurotransmitters have both a general effect in the CNS as well as effects outside the CNS. The general CNS effects pertain to large areas of the brain and spinal cord. Serotonin and norepinephrine appear to affect the basic "tonus" of the CNS, which elucidates why many of the antidepressants may worsen or, in toxic quantity, even cause epilepsy. This can be seen as a consequence of their interactive qualities. The antidepressants that potentiate norepinephrine and serotonin affect K_{+}- channels, changing the repolarization, the *recovery* or *regeneration* of the cell, thus influencing vegetative qualities.

5.2. Tricyclic antidepressants

After the release of neurotransmitters into the synaptic cleft, where they become active by binding to a receptor site on the postsynaptic neuron body, transmitters are normally either metabolized or retaken up into the presynaptic axon terminal. Tricyclic antidepressants (TCAs) block the reuptake of norepinephrine and serotonin from the neuronal synapse, which results in a prolonged activity of these neurotransmitters in the synapse. This changes the conductance in the K+ channel, affecting regenerative, vegetative qualities.

5.2.1. Molecular structure

The TCA's have three rings in their structure, to which is attached a tertiary or secondary amine (N) side chain that seems to be essential for their effectiveness (fig.5.1.). They are relatively lipophilic, indicating integrative qualities, and bind to plasma proteins and constituents of tissues.

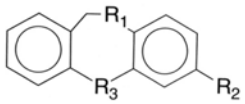


Fig.5.1. Structure of tertiary amine tricyclics (from Goodman & Gilman's, 2001)

TCAs have a structure suggesting integrative qualities; the essential molecular constituent for their activity, an amine, has interactive qualities.

5.2.2. Biochemical and pharmacological properties

The TCAs with a secondary side chain, such as desipramine and nortriptyline, are relatively more selective in their blockage of norepinephrine reuptake, and those with a tertiary side chain, such as amitriptyline, imipramine, and doxepin, variably block the reuptake of serotonin as well. The blockage of amine neurotransmitters occurs immediately and is sustained indefinitely. TCAs also affect adrenergic receptors in a variety of manners, which results in less availability of transmitter in the synaptic space, counteracting the effect of the neurotransmitter reuptake blocking! This mechanism may be in part responsible for the prolonged time period before a clinical effect is seen. Over time TCAs also seem to effect a decrease of the number of GABA and glutamate receptors. The effect of TCAs in the CNS is a complex process that has many interactive qualities, and over time it also affects integrative functions (GABA transmission). However, the precise manner in which the TCAs affect mood is still elusive, and some still have a completely unexplained pharmacological activity. In general, there is an increase of cyclic adenosine monophosphate (cyclic AMP, a compound for directly usable energy), and the activity of protein kinases acting on structural proteins is increased, suggesting increased catabolic activity, which may result in altered neuronal growth and sprouting. This suggests that the TCAs alter CNS metabolism to effect a breakdown of excess vegetative function, which would result in more awakeness and more available energy for the depressed patient.

TCAs are metabolized in the liver. They are partly oxidized, which results in the formation

of active metabolites, that then become partly conjugated with glucuronic acid, and thus enlarged, yielding metabolically inactive compounds. This can be compared to what was said in section 2.2. about the oxidation or breakdown of compounds resulting in active smaller compounds, and the conjugation to larger compounds, which have less activity.

The biochemical and pharmacological activity of the TCAs diminish vegetative excess by increasing vegetative qualities by increasing interactive qualities. They eventually depress integrative qualities.

5.2.3. Physiological activity

Clinically, patients seem at first to maintain functional homeostasis and the clinical effect of the tricyclics may take two to four weeks with repeated doses to become visible. TCAs lift the mood with repeated dosage over several weeks. Further interactive central effects include increased tendency to epileptic seizures. Sedation, which affects integrative capacities, is a common effect. A further effect is blockade of the vegetative nervous system, resulting in dry mouth, urinary retention, constipation, tachycardia, poor accommodation, hypotension, fatigue, and weakness. These peripheral effects indicate a decrease in integrated peripheral vegetative qualities. There is also weight gain; the origin of this is unclear, but it could also indicate an increase of unused vegetative qualities.

It seems that tricyclics increase some basic CNS interactive functions, such as lifting the mood, and at the same time decrease vegetative functions, as if the vegetative energy is used up by the increased interactive activity. There is also some effect on integrative qualities.

Physiologically, tricyclics increase general interactive qualities. The increased interactive function utilizes vegetative qualities, so that there is a lack in some parts of the organism. They also affect integrative function.

> *Tricyclic antidepressants are compounds with interactive qualities that appear to use up the energy of vegetative functions. They also affect integrative qualities.*

5.3. Selective serotonin reuptake inhibitors

As the name indicates, the selective serotonin reuptake inhibitors (SSRIs) are more specific in their action than the TCAs: they chiefly block the reuptake of serotonin.

5.3.1. Molecular structure

The structure of the SSRIs has one (fluvoxamine), two (fluoxetine and venlafaxine), three (citalopram and sertraline), or four (paroxatine) rings with an amine (nitrogen) moiety (fig.5.2.). Most of the SSRIs contain a fluoride ion, one (sertraline) a chloride ion. Venlafexine has neither.

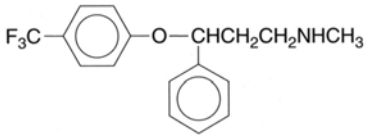


Fig.5.2. Structure of fluoxetine (from Goodman & Gilman's, 2001)

The SSRIs have integrative and interactive qualities in their structure.

5.3.2. Biochemical and pharmacological properties

Like the TCAs, the SSRIs interfere with K^+ conductance, affecting regenerative vegetative qualities. Inactivation of serotonin reuptake is immediate and indefinite. This is an interactive quality. However, complex secondary responses, including negative feedback mechanisms, exist and restore homeostasis. They may be responsible for the delayed clinical response. Many SSRIs also directly stimulate serotonin receptors.

SSRIs are demethylated in the liver to active (nor-) compounds (compare section 2.2.). They are excreted slowly.

SSRIs activate interactive neurotransmission pharmacologically and increase the expenditure of regenerative vegetative qualities.

5.3.3. Physiological activities

Clinical response to the SSRIs may be delayed for several weeks. SSRIs lift the mood of epressed patients. They have been associated with restlessness and agitation (akathisia), demonstrating activation of interactive effects. Other effects due to the potentiating of serotonin in the gastrointestinal tract include nausea, vomiting, diarrhea, and constipation. These demonstrate the interference of increased interactive qualities with metabolism, decreasing vegetative functions peripherally. The use of SSRIs may also be accompanied by headaches, tremor, and sexual dysfunction. These all have interactive quality. They also may have some sedative effect, affecting integrative function. Since they selectively affect serotonin, the SSRIs have been associated with the behavioral changes described in 5.1. on serotonin, such as aggressive behavior, which indicates a lack of integrative qualities.

