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Reviews

On the physiology of metazoa

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Abstract. The problem of integration and control of the various processes of the metazoan organism is a major challenge to the physiologist. The traditional research strategy in dealing with the problem is neuron-oriented and its roots extend back into the last century when knowledge of hormones was lacking. In the present article, the traditional strategy is analyzed in the light of available data and its logical basis is questioned. Different levels of communication are supposed to occur in the animal or human body. Circulating hormones are responsible for the highest level of communication that occurs between organs or tissues. The central concept in the article is that regulation of circulating hormones constitutes a higher level of control relative to regulation of intercellular hormones. This is regardless of whether the latter occurs in the nervous system or elsewhere. The approach is utilized in defining the mechanism that integrates and controls the part processes of the body. The mechanism is defined as endothelial; the vascular endothelial system is the controlling part and the nervous system is one of the subordinate parts. Thanks to the new approach, meaningful biological explanations of major psychiatric disorders are now possible.
Key words. Pulmonary endothelium; angiotensins; enkephalins; phenylethylamine; hallucinogens; schizophrenia; β-carbolines; affective and sexual behavior.

The first physiological concepts appeared in prehistoric times and still occupy a significant place in our language and thinking. According to what may be considered as the theory of the naive, the deepest part of one's nature resides in the chest. The so-called 'heart' is the source of emotions and governs the behavior of the person. The characteristics of the 'heart' are assumed to be relatively stable because the emotional responses of the individual are generally consistent over time. Since individuals respond differently to the same situation, the theory of the naive predicts an inter-individual variation in the characteristics of such 'heart.' These inferences are usually made unconsciously and are reflected in expressions that describe persons in terms of physical characteristics of the assumed 'heart,' e.g., big, hard, warm, etc. It should be noticed that that 'heart' is supposed to be present in the chest on the basis of subjective feelings. These feelings are present before and regardless of anatomical or physiological knowledge. Undoubtedly, the theory was examined both in animal and human bodies by early prehistoric thinkers. Although the name 'heart' was given to the organ found centered in the chest, neither that organ nor anything else matched the expectations about individual differences. The aggressive, the timid, the outgoing and the reserved showed similar hearts when their bodies were examined. They had thus to think of the governing entity of the body as hidden or invisible. Given a different name, e.g., soul, such an entity could then be thought of as present in the heart or elsewhere.

The problem of individual differences is still a major challenge to our understanding of the physiology of the organism. The prehistoric conceptual scenario is reminiscent of the breakthrough finding of the year 1944 when the transfer of DNA molecules into harmless bacteria appeared to be responsible for transforming them into virulent organisms[5]. The finding was important because it led to clear cut questions about the structure of DNA and how it controls the machinery of the cell. An interesting parallel can be noticed between the concept of the 'heart' in the theory of the naive and the concept of the genome at the level of the cell. Both indicate a stable physical entity or a 'nature' that governs the behavior of the system.

The river valleys of ancient ages were fertile lands for the growth of societies and technologies rather than for the growth of science. With a highly complex social structure and limited variability in the physical environment, the primary concern of theorists was social integration. They tended to explain the biological in terms of the social and the concept of an invisible governing entity was thus utilized in linking the individual with the immortal social system. However, the situation around the Aegean Sea was different. Ancient Greek societies developed as simple social units and their economies depended on trade and shipping. They were exposed not only to an extended and rich physical environment but also to the accumulated knowledge of the nearby civilizations. The Greek theorists needed to discern the unity in a multiplicity of physical and conceptual

worlds. They explained the complex in terms of the simple and the biological in terms of the physical.

According to the Hippocratic school of ancient Greek medicine[79,163], the highest level of control in the body is a stable unchanging entity associated with the heart and is called 'physis' (nature). The next lower level is the 'temperament,' a relatively stable blend of four humors: red blood, phlegm, yellow bile and black bile. An outstanding point of the theory of Hippocrates is that it could translate the enduring qualitative characteristics of the individual into a blend of dynamic elements, i.e. the humors. Each of the humors is supposed to be in a state of continuous formation and disposition. According to the theory, however, it is the proportions of these humors that are stable. The role of physis is to keep these proportions. If it fails, the assistance of the physician is needed to help in restoring the balance. This is probably how the word 'physician' was derived.

The control relationship is central to the theory of Hippocrates and is well defined. Thus, the relationships between the processes of the body are controlled by a relatively stable structure, i.e. the temperament. The temperament itself consists of processes and the relationships between these processes are controlled by the unchanging physis. The degree of perception of Hippocrates is remarkable in that he did not confuse the cognitive function with the control of the body. Within spiritualism, thinkers considered the cognitive function as the responsibility of a supernatural entity and, by definition, a control of the supernatural by the natural was unacceptable. Within Hippocratic thinking, on the other hand, there are two levels of control above the mind, i.e. the temperament and the physis. Galen, the greatest supporter of Hippocrates, made this point[61]: '....All of the best physicians and philosophers agree that the humors and actually the whole constitution of the body change the activity of the soul (mind)....Therefore, those who were ignorant of the activity of humors...did not dare to write anything about melancholy.' The challenging words of Galen attract our attention to the current situation of physiology in that it does not depend on a theory of control and does not provide biological explanations for any of the major psychiatric disorders.

While everybody uses terms as 'heart,' 'nature' or 'temperament' to denote a certain stable governing entity in the body, the concept of stability is not considered seriously by physiologists. It must be noted that the concept of a stable governing physical structure came to explain an important natural phenomenon, i.e. the unity and the consistency of the behavior of the individual over time. Since it is the only scientifically acceptable explanation, we should try to find out what and where such a stable structure is. We can then develop better explanations. That the concept is so common among people does not mean that it is not important. On the contrary, it should give the concept a priority in scientific inquiry.

From the period of the Renaissance until the nineteenth century, most scientists adopted the strategy of restricting their fields of studies to the body and leaving aside the problems of the immaterial soul. By doing that they were also restricting their perceptions and explanations to what is controlled and neglecting what controls. Within this strategy, a good deal of data and explanations accumulated over time until so-called materialism emerged in the nineteenth century. The body of data examined did not show an immaterial soul or a stable governing structure. It seems that physiologists of that time were too successful to be skeptical about their method. Probably, they thought that the laws of mechanics and physics alone have the power to control the body. In general, these laws are useful formulae that describe what is common between phenomena; they neither control nor represent what controls. They express ideas in the minds of scientists and using the word 'laws' for these formulae is indeed misleading. Actually, the concept that the laws of mechanics and physics control the body or that they are the laws of Nature expresses a vicious form of supernaturalism that spiritualizes the ideas of theorists but lacks a constructive social influence. Nevertheless, evolutionary thinking appeared about that time and it was considered as anti-essentialism, i.e. against the idea that the organism has a stable essence. The tradition thus received a major reinforcement from the success of the theory of evolution. Actually, neither the knowledge, the technology, nor the general environment of that time allowed the physiologist to break a tradition that survived many generations. A reliable knowledge of hormones was lacking and formulating a theory of control without such knowledge is almost impossible.