Physiologically, SSRIs chiefly affect interactive and vegetative function, but they also affect integrative capacity.

> *SSRIs increase interactive qualities and as a result dampen vegetative and integrative qualities.*

5.4. Monoamine oxidase inhibitors

Monoamine oxidase (MAO) is an enzyme that regulates the metabolic breakdown of catecholamines, such as norepinephrine and serotonin, both in the CNS and peripherally. MAO can be found in the outer membrane of mitochondria in, for example, nerve terminals in the CNS, the liver, and the intestinal mucosa. In the CNS, MAO oxidizes norepinephrine and serotonin at their (re-)entry into the axonal terminal and renders them ineffective. In the liver, MAO oxidizes circulating and ingested monoamines and detoxifies them. MAO has an extensive peripheral function.

5.4.1. Molecular structure

The monoamine oxidase inhibitors (MAOIs) in most frequent use, phenelzine and tranylcypromine, are themselves amine derivatives (fig.5.3.). MAOIs have one phenol ring and the amine moiety is on a side chain.

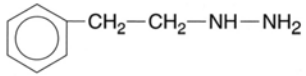


Fig.5.3. Structure of phenelzine (from Goodman & Gilman's, 2001)

The structure of MAOIs has interactive qualities, and little integrative quality.

5.4.2. Biochemical and pharmacological properties

The MAOIs also interfere with K^+ conductance and affect vegetative qualities. They downregulate the catabolism of serotonin and norepinephrine and potentiate their activity, interfering with interactive functions. The action of MAOIs is site directed and irreversible. Phenelzine, a characteristic example of MAOI, resembles MAO substrate. At first, MAO cleaves the MAOI, which renders active intermediates that subsequently inactivate MAO (compare section 2.2.). This increases interactive processes. The inhibition

of MAO is immediate. After termination of therapy, it takes at least two weeks to produce sufficient fresh MAO. MAOIs are inactivated by acetylation (compare section 2.2.). They are mostly long acting.

The pharmacological activity of MAOIs indicate interactive and some vegetative quality.

5.4.3. Physiological activities

MAOIs lift the mood of depressed patients. The mood change takes several weeks to be effectuated. MAOI use may be accompanied by excitation and a variety of peripheral effects, such as an increase in postural hypotension and an increase in diastolic blood pressure, affecting interactive qualities. Sedation is also a known effect, decreasing integrative qualities. Other effects may be severe and unpredictable. For example, due to the fact that MAO in the liver and intestinal tract does not degrade the tyramine in aged cheese, chicken liver, red wine, and beer, the excess tyramine then causes the release of large amounts of catecholamines in the CNS. This may cause severe hypertension with headache, tachycardia, cardiac arrhythmias, myocardial infarction, and stroke, indicating greatly increased peripheral interactive quality. MAOIs are very hepatotoxic and they can produce dry mouth, urinary retention, constipation, and poor accommodation, which represent a serious decrease in peripheral vegetative qualities. Much like the TCAs and SRIs, the increase in interactive qualities through MAOIs consumes vegetative qualities. Because of their strong peripheral effects, MAOIs are now only in use in depression refractory to other antidepressants.

Physiologically, MAO inhibitors increase interactive qualities centrally, but also have a strong peripheral
effect and decrease vegetative and integrative qualities.

> *MAO inhibitors are interactive compounds that strongly influence interactive functions and that consume vegetative qualities and override integrative functions.*

5.5. Profile of the antidepressants

In depression, we see excess vegetative qualities. Antidepressants increase interactive qualities in the CNS. They affect K_+ channels of neuron bodies, which affect the cell's regenerating possibility, and thus consume vegetative quality. Antidepressants dampen vegetative life processes while increasing interactive qualities. Antidepressants also dampen integrative qualities. This is pronounced in the SSRIs and the TCAs. The MAOIs have the strongest effect on peripheral interactive qualities and can easily become toxic, which shows us that we have to be careful about how to reinstate a new balance between different qualities. All antidepressants have an integrative quality in their structure.

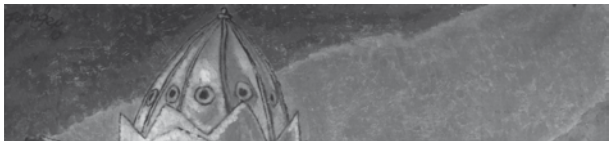
Street at Dusk (Strasse in Dämmerung), 1910.
Oil on canvas, 80 x 105 cm.

6. Antihypertensives

6.1. Introduction

Hypertension is defined as a blood pressure above 140/90 mm Hg. At least 90% of hypertension is essential. Hypertension may accompany serious cardiovascular, renal, or endocrine disease, such as left ventricular hypertrophy, coronary artery occlusion, cardiac failure, stroke, and renal failure without itself causing symptoms. Blood pressure is an interactive quality of the organism, and hypertension is a disorder of increased interactive function.

The importance of adequate control of hypertension is in preventing end organ damage. The major types of pharmacological treatment for high blood pressure are the angiotensinconverting enzyme (ACE) inhibitors, the diuretics, the beta blockers, and the calcium channel blockers. Antihypertensive treatment may either reduce cardiac output through the use of the beta-blockers and some of the calcium channel blockers (verapamil and diltiazem), or decrease peripheral resistance through the ACE inhibitors, the diuretics, and some of the calcium channel blockers (especially nifedipine). Adequate antihypertensive therapy often requires the use of two or more drugs. There is ongoing debate on the choice of initial treatment, with various studies showing varying results, depending on the age group treated, ethnic background, and accompanying disease. This chapter aims to add a dimension to this discussion.



6.2. ACE inhibitors

6.2.1. Molecular structure

The molecular structure of ACE inhibitors can be understood by looking at the way angiotensin II, a potent vasoactive substance, is formed from substrate. The conversion of angiotensin I to angiotensin II is catalyzed by angiotensin-converting enzyme (ACE). ACE is a mostly membrane-bound protein of endothelial cells consisting of more than 1200 amino acids, and has many substrates. ACE cleaves off dipeptide units from its substrates. Among the many substrates of ACE are angiotensin I and bradykinin.