Logic and adjustments

Our immediate reality is communication. Knowledge of the communication within a physical system is the most useful key to understanding the system and our concepts should conform, first of all, with such knowledge. Einstein gave priority to data concerning the speed of light and became skeptical about other data, a position that led him to the theory of relativity.

Studying the connections or communication between the parts of a whole is our primary concern in the attempt to understand how the whole is made out of the parts. It is logically invalid to explain how the whole is made out of the parts in terms of the communication occurring in one of the parts. However, physiologists of the last century thought that the communication occurring in one of the parts of the body, i.e. the nervous system, is primarily involved in the integration and control of the part processes of the body. The lack of

appropriate knowledge about circulating hormones and the fact that nerve fibers are distributed all over the body made them think of the nervous system as a channel of communication. A nerve fiber does serve as a channel of communication within a neuron, but a neuron is not the body. The nature of the nervous system is indeed very deceptive, and the communication occurring between the parts of its cells appear as if occurring between the parts of the body. Actually, the complexity of the nervous system makes it the last thing in the body that should be considered as a channel. The kind of communication that should concern us is that which occurs between organs or tissues. Nervous communications are either intra or intercellular. The data that were available during the last century and the idea that the nervous system is a channel of communication led to the research strategy that considered communication in the central nervous system to be the most relevant field for studying the integration and control of the part processes of the body. The strategy did not help to understand how the body works as a whole. It survived, however, for a long time and the gradual discoveries of hormones did not disturb it.

The knowledge available today is leading to a different perspective. Intercellular hormonal communication expresses and constrains activities of cells in the nervous system as in other organs. Circulating hormones reflect and constrain processes of organs or tissues. Exchanges of hormones between various organs occur through the circulation. Blood allows exchange of hormones or mediators between organs and tissues and serves as a real channel of communication. Circulating hormones and their regulations thus constitute the primary field for studying the integration and control of the part processes of the body. This hormone-oriented thinking is essentially different from the neuron-oriented one in that it takes into consideration the hierarchy in the levels of communications. It can also lead to very different consequences. If valid and useful, it should expose the contradictions in the concepts that appeared within the earlier orientation and enable us to understand how the body functions as a whole.

Understanding the control relationships in the body is a major objective of the present approach. In metazoan physiology, the control relationships require connections between cells or organs. Without the appropriate knowledge of hormones, their regulation and their mechanisms of action, it is impossible to define these relationships. The knowledge of hormones now available creates a new environment where one of the most important hypotheses of physiology can be examined. As discussed in the introduction, the idea that the body is governed by an internal stable structure is the only acceptable explanation for an important natural phenomenon. Although the hypothesis was neglected and left to die down, the phenomenon itself is still present and research is required.

Data accumulating over the past 25 years show that the vascular endothelium (VE), that envelops the circulating blood, is involved in many regulatory functions. The activities of the VE include regulating the circulating concentrations of a wide range of hormones and mediators[10,191]. From the viewpoint of integration and control, these data seem to be extremely important. The VE is a large part of the body. It possesses a huge surface area and occupies a strategic position. All exchange of hormones and mediators that occurs through blood is exposed to that extensive active surface. If circulating hormones reflect and constrain the part processes of the body then a mechanism that regulates the concentrations of these hormones and regulates their delivery to the tissues is what we are looking for as the controlling mechanism of the body. The activities of the VE, however, receive little attention from physiologists. In recent textbooks of physiology, for instance, these activities are described in no more than few lines. It looks as if the potential of the VE appeared too late and after all the major roles had been assigned.

Angiotensin II (AngII) is one of the circulating hormones regulated by the VE[191]. Among its widespread actions, it stimulates the secretion of corticotrophic releasing hormone, vasopressin and oxytocin from the hypothalamus[57]. It regulates the release of growth hormone from the anterior pituitary[150], and stimulates the sympathetic nervous system at different levels[169]. Physiologists used to imply that the hypothalamo-pituitary axis and the autonomic nervous system are mechanisms through which the brain exercises its controlling activities over the body. The data on AngII imply something different and show that both mechanisms are modulated by a circulating hormone that is regulated by the VE. The data conflict with the basic concepts that appeared within the old orientation. Basic traditional concepts are difficult to change. Scientists depend upon these concepts in judging new data and hypotheses. Data or ideas that conflict with these basic concepts appear as meaningless and receive little attention.

Indeed, our attention tends to go to sites of initiation of actions. Synthesis of a peptide hormone by a cell, for instance, is well appreciated, but inactivating a peptide hormone by an ectoenzyme of another cell appears as less impressive. However, if our objective is to find sites of higher control, we need to look for places where less action takes place and more influence is exercised over the system. The VE satisfies this principle by the fact that it acts on a broad spectrum of hormones at the same time. It is obvious that in social interactions sites of power and control are where suggestions and proposals are activated or inactivated and not where they are made. When AngI is activated into AngII by the angiotensin converting enzyme (ACE) of the VE cell, the concentration of ACE is not directly affected by the conversion. In this way, ACE mediates and ensures the

connection between two processes. The first process is reflected, indirectly, by circulating AngI and requires the release and synthesis of an enzyme, i.e. rennin. The second process results from the widespread actions of AngII. The relation of ACE to the two processes implies a control relationship. If this is the way the VE generally treats circulating hormones, one cannot claim that it is controlled by another system.

The control relationship may be analyzed into three logical elements: (1) the processes controlled, (2) a controlling structure, and (3) the connections that mediate the relationship. The processes are responses to the changing environment. That these processes are controlled means that they follow certain relatively stable laws or that they are constrained by being connected with a relatively stable physical structure. The stability of a controlling structure is relative to the controlled processes or to the connections that it mediates. At the multicellular level, a controlling structure is made of those epigenetic parts of the cells that are involved in the regulation of intercellular or circulating hormones, e.g. enzymes, uptake mechanisms and receptors. A controlling structure may be considered as among the processes controlled by a higher structure. In a hierarchy of levels of control, the higher the level the more it is stable over time and the less it is subject to the influences of the environment.