Certain dipeptides and amino acids inhibit ACE when they have structurally a length similar to the his-leu-dipeptide that is physiologically cleaved off by ACE (fig.6.1.). Pit viper venom was found to be similar in morphology to this dipeptide. It is an amino acid derivative and was shown to inhibit the catabolism of the vasodilator bradykinin by ACE. Pit viper venom prolongs the duration of action of bradykinin and acts as a vasodilator in snake bite victims.

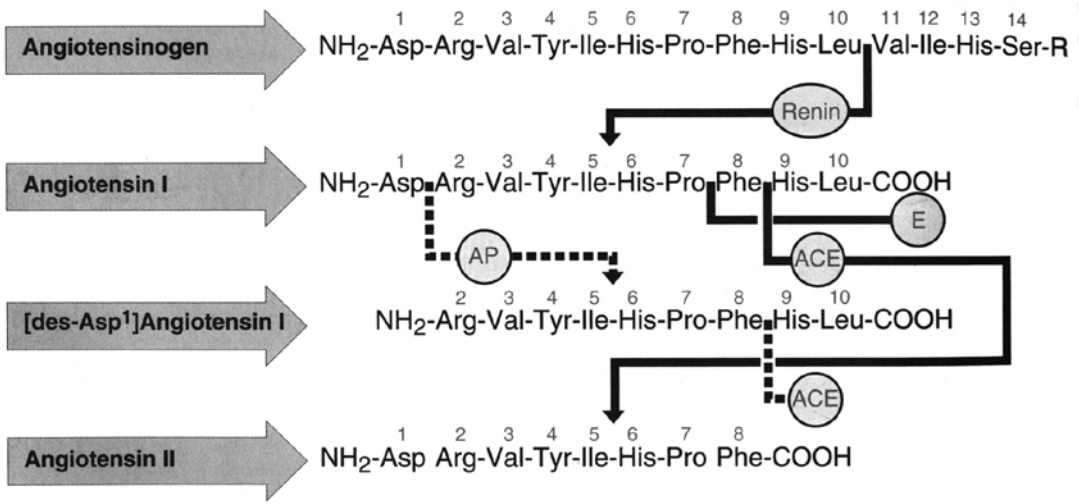


Fig.6.1. Formation of angiotensin peptides (after Goodman & Gilman's, 2001)

Fig.6.1. Formation of angiotensin peptides (after Goodman & Gilman's, 2001)

The first ACE inhibitor, captopril, was developed from pit viper venom in the 1960s by making a morphologically similar compound. It was developed as a succinyl amino acid that has the same length as the dipeptide, suggesting interactive properties. Following a rational approach, further ACE inhibitors were found by making them morphologically similar to captopril (fig.6.2.). This means a similarity on the basis of physical qualities. Captopril and lisinopril are the active form of the drug. Other ACE inhibitors are pro-drugs and need to be hydrolyzed by the liver to be activated.

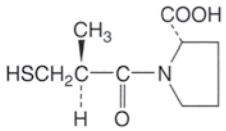


Fig.6.2. Structure of captopril (from Goodman & Gilman's, 2001)

The structure of ACE inhibitors has interactive properties. There is morphological similarity between the ACE inhibitors and the dipeptide that is cleaved off by ACE from its substrate. This is a physical quality.

6.2.2. Biochemical and pharmacological properties

The biochemical and pharmacological activity of ACE inhibitors is based on structural physical blocking of the enzyme's activity. Since enzyme activity is interactive, ACE inhibitors inhibit interactive processes. This action is passive in nature since the drugs' only activity is to take the place of the dipeptide unit of the substrate.

The kidneys clear most active forms of ACE inhibitors in largely unchanged form. The effective half life of these drugs is more dependent on their binding to ACE than on the plasma half life, pointing to the importance of the physical quality in their activity.

ACE inhibitors block interactive biochemical and pharmacological activity through physical qualities.

6.2.3. Physiological activity

ACE is an enzyme that is active in a cascade of compound conversions, the Renin-Angiotensin-Aldosterone-System (RAAS). This cascade affects cardiovascular muscle tone, renal excretion of Na_+, and cardiovascular morphology (fig.6.3.). The cascade can unroll systemically or be a local system in an organ. Events such as dehydration or bleeding reduce circulating blood volume and/or arterial blood pressure and activate the systemic cascade.

In the *kidneys*, the cascade starts off with the production of renin, a proteolytic enzyme from the juxtaglomerular cells. The renin production is a response to altered pressure or filling in the renal vessels. The peptidase renin catabolizes angiotensinogen, a globular glycoprotein produced in the *liver*, which results in the formation of the decapeptide angiotensin I. Then the cascade moves to the endothelium of the vessels in the lungs, where angiotensin-converting enzyme (ACE) metabolizes the relatively inactive angiotensin I to the hundred fold more active angiotensin II (compare section 2.2.). Angiotensin II acts on the *heart and blood vessels*, increasing blood pressure. It also stimulates the production of aldosterone in the adrenal cortex, which increases renal reabsorption of Na^+, and with it water, increasing blood volume and blood pressure. The increased arterial pressure affects renin release through the juxtaglomerular apparatus in a negative feedback mechanism.

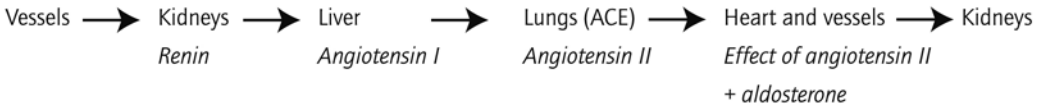


Fig.6.3. The Renin-Angiotensin-Aldosterone-System (RAAS) cascade

Angiotensin II has 3 major direct effects in the organism. It increases blood pressure by

- *acutely increasing total peripheral resistance* through vasoconstriction, called the "rapid pressor" response,
- and *by slowly decreasing renal excretion of sodium*, called the "slow pressor" response, helping to stabilize blood pressure over the long run;
- in addition it causes *hypertrophy of the vascular and cardiac muscle cells* and changes

the morphology of the cardiovascular system through proliferation of smooth and cardiac muscle cells and by increase of extracellular matrix.

ACE inhibitors affect all systemic actions of angiotensin II. They lower blood pressure and reduce morphological vascular changes. Since ACE also has substrates other than angiotensin I, ACE inhibitors act as a double edged sword on blood pressure when they also cause increased levels of the vasodilator bradykinin (fig.6.4.).