The brain is the most important part of a person. It is the seat of intelligence, experience and judgement. When these characteristics are good the whole person looks good. When these are disturbed, the whole person appears disturbed. A perfectly working digestive system does not make the individual more important. The role of the brain is not of the same order as that of the gut or kidneys. But this evaluation of the role of the brain uses a social frame of reference. If our frame of reference is biological, the situation becomes different. The digestive system is as important and vital as the nervous system. Each of the two is responsible for regulating a part of the external environment, and in this sense both are peripheral. The first takes up and processes nutrients and the second takes up and processes information. Both these and other similar systems are exposed to changes in their environment and they adapt by changing their activities and structure. The changes in activity or structure of these different systems need to be integrated according to real, not supernatural, laws. In other words, a central stable structure is essential for the control of the processes of the body.

The VE may be viewed as the most inner cellular layer in the body. Embryologically, it arises from the mesoderm (mesenchyme), the internal layer of the early embryo. The nervous system arises from the ectoderm, one of the two outer layers. There is a certain parallel between the vascular system in a vertebrate and the mesenchyme of a simple avascular metazoan like a flatworm. The ground substance of the mesenchyme corresponds to the circulating fluid, in that both represent a medium where communication between organs or tissues takes place. The mesenchymal cells, like the vascular endothelial cells, are in a position that allows them to interfere with such communication and thus integrate and control the part processes. It is well recognized that differentiation of tissues during early embryonic life is governed by the mesenchyme. The idea that the highest level of control of the metazoan body lies in the nervous system thus seems to be inconsistent with the fact that early growth and differentiation of that system are controlled by the mesynchyme. The controlling role of the VE may thus be viewed as an evolution of the role that was originally played by the mesenchyme of early metazoan ancestors.

From a practical point of view, the role of the VE is not expected to be important. Physiological studies are motivated by medical problems. Explanations of normal function are invoked by the need to understand pathology. What are the medical problems that arise from a disturbance in the VE? Judging by what appears in the literature, there are no important diseases that arise from the VE. This would be a very acceptable logic if we had explanations for all diseases. However, the etiologies of diseases like essential hypertension, late diabetes and psychiatric disorders are not understood. Nor are the sites of the primary disturbances known. These diseases are identified functionally, appear as extremes of individual differences, and seem to be related to higher levels of control. If the method adopted in searching for the etiologies of these diseases is that of searching for a needle in a hay stack, at least we should be able to define the appropriate stack.

The VE has not been perceived as a system. Data about its activities appeared isolated in different fields of research. Attempts to explain activities relevant to a certain specialty are very limited and reflect only the interests of that specialty. Although investigators concerned with the vascular system gave more attention to the VE[191], they were interested only in the vasoactive aspects of hormones and their explanations reflected only that aspect. It does not need to be emphasized that the field of action of circulating hormones extends beyond the vascular system. Circulating peptide hormones like enkephalins cross the blood brain barrier (BBB) and modulate behavioral and cognitive functions of the brain[77,87,88]. Different types of transport mechanisms have been described for these peptides[16,204]. The amounts of hormones that cross the BBB are very small, but the brain is a highly hierarchical organ and very small amounts that hit certain triggering mechanisms can be enough to modulate its function.

The problem of specialization not only made perception of the VE as a system very difficult but also distracted scientists interested in the control of the body from the most relevant data.

Vascular endothelial system

The vascular endothelial system (VES) can be considered to consist of:

a) The Central Vascular Endothelium (CVE). In vertebrates, this consists of the endocardium and the vascular endothelium of lungs or gills. It does not include the endothelium of the cardiac or bronchial vascular beds. The CVE is unique in that all blood crosses it before being redistributed to various organs. Since gas exchanges in the lungs or gills occur by passive diffusion, there is a large space (about 70 m^2 in man)[59] for activities that match this strategic position; that is, central regulation of the hormonal composition of blood. In invertebrates with a closed vascular system, e.g. annelids, the CVE is very primitive and may be viewed as consisting of the endothelial lining of the main vessels that distribute blood (hemolymph). Since the endocardium represents a negligible area and because mammals are the focus of the present work, 'CVE' will be used interchangeably with 'pulmonary endothelium.'

b) The Peripheral Vascular Endothelium (PVE). This consists of vascular endothelial areas other than the CVE. The structure and regulatory activities of various components of the PVE are adapted to serve the functions of the corresponding organ or tissue. Examples are the vascular beds of the heart, brain and kidneys. The endothelial lining of arteries and veins represents a very small part of the VES compared to that represented by the capillaries. The endothelial lining of a large vessel may be considered as the part of the PVE that serves the regulatory function of that vessel. This may apply also to the pulmonary arteries and veins. In invertebrates with open vascular systems, e.g. arthropods, there is no peripheral circulation and the VE may be responsible for central regulation of circulating hormones.

Several reviews have stressed the important role played by the pulmonary endothelium in regulating circulating concentrations of biogenic amines, polypeptide hormones, and prostaglandins[10,59,190]. The metabolic efficiency of the CVE is remarkable. For example, after a single passage through the lung, sixty percent of serotonin (5HT) is extracted in anesthetized humans[67], and two-thirds of AngI are converted to AngII in anesthetized rats[82]. A pioneering role in this area of research was played by Vane who drew the attention of investigators to these nonrespiratory activities of the lung[190]. Similar activities have also been reported to occur in the gills of fishes[124,128] and the CVE seems to play a comparable role in all vertebrates.

From the viewpoint of communication, the CVE occupies a strategic position relative to the PVE and the rest of the body. Various hormones and mediators must cross it during circulatory exchange. While directly connected through the circulation with the various systems, the CVE has the unique potential of affecting communication between all systems of the body. This makes the CVE the expected site for integration and control of the part processes of the whole body.

Hormone-oriented thinking is leading to a very different position, i.e. that the CVE is a place for the highest levels of control of the body. There are important logical consequences that follow from this conclusion. First, the controlling structure of the CVE cells is expected to be relatively stable over time because it represents the highest levels of control. Second, inter-individual differences in the structure of these cells are expected to be responsible for inter-individual differences in the behavior of the whole organism. Third, the controlling structure of these cells is expected to be genetically determined to a large extent. These cells are the last to adapt to environmental changes and there are no higher levels that control their structure except their own genome.

It should be noted that the structure of the CVE cells depends on their position. They are not expected to keep their structure if they are, for instance, grafted in a different place in the body. Being in such a central position allows these cells to regulate the adaptations made by lower levels and their stable structure should depend on these adaptations.