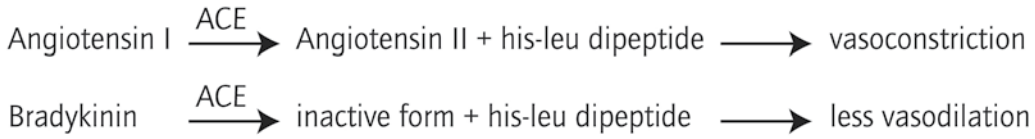


Fig.6.4. The double edged effect of angiotensin convering enzyme on vessels

Some of the morphological changes through ACE inhibitors become visible in their effect on the growth of the fetus during pregnancy. *Fetal cells have many ACE receptors*, though their distribution is restricted. During the first trimester there are no known fetal effects, but in the second and third trimesters ACE inhibitors can be teratogenic. There may be pulmonary and calvarial hypoplasia, both morphological changes, growth retardation, and death. Effects like oligohydramnios or anuria may in part be due to fetal hypotension.

ACE inhibitors are active in the endothelium of the lungs. One of their non-blood pressure related effects is an irritating cough, which is probably related to the inhibition of bradykinin breakdown in the lungs. We have characterized the lungs as organs whose physiology is dominated by physical processes.

ACE inhibitors are described as antihypertensives especially for whites and the elderly.

ACE inhibitors decrease blood pressure and also characteristically decrease the morphological changes in the heart and blood vessels that accompany hypertension. Their main action is in the lungs, organs with characteristic physical features.

ACE inhibitors block the increased interaction in hypertension by ***remodeling physical qualities.***

6.3. Diuretics

Volume regulation is an important factor in all types of hypertension. A large circulating extracellular volume will increase blood pressure. A circulating volume that is too small will be accompanied by hypotension.

Volume regulation of the extracellular fluid compartment of the human organism is primarily a function of the kidneys. Several different mechanisms are employed to achieve the balance that fits the organism at a given time (see also Physiology, section 4.4.):

- regulation of the glomerular filtration rate, which directly affects the amount of water that is excreted by the kidneys,
- regulation of tubular reabsorption and excretion of anions and cations, which is accompanied by the passive reabsorption or excretion of water.

Diuretics affect the self-imposed balance of the organism by excreting water and thus decreasing the extracellular fluid compartment. All diuretics influence sodium and water reuptake in the kidneys in some form. Most diuretics act by inhibiting tubular reabsorption of sodium and water.

The diuretics form a diverse group of substances. Their names may refer to their structure (such as in the thiazide diuretics), their site of action (such as in the loop diuretics), or their way of action (such as in the osmotic diuretics or aldosterone antagonists). Most widely used are the thiazide and thiazide-like diuretics, such as hydrochlorothiazide (the thiazides) and the loop diuretic, furosemide.

6.3.1. Molecular structure and classification of diuretics

The thiazides, loop diuretics, and carbonic anhydrase inhibitors are organic acids (fig.6.5.). The K^+-sparing diuretics are mostly organic bases. Through their electrical charge as acids and bases they bind water. This association with water suggests that they influence vegetative functions (see section 2.1.3.2.). The structure of the osmotic diuretics varies, but is designed to bind water. This gives them a relation to vegetative functions. Spironolactone has a steroid-like ring structure, and is a lipid, which suggests that it acts rom the integrative level.

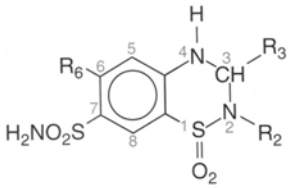


Fig.6.5. Structure of the thiazides (from Goodman & Gilman's, 2001)

All diuretics except spironolactone, and some osmotic diuretics, such as mannitol and lycerin, have nitrogen in their molecular structure, suggesting interactive qualities.

Diuretics have varying structures. The thiazides and the loop diuretics have structures suggesting interactive and vegetative properties. The structure of osmotic diuretics is related to water and vegetative processes. Spironolactone has integrative properties.

6.3.2. Biochemical and pharmacological activity

Diuretics may affect any part of the kidneys. Since the physiology of the kidneys has many interactive qualities (section 2.1.3.3.), diuretics mainly block interactive functions. The organic acids and bases are secreted by the organic acid and the organic base transport system, respectively, in the cells of the proximal tubules. Then these diuretics work on the organism from the tubular lumen side of the kidneys onto the tubular cells, in fact from outside. The *carbonic anhydrase inhibitors* almost totally stop $NaHCO_3$ reabsorption in the proximal tubule. The *loop diuretics* block the Na-K-2Cl symporter systems in the thick

ascending limb of Henle's loop, attaching to and competing for the Cl^- binding site. This blocks the resorption of chloride. The thiazide diuretics block the Na-Cl symporter system in the distal convoluted tubule, also possibly attaching to and competing for the Cl^- binding site. In all cases, water follows the ion secretion passively, with a resulting diuresis.

The *K^+-sparing diuretics* with the exception of spironolactone, inhibit Na^+ channels in the luminal membrane of principle cells of the late distal tubule and collecting duct. This blocks the reuptake of Na^+ and consequently also blocks the mandatory secretion of K^+ in this area.
Spironolactone binds to mineralocorticoid receptors in the late distal tubule and collecting duct cells, and competitively inhibits the binding of aldosterone, a steroid hormone from the adrenal cortex. The inhibition of aldosterone causes a change in the expression of DNA in the distal tubule cell nuclei, which, among other effects, inhibits the number and function of Na^+ channels and Na^+ pumps. This decreases Na^+ reuptake through the same mechanism as described above for the other K^+-sparing diuretics.

Osmotic diuretics extract water from intracellular compartments, expanding the extracellular volume compartment. The consequent increase of blood flow in the kidney system leads to a diuresis.

Biochemically, diuretics block interactive kidney function by increasing the passive secretion of water, a vegetative process.

6.3.3. Physiological effect on the organism

Diuretics are important medications in hypertension and cardiac failure. The effect of all diuretics is a contracted extracellular volume, a reduced cardiac output, and a reducedafterload of the heart as a result of the increased excretion of sodium and water. This affects vegetative functions: diuretics reduce the edema that complicates hypertension, and may cause hypotension. Further, it is generally known that they decrease glucose tolerance, probably through reduced insulin secretion, which may expose a latent diabetes mellitus, and that plasma concentration of total and LDL cholesterol and triglycerides may increase. An important diuretic side effect is fatigue.

Diuretics are especially used for hypertension in black patients and in the elderly.

Diuretics affect vegetative qualities to reduce the increased interactive qualities in hypertension.