The CVE can be viewed as a central processor of information with an input from the right ventricle and an output into the systemic circulation. Each part of the PVE can also be considered as a processor of information, where the input comes from arterial blood and the corresponding tissue and the output goes to venous blood and to the tissue. The change in the informational content of blood during its passage across the CVE can be considered as a central decision that depends on the hormonal content of venous blood and on the structure of the CVE cells. The decision is distributed through arterial blood to various parts of the body. At the various parts of the PVE, the decision becomes adjusted to local conditions. The adjustment represents a second level of decision-making and it depends on the structure of the local endothelial cells and on the concentration of hormones and mediators on both sides of the capillaries. Thus, the information reaching the periphery depends on two levels of decision-making, i.e. a central one at the CVE and a peripheral one at the corresponding PVE.

We return to the case of ACE to exemplify how decisions are made by the CVE cells. AngI is not the only substrate for ACE. The enzyme has a broad substrate specificity and also acts on bradykinin, enkephalins, substance P and LHRH[175]. This is not promiscuity, but seems to be an integrative function. For example, while bradykinin is inactivated by ACE it also inhibits the enzyme. This may minimize the conflict between a local

need for vasodilatation at a certain tissue and a general need for vasoconstriction expressed by circulating AngI. Enkephalins are largely released from the adrenal medulla and are associated with sympathetic stimulation and vasoconstriction. Inhibition of ACE by enkephalins thus may minimize duplication of actions. The substrates of ACE are also inactivated by other peptidases of the CVE cells that again have broad specificities and act on other hormones which regulate other processes in the body. In other words, the degree of conversion of AngI to AngII at the CVE can be considered as a central decision that depends on the concentration of many enzymes in the CVE and on the concentration of many hormones that reflect relevant processes in the body. The decision is distributed to all components of the PVE where it becomes adjusted to the local situations. For example, in some areas of the PVE more AngI is converted by ACE. In some others some AngII is inactivated by angiotensinases.

The renin-angiotensin cascade occurs not only within the endothelial system but also in peripheral organs like the brain and kidney. The central and peripheral cascades are involved in mechanisms of cardiovascular and fluid regulation. For example, brain mechanisms are involved in regulation of blood pressure, stimulation of drinking, and release of vasopressin from the hypothalamus[139]. The CVE mechanism stimulates these neural mechanisms as well as those of other peripheral organs. In other words, the CVE mechanism is the prevailing one.

Many of the enzymes found in the CVE cells are present in very small amounts in plasma. Although other places may share in producing these enzymes, the CVE is expected to be a major source. This is because it represents the largest capillary bed and receives the entire cardiac output. Thus, the characteristics of such plasma enzymes may reflect the characteristics of the CVE cellular enzymes. This is particularly so if the enzymes are highly represented in the CVE as in the case of plasma ACE where it has been suggested that the enzyme originates from pulmonary endothelium[38,55,130].

In large series of normal individuals, plasma ACE levels were found to differ greatly from subject to subject. However, when measured repeatedly in a given individual, the ACE levels remain remarkably stable[1]. The inter-individual variability in plasma ACE levels could not be explained by candidate environmental or hormonal parameters[1]. A study conducted in nuclear families showed that plasma ACE levels are, at least in part, genetically determined[36].

There are, however, many other vasoactive circulating hormones that are regulated by the CVE[10,59]. The uptake of norepinephrine or serotonin or the inactivation of endothelin, for instance, are expected to play an important role in determining the level of blood pressure. From the viewpoint of control, the study of these elements is a study of the primary control parameters that determine the level of blood pressure and should enable us to understand the 'essence' of essential hypertension. This principle should apply also to other physiological activities. For example, if circulating enkephalins play a role in motivating behavior, then the control parameters of such motivation should be expressed by the CVE enzymes responsible for their regulation. We should expect, then, an association between the concentration of these enzymes and the readiness of the organism for motivation.

It should be noted that the CVE is not an organ. The controlling system of the CVE is cellular. Organic lesions of the lung will not generally affect the structure of the remaining CVE cells. The regulation of circulating hormones depend on the structure of the CVE cells and not on the structure of the lung. Physiologists used to study the function of organs by studying the effects of pathological or induced lesions on these organs. In these cases the changes in function that occur result from disturbing the organization between cells. In the case of a destructive lung disease, the corresponding capillaries will be functionally excluded from being in contact with blood and other ones will be recruited. If the disturbance is more than the reserve, an increase in the cardiac output will compensate for the loss in the surface area. This will serve the passive exchange of gases as it will serve the regulatory activities of the CVE. A disturbance in the function of the CVE is expected to result from an imbalance within the structure of its cells, e.g. between the activities of certain enzymes. For such imbalance to be effective it is presupposed that the cells are in contact with blood. In other words, disturbances of the CVE are expected to be functional, adaptive or genetic but not organic. Undoubtedly, a difficulty in distinguishing between the function of the lung as an organ and the function of the CVE as a cellular system made appreciation of the role of the CVE very difficult.

It looks as if nature intended to camouflage the role of the CVE. The cells are distributed between two lungs that have another vital function. Pulmonary endothelium is functionally positioned between the right and left hearts, but the physical appearance shows a heart surrounded by two lungs. Diseases of the lungs are common but significant associated disturbances in the integration and control of the body are not observed.

Control of psychological functions of the brain

An attempt will be made here to explain how psychological activities of the brain are modulated by the CVE. Since the control relationship is supposed to be mediated through circulating hormones, explanations will be made in terms of the effects of certain psychoactive hormones on brain activities and in terms of how

these hormones are regulated by the CVE cells. Regulations of these hormones will be discussed one after the other and a preliminary model of control will be gradually built. Because the concerned hormones are regulated by the structure of similar CVE cells, the model of control is essentially one cell model. It must be noticed that the brain is a highly hierarchical organ with many levels of control. Studying these levels is essential in understanding the various psychological functions of the brain. However, the focus of this work is on the control relationship between the CVE and the brain. Dealing with the control relationships within the nervous system is a gigantic task and will not be attempted in this article.

Motivation

The general role of enkephalins in the brain seems to be motivation of behavior[13]. This is regardless of whether the motivation is aversive or rewarding. The role also includes overcoming stimuli that impede motivation, e.g. painful stimuli. This last effect, however, was the first to be known and led to the classification of enkephalins as opioids. Enkephalins also stimulate the locomotor activity of leukocytes[180]. This seems to be consistent with the general role of motivation. During enhanced activity of the organism, there is a greater incidence of injuries and stimulation of leukocytes is an appropriate prophylaxis. Interestingly, the motivational actions of enkephalins became known by observing their effects after systemic injections[86]. When Kastin and associates studied the ability of hungry rats to run a complex maze for a reward of food, animals receiving an intraperitoneal dose of met-enkephalin negotiated the maze faster and made fewer errors than animals receiving the vehicle[88].