> *Physiologically, diuretics block the increased interaction in hypertension by regulating the fluid compartment, a vegetative quality.*

6.4. Beta-adrenergic receptor blockers

The ß -adrenergic receptors of the sympathetic nervous system are coupled with G- proteins. The seven membrane spanning domains of these transmural proteins probably contain the ligand-binding pocket. The receptor activates intracellular cyclic AMP with resultant phosphorylation of intracellular effector proteins. Activation of ß-adrenergic receptors inhibits smooth muscle response in the organism, including the intestines, and increases heart rate and contractility. Receptor activation facilitates the response of the organism to stress and exercise, hence the use of its blockers in sports and in the performing arts. ß -adrenergic receptors are involved with interactive functions.

6.4.1. Molecular structure

ß-Blockers bear structural resemblance to the catecholamines active in the sympathetic nervous system. Catecholamines are part of the protein family of substances, and ß-blockers all have an amino-nitrogen component (fig.6.6.), which points to interactive properties. Almost all ß -blockers contain one or two benzene rings, which makes them lipophilic, like the catecholamines themselves; therefore they can easily enter the central nervous system. This would add an integrative component to their interactive properties.

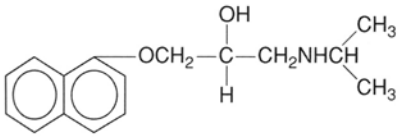


Fig.6.6. Structure of propranolol (from Goodman & Gilman's, 2001)

The molecular structure of b ß -blockers indicates that they have interactive properties with an integrative component.

6.4.2. Biochemical and pharmacological activity

The catecholamines that are blocked by the ß-blockers are neurotransmitters, making ß-blockers compounds that inhibit interactive functions. Because of the similarity in structure to the physiological catecholamines, almost all ß-blockers are competitive inhibitors and they sometimes also act as competitive (partial) agonists. Competitive inhibition is an interactive process. 90% of propranolol is bound to plasma proteins. Its metabolites are excreted in the urine.

ß -Blockers are competitive inhibitors of neurotransmission. They have pronounced interactive activity biochemically.

6.4.3. Physiological activity

The ß-adrenergic response includes an increase in cardiac output and blood pressure, a decrease of peripheral resistance, and relaxation of the muscles of the bronchial tree. $ß_1$-adrenergic receptors are situated in the myocardium, $ß_2$ receptors in smooth muscles and most other sites, including the bronchi. ß-Blockers affect this response by blocking the activity of ß-adrenergic receptors.

ß-Blockers have little effect on the heart of a healthy person at rest, but when sympathetic

activation of the heart is dominant, as in exercise or stress, when there is increased interactive function, the impact is profound. The effect of the interaction between the environment and the organism is blunted. This effect can be likened to the changes that occur with healthy aging: the impact of adrenergic stimulation on the heart rate is blunted, while cardiac output is maintained. The bronchial smooth muscles contract, which can induce an asthma attack in sensitive individuals. ß-Blockers also block the noradrenaline effect in the central nervous system, causing depression. This indicates that vegetative qualities have increased (compare section 5.1.).

In people with hypertension, ß-blockers slow the heart rate and decrease contractility, but they seem to have their main effect in decreasing blood pressure by lowering peripheral resistance by an as yet unknown mechanism. They are most effective in hypertension where stress plays a prominent role. One might conclude that people with hypertension for whom ß-blockers are effective must be in stress. ß-Blockers are less effective in the elderly, possibly because the elderly already have a physiological ß-blocking effect. ß-Blockers are used for hypertension especially in whites and young people, those most susceptible to stress.

The physiologically unique effect of ß-blockers is in hypertension where interactive processes such as stress play a prominent role.

> *ß-Blockers reduce the increased interactive effects of hypertension directly. They reduce the effect of stress.*

6.4.4. Angiotensin II receptor blockers and renin receptor blockers

The **angiotensin II receptor blockers** are compounds with few other effects but the lowering of blood pressure. They interfere directly with interactive processes when they competetively block receptors of angiotensin II. They do not block the breakdown of bradykinin and do not cause a cough as the ACE inhibitors do, but they do not effect the same morphological changes in heart and vessels either. They are specifically indicated in patients with microalbuminuria, such as in hypertension and the nephropathy of diabetes mellitus because they reduce the protein output in the urine. Again, this would indicate that their activity is in reducing interactive qualities directly, rather than influencing physical

qualities to reduce the excess interactive quality in hypertension, as the ACE inhibitors do.

The **renin receptor blockers**, which are presently being developed for the treatment of hypertension, are also receptor blockers and thus interfere directly with interactive processes. They also reduce microalbuminuria and possibly will improve retinopathy. Recently it has been established that there is a high concentration of renin receptors in the eyes.

6.5. Calcium Channel Blockers

Smooth muscle contraction occurs in at least three distinct steps that involve Ca^{2+}-ions (*Physiology Companion*, section 5.4.2.). Ca^{2+}-ions provide the coupling between excitation and contraction in smooth muscle cells.

1. When depolarization of the cell membrane occurs through the action potential, *voltagedependent* slow Ca^{2+} channels open to allow extracellular Ca^{2+} to move into the smooth muscle cell. There are also *receptor operated* Ca^{2+} channels in vascular smooth muscle cells that allow the influx of extracellular Ca^{2+}. These receptors are activated by ligands such as the adrenergic hormones.
2. When enough Ca^{2+}-ions have entered the myocyte, they facilitate the fast release of intracellular Ca^{2+}-ions from the sarcoplasmic reticulum, which further increases the intracellular Ca^{2+} concentration.
3. This leads to the binding of Ca^{2+} to calmodulin. This complex *activates* the kinase on the myosin light chain, resulting in phosphorylation of the light chain, which in turn intensifies the actin/myosin interaction. This increased interaction becomes visible as the contraction of the smooth muscle cell.

In cardiac myosites, Ca^{2+} binds to troponin. This releases the *inhibiting* activity of troponin on the contractile apparatus of the heart cells. The influx of Ca^{2+}-ions is also important in the rhythm of the action potentials in the sino-atrial and atrioventricular node. Depolarization

is mostly dependent on Ca^{2+} channels. Thus, **the influx of Ca^{2+}-ions in cardiac tissue affects an integrative process**, whereas **in the peripheral smooth muscle cells it affects interactive quality** when it activates calmodulin.

Voltage dependent calcium channels can be found in many different tissues. However, calcium channel blockers principally affect the vascular smooth musculature and the myocardium.

6.5.1. Molecular structure

Calcium channel blockers have diverse structures, ranging from phenylalkylamines (verapamil) to dihydropyridines (diltiazem) and benzothiazepines (nifedipine and others). All of them have 2 or more rings and N-atoms in their structure (fig.6.7.).