The lung appears to be an effective metabolic organ for clearing enkephalin activity rapidly from the circulation[106]. Captopril and bestatin significantly inhibited the degradation of enkephalins in the rat lung, suggesting that ACE and an aminopeptidase play a major role in the metabolism of enkephalins by the pulmonary endothelium[65,106]. According to the perspective of the present theory, therefore, the concentration of these two enzymes is expected to be relatively stable over time, genetically determined to a large extent, and to be responsible for individual differences in the potential or readiness for motivation. The two lung enzymes, of course, have not been studied in relation to behavior, but they are expressed in the blood of the rat where they are the primary enzymes responsible for metabolizing enkephalins in plasma[195]. The situation in the rat brain seems different and captopril does not significantly prevent degradation of met-enkephalin in brain slices from rat striatum[136].

In an interesting study, blood samples were collected from rats immediately before they were given footshocks[110]. The investigators found a very high correlation between latency of rats to escape and the rate at which leu-enkephalin is hydrolyzed in plasma. They were surprised by the finding and wondered: 'Why should a biochemical measure in plasma be so correlated with the behavior of the whole organism?' They concluded that a regulatory enzyme system exists for enkephalins in plasma and that the system may be important for modulating behavior. The finding also suggests that the VES and particularly the CVE may play a major role in regulating the motivation of the organism.

The ACE inhibitor captopril has been reported to be associated with mood elevation and mania[205]. Following the report, other investigators noted reversal of captopril-induced psychosis with the opioid antagonist naloxone, implying a role for endogenous opioids in the mechanism of action of captopril[69]. The drug was evaluated for potential antidepressant activity in the forced swim-induced behavioral despair (immobility) test in mice[64] and the learned helplessness paradigm in rats[109]. Captopril significantly reduced immobility and naloxone blocked the effect in both studies. These findings are very interesting because, as mentioned before, captopril does not seem to affect the degradation of enkephalin in the rat brain significantly. Also, captopril given orally but not intracerebroventricularly significantly enhanced stereotypy and the number of conditioned responses in rats[33]. On the other hand, degradation of enkephalins by the CVE is significantly inhibited by captopril. This suggests the involvement of the CVE in the positive motivational effects of captopril.

A reasonable experimental design that can give a better idea about the role of the CVE in relation to motivation of behavior is to use an ACE inhibitor that does not cross the BBB. The effects of acute and chronic doses of the ACE inhibitor ceronapril (SQ 29,852) were studied in rats. ACE in the CSF and in structures of the brain within the BBB was not inhibited by ceronapril[38]. Interestingly, prior to that study, the effects of intraperitoneal doses of captopril and ceronapril on the performance of mice and rats in behavioral tests were studied[42]. Both drugs reduced the latency of movement and improved cognitive performance, but ceronapril (which does not cross the BBB) was more effective.

Arousal

β-Phenylethylamine (PEA) is an endogenous amine that resembles amphetamine structurally and pharmacologically. PEA crosses the BBB and when administered systemically it produces amphetamine-like behavioral and electrophysiologic effects[165]. PEA is described as a neuromodulator[135,163] and its function has been suggested to be the sustaining of attention and

mood[163]. In the tissues of the mouse, the concentration of PEA in blood is more than eight times that within the brain. The highest concentration is present in the gastrointestinal tract[189]. This makes it unlikely that the PEA of the blood originates from the brain. It is interesting that the gastrointestinal tract seems to be the main source of plasma PEA. This may give the impression that PEA is not important in relation to behavior. Urinary excretion of PEA was markedly elevated in human subjects after their first parachute jump[140]. Free and total plasma PEA was significantly lower in patients with attention deficit disorder[9]. Urinary phenylethylamine correlates positively with hypomania and negatively with depression and social introversion when a psychometric test was used for assessment of personality[115]. These data are consistent with a relation between circulating PEA and arousal, attention and mood.

PEA is rapidly and extensively deaminated when perfused through rabbit lung[158]. Two enzymes are responsible for this deamination. The first is similar to the mitochondrial enzyme, monoamine oxidase type B (MAO-B) which is also present in the brain, blood platelets and elsewhere. The second is the semicarbazide-sensitive amine oxidase (SSAO), which is similar to the enzyme known as plasma amine oxidase. Both enzymes are suggested thought to be associated with pulmonary endothelium[158]. The two enzymes have different cofactors and substrate preferences[98] and are encoded by different genes[119]. The most interesting thing about SSAO is that it is not detectable in the brain[35,98]. The highest concentrations of the enzyme in humans are in the aorta and lung[98]. Considering its huge surface area, the CVE is expected to be a main site of origin of plasma SSAO.

From the viewpoint of the present theory, these enzymes are expected to share in controlling the attention of the organism. We can also expect that their concentration is genetically determined to a large extent and that inter-individual differences in concentration will correlate with differences in arousal and attentiveness. The enzymes of the lung have not been studied from this perspective. However, plasma SSAO activity has been shown to be heritable and stable over time[21,125] and correlates with personality variations in normal individuals. Low plasma SSAO activity was associated with higher sensation seeking scores, positive affect and higher leisure time activity levels[120,170]. Clearly, this profile is consistent with an increased arousal and attentiveness and also with a positive mood. Can a brain model of control explain these findings about an enzyme that does not exist in the brain?

Carbidopa is a 'peripheral' decarboxylase inhibitor and also an inhibitor of SSAO[39]. The drug is generally used in combination with L-dopa in the treatment of Parkinsonism. Because carbidopa does not penetrate the BBB, the effects of the combination (known as sinemet) on behavior are usually attributed to L-dopa. For example, in an experimental study,90 sinemet was used in the treatment of a neuroleptic non-responsive schizophrenic. The treatment reversed the worsening trend in attention and withdrawal. Although the investigators attributed the improvement to L-dopa and ignored carbidopa, it is likely that inhibition of SSAO by carbidopa played a significant role in that improvement.

There is no enzyme in plasma that corresponds to MAO-B of the CVE cell. However, blood platelets have a mesenchymal origin similar to that of the CVE. Next to bone marrow, pulmonary capillaries appear to be the most frequent location of megakaryocytes and new data indicate that the lung plays a major role in controlling the formation of platelets[89,97,188]. Thus platelets or blood cells in general share with the CVE a similar origin, location and environment and they are responsive to similar concentrations of inhibitors and stimulants.

Platelet MAO-B activity appears to be under genetic control and is relatively stable over time[125]. Low platelet MAO activity has been associated with sensation seeking scores, positive affect, and higher leisure time activity levels[120,170]. Thus both platelet MAO-B and plasma SSAO are associated with behavioral characteristics that are consistent with their role in inactivating PEA, despite the fact that there is a complete lack of correlation between the two enzymes[170].

Hundreds of studies of platelet MAO have been published in the last two decades, and were based on the assumption that regulation of MAO-B activity in human platelets mirrors its regulation in the brain. It is obvious that blood cells and the nervous system have different environment, locations and origins. Furthermore, there is no correlation between the activities of brain and platelet MAO-B[202].

PEA is not the only circulating hormone that is involved in modulating arousal. Although it is usually stated that epinephrine (EPI) does not cross the BBB, small intravenous doses of EPI are known to cause behavioral change and EEG arousal[60]. As discussed before, undetectable amounts of a hormone that cross the BBB may be capable of modulating brain function. The synthesis of EPI has been studied in the rat lung in vivo[91]. The lungs of demedullated animals contained 30% of the amount of the control group. However, the role of the lung seems to have been underestimated in that study. As the investigators indicated, the rate of formation of EPI depends on the concentration of the substrate, norepinephrine (NE). Their estimation was based on measurements made in demedullated sham-operated rats where plasma NE was about one-third of the control group[91]. Probably, formation of EPI by the lungs occurs only when the sympathetic release of NE is particularly high; otherwise EPI may even be partially

taken up from circulation and metabolized, as in the lungs of anesthetized dogs where 8% of circulating EPI is reported to be removed[52]. Interestingly, the heart contains the same lung enzyme that synthesizes EP[171] and it has been reported that EPI spills over in significant amounts from the human heart into the circulation during aerobic exercise but not during rest[56]. It should also be noted that the CVE is involved in regulating the concentration of circulating EPI indirectly by regulating the concentration of hormones that modulate the activity of the sympathetic nervous system, e.g. angiotensin II. Furthermore, the enzyme monoamine oxidase type A (MAO-A) that inactivates EPI and NE is present in the endothelial cells of the adrenal medulla and not in the chromaffin cells[201], indicating that the vascular endothelium regulates the release of these amines into the circulation.

Introversive and extroversive behavior

The *N*-dimethylindolamines, dimethyltryptamine (DMT) and 5-methoxydimethyltryptamine (5MoDMT), are hallucinogens that have been unequivocally identified in the body fluids of normal humans[3,122,123,129,151]. These hallucinogens resemble endogenous opioids in being normally present in the body and in their relationship to drugs of abuse. They are different, however, in that scientists do not know their normal function. The *N*-methyltransferase that synthesizes these hallucinogens was discovered in 1961 by Axelrod[6]. A characteristic feature of this enzyme is its high concentration in the lung[6,7,103,104]. Although trace amounts of activity were reported to occur in the brain[102], the existence of such activity was later questioned on the grounds that inadequate procedures were used[30]. The enzyme depends on S-adenosylmethionine (SAM) as a methyl donor and is capable of methylating a variety of amines. It thus has an integrative function, and serotonin and norepinephrine, for instance, are among its substrates. Dimethylserotonin (bufotonin) accumulates poorly in the brain[186] and is not considered as a hallucinogen.

The cellular location of this *N*-methyltransferase (NMT) in the lung has not been studied. However, the enzyme is present in smaller amounts in blood cells[199], a fact that makes the CVE an expected site. It is interesting that the lung is also a major site for taking up and metabolizing these compounds[167,186]. If endogenous hallucinogens, which have very short half-lives[174], play a role in modulating thought and perception one would expect their regulation to be a very fine one.

DMT is the most studied of the endogenous hallucinogens (EHs). It is the *N*,*N*-methylated product of tryptamine (TR). The formation of DMT has been demonstrated in vivo. When rabbits were given monomethyltryptamine intravenously, DMT appeared in carotid arterial blood, peaking within the first minute after injection[105]. 5MoDMT is the *N*,*N*-methylated product of 5-methoxytryptamine (5MoTR). Behavioral studies in animals show that 5MoDMT is more potent than DMT[178].

Previous thought would not have accepted that perception or thought can be modulated by hormones formed in the lungs. Thus, the role of these interesting psychoactive hormones was difficult to appreciate. Within the present concept, the difficulties are largely removed.

Hallucinations are normal physiological phenomena during sleep and also during the state inbetween sleep and wakefulness. In a recent study, normal volunteers remarked on the degree of similarity between dreams and their experience after an intravenous dose of DMT[183]. In agreement with the idea that EHs play a role in the physiology of sleep is the finding of significant fluctuations in the activity of plasma NMT in accordance with a possible influence on the mental activity during the NREM stage of sleep[182]. Also, 5MoDMT significantly potentiates hexobarbital sleeping time in mice[24].

The behavior of the individual can be considered to modulate between two extremes. One is represented by sleep and the other occurs when the subject is markedly involved with the external environment. Patterns of behavior on the sleep side of the dimension may be described as introversive and those of the other side as extroversive. Meditation and day dreaming, for instance, can be considered as introversive behavior. This modulation of behavior includes changes in motivation, arousal and cognition. Obviously, motivation and arousal are minimal during sleep. The changes in cognition, however, are qualitative rather than quantitative. Introversive cognition depends on stored information. Ideas are loosely structured and the association between them depends on internal drives rather that on conditioning or learning. On the other hand, extroversive cognition depends largely on external information and learned rules, and the ideas are tightly structured. The growth of experience depends on the interplay between both modes of behavior. Synthesis of dreams, plans and hypotheses requires more of the introversive mode. In executing plans or putting hypotheses to the test, the extroversive mode is needed. Formation of new ideas stimulates extroversive behavior. Failure to apply ideas stimulates introversive behavior. Within this definition, the physiological regulation of intro-extroversive behavior will be discussed.

As a prototype of the hallucinogenic group of drugs, LSD has been extensively studied for its effects on mental activities. With low doses of LSD, some subjects were able to express remote and unique ideas[203], or experienced enrichment in their imagery, fantasy and personal recollection[22]. EHs may thus be involved in the physiological mechanism of facilitating novel ideation. If an idea is considered novel in the sense that it is new

to and expressive of the individual involved rather than dictated by someone else, then the delusions of psychotics are at least as novel as the ideas of leading artists or scientists. Presumably, individuals with a high potential of novel ideation synthesize inappropriate amounts of EHs. The nature of their thought product may then be determined by other biological and experiential factors.