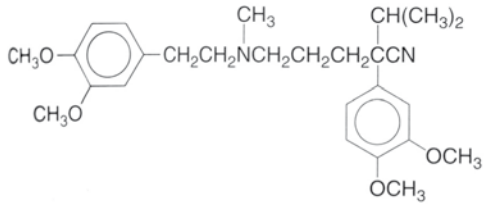


Fig.6.7. Structure of verapamil (from Goodman & Gilman's, 2001)

Calcium channel blockers have diverse chemical structures that all have interactive and integrative qualities.

6.5.2. Biochemical and pharmacological effect

Calcium channel blockers bind to different segments of the pore forming unit of the voltage dependent calcium channel. The resulting blockage of the channel actually means that it cannot open any more. Blockage prohibits the flow of Ca^{2+}-ions from the extracellular milieu into the vascular smooth muscle cell, or heart cell. In the sinu-atrial and

atrioventricular nodes in the heart, this becomes visible as a slow recovery of the cells after depolarization. The biochemical and pharmacological effect of calcium channel blockers is that they *prolong the inhibitory phase* of these cells. This means they affect integrative functions. Their effect is very brief, elucidating the experience that these medications are frequency or use dependent. It also means that when the heart is beating at a slower or normal rate, their effect is less prominent because the refractory period is then longer anyway. For a sustained effect, frequent dosing or sustained release preparations are mandatory. The briefness of their effect and their rapid metabolism also points to their relation to integrative functions (compare section 2.3.1., fourth step). Calcium channel blockers undergo an extensive first pass hepatic metabolism, which strongly reduces their bioavailability. Only when the metabolizing enzymes are saturated after several doses does the availability improve.

Calcium channel blockers enhance integrative qualities as they block interactive qualities in their biochemical and pharmacological effects.

6.5.3. Physiological activity

As stated earlier, the heart and circulation are directly affected by these agents. We described the heart and circulation in the *Physiology Companion*, chapter 5 as an example of an integrative organ system. Calcium channel blockers relax arterial and cardiac muscle, including the coronary vessels. This is an interactive effect. They have little effect on venous myocytes, which may also be due to the fact that these drugs briefly prolong the inhibitory phase of cells, which would naturally be longer in the venous system. Calcium channel blockers do not improve diastolic ventricular function.

Verapamil acts most strongly on the heart. Nifedipine acts mostly in the peripheral vascular bed, and diltiazem's action is in between these two. Verapamil and diltiazem slow the heart rate through their effect on the sinu-atrial node, and they suppress cardiac conductivity through their effect on the atrioventricular node. These affect the integrative funcions of this system (section 2.1.3.4.). They suppress the contractility of the myocardium, an interactive function. Nifedipine produces coronary vasodilatation, which improves coronary flow and reduces peripheral resistance in the arteriolar bed. This influences interactive activity.

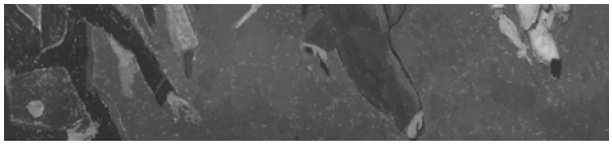
Calcium channel blockers all have a light diuretic effect and potentially give some reduction of left ventricular hypertrophy. These effects pertain to vegetative and physical functions respectively. They may cause gastro-esophageal reflux through relaxation of the lower esophageal sphincter. Relaxation of other smooth musculature may result in flushing, headache, hypotension, and ankle edema, which are all interactive effects.

When we discussed the integrative activity of heart and circulation in the *Physiology Companion* (section 5.7.), it became clear that integrative qualities affect all other activity levels. The physiological activity of the calcium channel blockers shows this also: their main activity is to increase integrative functions, but they also reduce physical, vegetative, and interactive activity, so that they eventually affect all levels.

Calcium channel blockers appear most effective in low renin hypertension, as in black and in elderly patients.

The calcium channel blockers affect integrative qualities, which includes effects on physical, vegetative, and interactive activity.

> *Calcium channel blockers block the increased interactive effects of hypertension by increasing integrative inhibition.*



6.6. Profile of the antihypertensive drugs

The four different classes of antihypertensives that have been described affect the pathologically increased interactive functions in hypertension from different angles. Each of the four main groups of antihypertensive compounds affects the reduction of the increased interactive quality in a different way. The *ACE inhibitors* characteristically affect the physical quality of hypertension by reducing the hypertrophy of the heart and vessels. The diuretics

characteristically affect vegetative function by reducing the fluid compartment. Both give the increased interactive quality less hold on the organism. The characteristic action of the *ß-blockers* is that they directly interfere with the increased interactive functions. The *calcium channel blockers* characteristically increase the integrative functions to block the excess interactive qualities. To effect an altered balance in hypertension, we can employ any of the different qualities. By looking at the hypertensive individual's basic make-up in terms of these qualities, we may better be able to choose the most effective therapy.

End of the Session (Fin de Seance), 1910.
(After Men rushing from the Stock Exchange, 1908.)
Oil on canvas, 95 x 85,5 cm.

7. Review and conclusion

In this *Pharmacology Companion,* we used a framework of four qualities that we had found in studying the healthy organism in order to find more coherence in the facts we learn in pharmacology. We described the framework qualities in terms of biochemical and physiological attributes as well as types of consciousness. We applied the framework to four different classes of drugs, the sedatives and hypnotics, the antiseizure drugs, the antidepressants, and the antihypertensives. This framework can also be applied to the other pharmacological classes of drugs to increase our understanding of them.

7.1. Review of the sedatives and hypnotics

The physiological characteristic of the typical sedative and hypnotic drugs, the benzodiazepines and the barbiturates, is that they inhibit integrative functions of consciousness. Integrative functioning gives us acute awareness and awakeness to answer new questions, as well as the capacity to use our memory to find new ideas. Biochemically, sedatives and hypnotics enhance inhibitory $GABA_A$ activity. The GABA receptor forms a negatively charged chloride channel*, and has an inhibitory function in the CNS, and GABA* is a compound that has lipid quality. We had described earlier that integrative functions are related to inhibitory activity and biochemically to the lipids (section 2.1.2.3.). The benzodiazepines are most specific in their effect on the GABA receptor, and indeed affect integrative awareness most strongly. This we may conclude from the occurrence of amnesia with their use, from the relative absence of effects in the rest of the organism, and from their strong lipid solubility. These effects suggest that the voltage-gated GABA receptors play an important role in integrative functions.

The barbiturates have an effect that is not limited to GABA receptors, but also includes Na^+ receptors, which are distributed throughout the organism. They have unpleasant remaining central and peripheral interactive symptoms after the sedative effect is finished. In addition to the integrative effect, barbiturates have interactive activity that is mainly responsible for the remaining symptoms. These examples show that integrative function is either present or not. We had already described in section 4.3.3. that there is a delicate balance between catabolic (integrative and interactive) and anabolic (vegetative) qualities, and in sections

2.3.1. and 6.5.2. that integrative function is based on brief, momentary effects. When its inhibitory effect is prolonged, as in sedative use, this may cause amnesia and other symptoms. **Integrative function is a labile equilibrium.** We may compare this equilibrium to the balance of upright posture. Uprightness is a labile equilibrium that can be upset much more readily than the sturdy balance of the quadrupeds. An interesting feature of a labile equilibrium is that it keeps possibilities open to go in any direction. In other words, it creates the possibility for freedom of choice in the field in which this type of equilibrium is created, whether that be in mechanics, biochemistry, or in mental functioning.

7.2. Review of the antiseizure drugs

We described epilepsy as a disease with increased electrical activity in the CNS, and antiseizure drugs as suppressive of the excess excitation. The antiseizure drugs do this characteristically by suppressing the *positively charged sodium channels* that exist in the CNS and that are mainly responsible for excitations in the CNS but also in other regions of the organism. Antiseizure drugs that have more general sedative action, such as phenytoin, also influence the GABA channels, this time by interfering with the metabolism of GABA. Most antiseizure drugs also have effects on a vegetative level, such as increased growth and anti-diuretic effects. The activity of antiseizure drugs can originate

a. on an integrative level (valproic acid), inhibiting interaction by enhancing inhibition.
b. on an interactive level (phenytoin and carbamazepine), directly inhibiting interactions.
c. on a vegetative level (topiramate), inhibiting interaction by increasing vegetative function.

The four different qualities of our framework interrelate and mutually influence one another.

7.3. Review of the antidepressants

In depression we see a deregulation of vegetative qualities: the tendency to sleep disorders, fatigue, loss of libido, and changed activity level.. We can apparently influence this state by giving medications that enhance interactive qualities. Antidepressants are interactive compounds, which work apparently by prolonging the effect of the interactive neurotransmitters serotonin and norepinephrine. Serotonin and norepinephrine affect K_+ channels, keeping them open, which *changes the target cell's regenerating possibility*. Regeneration is a vegetative quality. Therefore, antidepressants change vegetative vital processes through the interactive qualities that they bring. We can see the same effect of changed vegetative quality through the treatment of depression with light therapy or sleep deprivation therapy.

The framework can also be used to describe illness, which makes our therapeutic aim more visible.

7.4. Review of the antihypertensive drugs

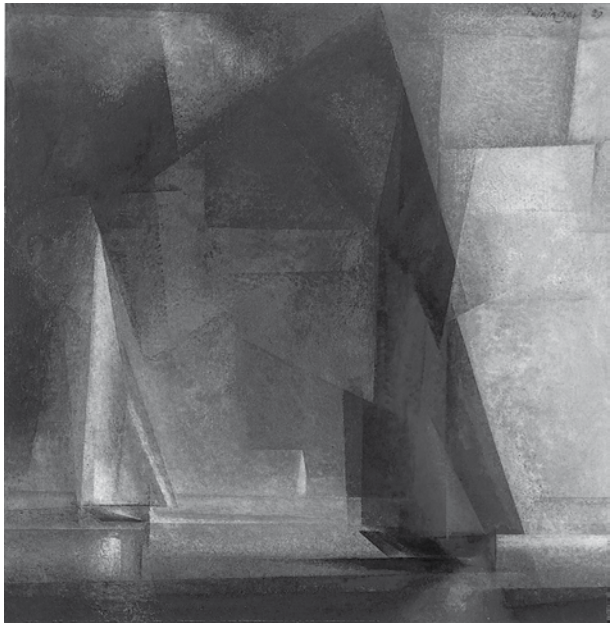
Like epilepsy, hypertension is characterized by a deregulation of interactive functions. Here, interactive functions are disturbed in the heart and vessels, rather than in the CNS as in epilepsy. The four different classes of antihypertensives that were described affect the pathologically increased interactive functions in hypertension from different angles. ACE inhibitors affect the *physical* quality of hypertension by reducing the hypertrophy of the heart and vessels. The diuretics affect *vegetative* function by reducing the fluid

compartment. The ß-blockers directly interfere with increased interactive functions. The calcium channel blockers increase *integrative* functions to block the excess interactive qualities. Thus, interactive qualities in general are inhibited by integrative qualities, consume vegetative qualities, and cause an increase in physical qualities, when they use up regenerative vegetative functions.

We can formulate the differentiated way in which the four qualities of the framework interact to make our therapeutic aim more explicit.

7.5. Conclusion

In this Companion we have found that a framework with four characteristic qualities that has been derived from our study of the healthy organism helps us find more coherence in studying pharmacological compounds, because compounds tend to affect one of the four qualities more than others. We have seen how this framework may assist us in understanding disease processes and the way our drugs work on them. We have begun to see how the four qualities of the framework interact in the organism and how we can formulate explicit therapeutic goals with them. In the future, we will try to show how disease processes and **therapeutic goals** can be further understood by using this framework.



Quiet Day at the Sea III (Stiller Tag am Meer III), 1929.
Oil on canvas, 49 x 36,2 cm

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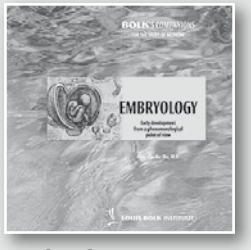
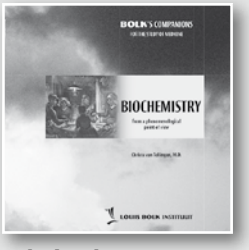


Embryology
Early development from a Phenomenological Point of View

Guus van der Bie, M.D.
Publicationnumber GVO 01

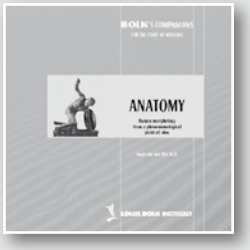
Can we give a scientific basis to our feeling that humans have unique human features? Are the human mind and the human organism 'nothing but' another variation of animal life? Can we find answers for the questions that satisfy both head and hart?
How these quetions are answered depends on the scientific method we use: the current scientific method to learn about biological facts and the phenomenological method to understand more about the meaning of these facts.
Early embryological development can teach us about the unique and characteristic qualities of the human being.
The result is, for example, a possibility to understand the relation between consciousness, psychology, and behavior and the shape of the body.