A transport system for enkephalins that is inhibited by $5HT_{1A}$ agonists has been characterized in the BBB. The system is regulated from the brain side and has been suggested that it may be capable of bi-directional transport[15,16]. Both DMT and 5MoDMT cross the BBB readily and are $5HT_{1A}$ agonists[44,176]. They may thus play an important role in regulating the transport of enkephalins into the brain. This may explain the decreased motivation or volition that characterizes introversive behavior. It could also explain the feelings of lack of control and volition that normal volunteers expressed after intravenous doses of DMT[183].

EHs have been implicated in the etiology of functional psychosis[3,122,123,151]. DMT can mimic some psychotic symptoms when given in single doses to human volunteers[66]. A general relationship has been found between psychotic symptoms and urinary DMT and a significant number of patients with schizophrenia excrete detectable DMT[151]. The activity of NMT in platelets of psychotics was significantly higher than that of controls[199]. A positive correlation was also found between the serum level of NMT and the severity of delusions in psychotic patients[181].

The assumption of a partial connection between genius and madness is a very common idea. The results of a genealogical study of schizophrenics suggested that the schizophrenic genotype leads not only to reduced resistance to stress but also to an increased potential for creativity and superior judgment, although the potential may be fulfilled in only a few persons[85]. In a follow-up study of foster-reared children born to schizophrenic mothers, several gifted persons existed when compared to a control group[78]. These data also imply that even with similar genetic constitution, the role of experiential factors can be as big as the difference between genius and madness.

Circulating EHs are not the only factor in the production of hallucinations. It should be noted that what makes hallucinations abnormal is that they happen during wakefulness. One can put this a little differently and assume that what makes a hallucinogenic concentration of circulating EHs pathological is that it occurs while the person is not sleeping. EHs are capable of modulating cognition and motivation but not arousal. Accordingly, it can be hypothesized that hallucinations and delusions are the result of an incongruity between the modulation of cognition and arousal. If PEA is involved in the regulation of arousal, as has been suggested before, one should expect then that regulation of circulating PEA plays an important role in the pathogenesis of hallucinations and psychotic phenomena. The concept of incongruity can explain why amphetamines can produce hallucinations and psychosis. Actually, amphetamine psychosis is often clinically indistinguishable from paranoid schizophrenia[23]. Amphetamines are not hallucinogenic per se but they resemble PEA structurally and pharmacologically and stimulate arousal. They may thus be capable of associating wakefulness with the hallucinations and dreams of sleep. Another support for the idea of incongruity comes from observations on the psychotic manifestations that sometimes occur as a side effect during the treatment of Parkinsonism. A higher incidence of hallucinations occurs when carbidopa or deprenyl is added to L-dopa[70] Carpidopa and deprenyl are inhibitors of the two lung enzymes that inactivate PEA, that is SSAO and MAO-B. The concept of incongruity can also explain the finding of decreased plasma SSAO activities in schizophrenic patients[21,192].

The phospholipid, phosphatidylserine (PS), has been described as a strong and specific endogenous inhibitor of MAO-B[34]. Both TR and PEA are substrates of MAO-B. An increased concentration of PS in the CVE cell can thus lead to a greater formation of DMT and to higher circulating concentration of PEA. This suggests that regulation of intracellular PS may play a very important role in the pathogenesis of schizophrenia. Actually, the concentration of PS has been found to be significantly increased in the platelets of paranoid schizophrenics compared to controls[131]. It is possible that an increase in circulating DMT and PEA is a combination that induces the suspiciousness and ideas of persecution that characterizes paranoid behavior. In a study of DMT blood levels in schizophrenics, an increase was associated with high suspiciousness scores[3]. Increased urinary excretion of PEA was also found in paranoid schizophrenics[200]. MAO-A is the enzyme that oxidizes 5MoTR[146] and it is not inhibited by PS[34]. For reason that will be discussed later, an increased formation of 5MoDMT is not expected to be associated with feelings of persecution.

β-Carbolines and extroversive behavior. Incubation of the rabbit lung with 5-methyltetrahydrofolic acid (MTHF) and TR or 5HT was found to yield the corresponding β-carboline[157]. When the in vivo metabolism of a possible precursor of the endogenous β-carboline, tetrahydroharman, was investigated in rats, the highest time-dependent formation of tetrahydroharman was found to occur in the lung[185]. The lung may thus play a major role in the biosynthesis of β-carbolines (BCs). Unlike EHs, BCs have stimulatory effects on behavior. For example, tryptoline and 5-methoxytryptoline (the β-carboline derivatives of TR and 5MoTR) produce desynchronization in electrocortical activity and an in-

crease in locomotor and exploratory behavior[126]. It can be assumed that formation of BCs is one of the metabolic pathways for the indolamines in the CVE cell and that it is involved in inducing an extroversive mode of behavior. In this way, modulation of behavior along the intro-extroversive dimension will depend on the ratio of BCs/EHs. If MTHF is important for endogenous formation of BCs, then its intracellular concentration might affect behavior along the intro-extroversive dimension. Interestingly, a deficiency in methylene-tetrahydrofolate reductase, which catalyzes the reduction of methylenetetrahydrofolate to MTHF, has been associated with a schizophrenia-like syndrome in a 15-year old girl with a history of hallucinations and delusions[118]. Biochemical studies revealed a profound decrease in the activity of the enzyme. A therapeutic trial of folic acid decreased the psychotic symptoms. It is possible that a lower concentration of MTHF in the CVE led to the psychotic symptoms by decreasing the BC/EH ratio.

Tryptoline and 5-methoxytryptoline have been identified and quantified in the adrenal gland and brain of rats[20]. Their concentration in the adrenal gland was about 30 times that of the brain. It is worth mentioning here that next to the rabbit lung, the adrenal gland has the highest activity of NMT[7]. Following the theoretical considerations that have been discussed before, one may expect that these two tryptolines are synthesized in the mesodermal cortex rather than in the medulla and in the endothelial rather than in the endocrine cells.

BCs have antidopaminergic properties in the brain[134,152]. On the other hand, DMT given acutely or chronically was found to increase striatal dopamine (DA) turnover in rats[177]. The effect of DMT on DA turnover is possibly mediated indirectly through decreasing the transport of enkephalins to the brain. The BC/EH ratio may thus be involved in modulating the dopaminergic system of the brain. A decrease in such a ratio and a resulting elevation in brain DA turnover may explain the decrease in locomotion that characterizes introversive behavior.