Biochemistry
Metabolism from a Phenomenological Point of View

Christa van Tellingen, M.D.
Publicationnumber GVO 02

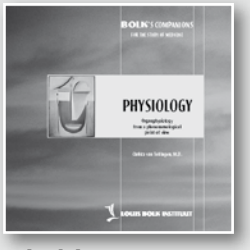
Biochemistry offers insight into the continuous changes within the human organism. But can we maintain awareness of the coherence of the (changing) organism as we study the details? How can the many processes be understood as prototypical aspects of a unique organism?
The scope of the answers to these questions can be enhanced by using a combination of the current scientific method and a phenomenological method developed specifically to research the coherence of processes within living organisms. The current scientific method is used to discover biological facts. The phenomenological approach helps us in finding the meaning of the facts.
What emerges is a new grasp of the interrelations between biological processes, consciousness, psychology, and behavior.



Anatomy
Morphological anatomy from a Phenomenological Point-of View

Guus van der Bie, M.D.
Publicationnumber GVO 03

Can we give a scientific basis to our feeling that the human being has unique human features? Are the human mind and the human body 'nothing but' another variation of animal life? Can we find answers for these questions that satisfy both our head and our heart?
How these questions are answered depends on the scientific method we use. In this publication two methods are used: the current scientific method to learn about anatomical facts and the phenomenological method to understand the meaning of these facts.
Human morphology can then be understood as an expression of the unique and characteristic qualities of the human being.
This results in new possibilities for understanding the relation between consciousness, psychology, behavior, and morphological aspects of the body.



Physiology
Organphysiology from a Phenomenological Point of View

Christa van Tellingen, M.D.
Publicationnumber GVO 04

Can physiology give more insight into the living human organism than the mere facts reveal at first? Is the level of activity the same for all organs? Are the vital qualities at work in organs unique for organisms and limited to biological activity? Can we find a scientific basis to research the coherence between organ systems?
By enhancing the current scientific method with phenomenological points of view we can find meaning in the facts and understand them as an expression of life itself. The phenomenological method makes the relation between organs visible and comprehensible. It approaches scientific facts from the point of view of their coherence and can give totally new insights this way.
What emerges is a grasp of the interrelations between biological processes, consciousness, and nature.

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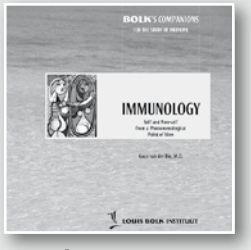


Immunology
Self and Non-self from a Phenomenological Point of View

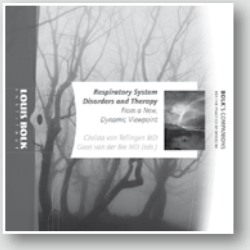
Guus van der Bie MD
Publicationnumber GVO 05

Why write this new booklet on immunology when there are already so many excellent texts on the subject? This Companion is about questions such as: why is it that the immune system functions as one organ? What coordinates the immunological functions?
Here, an attempt is made to develop a viewpoint to answer these questions. By using a phenomenological approach, the factual knowledge obtained through reductionism is placed in a larger perspective.
The concept that is presented in this Companion is derived from the functioning of organisms, observed in the way that was introduced by Goethe in his phenomenological method. This also includes the acquisition of insight into the holistic concept behind the immune system. Moreover, the organism as a whole can then be seen as an expression of the same concept.

The Healing Process
Organ of Repair

Guus van der Bie MD
Tom Scheffers MD
Christa van Tellingen MD
Publicationnumber GVO 07

After finalizing the series BOLK'S Companions for the Study of Medicine for the moment, this module on The Healing Process introduces a new series of BOLK'S Companions that studies the Practice of Medicine. In it, we research the healing process itself. There proved to be an enormous volume of scientific literature on the subject. It is easy to loose oneself in the countless details included in the descriptions of this process.
The phenomenological method of systems biology makes it possible to examine physiological and pathological processes in terms of the processes themselves. This results in a characterization of the various phases of the wound healing process. Out of this, new insights into the origin of health and disease emerged that also offer possible leads for medical practice.



Respiratory System Disorders and Therapy
From a New, Dynamic Viewpoint

Christa van Tellingen MD
Guus van der Bie MD (eds.)
Publicationnumber GVO 08

In this Companion, the experience of three of our own patients with asthma and pneumonia is used as backdrop for our study of airway disorders. Nearly all of us have had some experience with respiratory disease, given that colds, flus, sinusitis, and bronchitis are so common. Most physicians and therapists know people with asthma and pneumonia from own experience and will readily recognize the descriptions we provide.
The experience with these patients leads us through a study of airway disease which eventually opens up to a wider view with new insights and innovative avenues of treatment for respiratory disorders in general.
Our research has alerted us to the part rhythm plays in the healthy respiratory tract and in the treatment of its disease. Rhythm, consequently, is the subject of the final paragraphs of this Companion.

Depressive Disorders
An Integral Psychiatric Approach

Marko van Gerven MD
Christa van Tellingen MD
Publicationnumber GVO 09

The treatment of depressive disorders is increasingly under scrutiny. We classified the risk factors of depressive disorders according to the scientific method applied in systems biology and phenomenology. The ordering in four biological levels that resulted from this, helps clarify the causes of the disorder. Together with the developmental history, it can lead to an individualized treatment of the patient, tailored to his or her specific situation. The treatment aims at restoring the deficient forces of self-healing.
This Companion presents a working model based on this methodological approach, as well as a variety of case histories to illustrate how applying this model can aid diagnosis and treatment in practice. Tables are added ordering well-researched regular and integral treatment methods according to the four biological levels.

For ways to order the Companions see inside of front cover or check our website: **www.louisbolk.org/companions**

Pharmacology

Pharmacology gives us insight into the way organic processes change when foreign compounds are introduced into the organism. Pharmacology is a changeable subject, depending on the needs and knowledge of the time. Can we find an inner coherence in the manifold ways compounds influence organisms? Can we formulate a framework that can be used in the study of pharmacology that will promote such a coherent view? What should such a framework be based on? How can we understand the effect on human consciousness that most compounds have?

We can enhance the scope of the answers to these questions by using a combination of the current scientific method and a phenomenological method. The specific phenomenological method employed here was developed to comprehend the cohterence within living organisms. It illuminates the known facts about the activity of compounds in organisms, and provides the means to find their significance.

What emerges is a new grasp of the interrelations between pharmacological and biological processes, and consciousness, psychology, and behavior. This leads to a more rational understanding of the effect of compounds in health and disease.

LOUIS BOLK
INSTITUTE