Regulation of lung NMT. According to the present model of control, the ratio BCs/EHs is minimal during sleep and highest during fights or flight. Studying the regulation of lung NMT may thus reveal the factors behind any possible changes in the BC/EH ratio. Phospholipids, for instance, seem to be involved in regulating the formation of EHs. It has been reported that PS binds or forms complexes with TR or 5MoTR but not with any of the many tested amines[83]. This characteristic is expected to bear an important relation to the formation of the corresponding EHs and/or BCs. The findings that PS is an inhibitor of MAO-B and that it is increased in the platelets of schizophrenic patients suggest that it may protect the accumulation of these two amines. It is also possible that making complexes with PS facilitates the process of *N*-methylation. Regulation of NMT is also expected to depend on the availability of its inhibitors. We shall discuss the regulation and significance of three of these inhibitors.

Methylthioadenosine (MTA). The rate and pattern of protein synthesis in the organism depend on environmental conditions. For example, when organisms, ranging from bacteria to humans, are subjected to certain environmental insults, the formation of stress or 'heat shock' proteins is observed[117]. The polyamines putrescine, spermidine and spermine regulate the synthesis of proteins and are essential for cellular growth and proliferation[80]. It seems that the differential regulation of the intracellular concentrations of these polyamines, is responsible for different patterns of protein synthesis. Ornithine decarboxylase catalyzes the rate-limiting step in the biosynthesis of the three polyamines, and S-adenosylmethionine decarboxylase (SAM-DC) is rate limiting in the synthesis of spermidine and spermine[80]. MTA is a co-product in the process of formation of spermidine and spermine by SAM-DC. MTA is especially important to the CVE cell model because it is an inhibitor of lung NMT[142]. It also leads to an increased concentration of S-adenosylhomocysteine (SAH), another inhibitor of lung NMT[142], by inactivating SAH hydrolase[58]. Thus, the rate of formation of EHs in the CVE cell model is inversely related to the activity of SAM-DC.

The regulation of SAM-DC of the adrenal gland has been studied in relation to stress in rats. The stress of immobilization or the administration of insulin or 2-deoxyglucose (as a metabolic stress) decreased the activity of adrenal SAM-DC[53]. The DA receptor D_2 agonists peribedil and bromocriptine also caused decreases in the activity of the enzyme. The decreases in activities were more marked and significant in the cortex than in the medulla[53]. Probably, the effect of restraint and metabolic stresses on the activity of SAM-DC were mediated through circulating DA. In support of this hypothesis is the finding that glucocorticoids increase DA production in PC12 cells[25]. Also, the administration of dexamethazone to human volunteers produces pronounced increases of plasma free DA but not of other catecholamines[159]. Interestingly, restraint stress, as well as the DA receptor D_2 agonist SQP, induce expression of the stress protein HSP70 in adrenal cortex and aorta[29]. The D_2 receptors also mediate inhibition of growth in cells that are derived from a clone from a rat pituitary tumor[171]. Bromocriptine inhibited the growth of a cell line of human small cell lung cancer grown in medium. The effect was dose-dependent and co-incubation with D_2 antagonists completely blocked the inhibition of growth[81]. These data suggest a link between D_2 receptors and the activity of SAM-DC. The D_2 receptors have not been studied in the CVE but they are expressed in the capillary endothelium of the brain[8] and

are also expected to be expressed in the CVE. The idea of linking the D_2 receptor with the activity of SAM-DC is indeed intriguing because it means that DA via the D_2 receptor can enhance the activity of lung NMT leading to increased formation of EHs. This is particularly important because D_2 antagonists are known as effective antipsychotic drugs. Furthermore, the D_2 agonist ^{3}H-spiperone showed significantly higher binding to the platelets of unmedicated schizophrenics compared to healthy subjects[173]. Plasma DA concentrations in acute unmedicated schizophrenics were higher than those in controls[168]. These data lead us to include the D_2 receptor in our CVE model as an important element in the regulation of behavior along the intro-extroversive dimension. It should be noticed that although NMT and D_2 receptors may both play important roles in regulating the synthesis of EHs, many other elements of the CVE cell are expected to be involved. The density of D_2 receptors in the CVE cell model does not need to be significantly higher in individuals predisposed to schizophrenia. This applies also to lung NMT, and different combinations are expected to result in qualitatively different traits.

It seems that the D_2 receptors are involved in determining the physique of the body. Recent data show that the DA receptor D_2 gene plays a major role in the regulation of weight and height[40]. Administration of antipsychotic drugs increases body weight in humans[48] and rats[17] There is also a linear relationship between the dose of sulpiride, a receptor D_2 antagonist, and body weight. The effect is counteracted by bromocriptine, a specific receptor D_2 agonist[17]. These data are consistent with a link between SAM-DC and the D_2 receptor and suggest that individuals with high density of D_2 receptors on the CVE cell may be characterized by an asthenic physique. Accordingly, one may expect the D_2 receptors to be particularly involved in the pathogenesis of schizophrenia in subjects with asthenic physique.

There is a diurnal rhythm in the plasma levels of homovanillic acid, the principal metabolite of DA. The levels are highest during the night[47,166]. It has also been suggested that plasma homovanillic acid is regulated by a circadian oscillator[166]. Considering the possible role of DA in inducing introversive behavior, these findings suggest that circulating DA may be involved in the regulation of sleep. This does not necessarily mean that DA infusions can induce sleep. On the contrary, DA infusions may inhibit rather than stimulate the synthesis of EHs because DA is one of the substrates of lung NMT[7]. DA is actively taken up from circulation by the CVE and the uptake is particularly effective when the plasma DA levels become high[184]. This also indicates that the uptake of DA by the CVE is another important factor in the regulation of the synthesis of EHs. Consistent with this hypothesis is the finding of a significant inverse correlation between DA uptake by platelets and the rating for delusions in schizophrenic patients[43]. An increase in plasma concentration of DA does not necessarily mean more formation of EHs.

Norepinephrine (NE). Circulating NE is actively taken up by pulmonary endothelium and subsequently metabolized by MAO-A and also by catecholamine-O-methyl transferase (COMT)[158]. Thus, the concentration of NE in the CVE cells should depend on the concentration of the amine in circulation and on the rate of its uptake and metabolism by the lungs. About 25 percent of circulating NE is reported to be extracted by human lungs[68,179]. The greater part of circulating NE is released as a neurotransmitter from the sympathetic nerve endings and a small portion is secreted by the adrenal medulla. Circulating NE increases in response to various physical and mental stimuli and it can be several fold higher than its base levels. In the CVE model, NE thus seems to be a suitable NMT inhibitor for moment to moment regulation of intro-extroversive behavior and also when a particularly high BC/EH ratio is necessary, e.g. in conditions of flight or fight or when danger is anticipated (fear). The responses of the individual in these situations may depend in part on the density of the NE transporters and on the concentrations of COMT and MAO-A. It can be assumed that high density of the transporter and/or low concentration of COMT can lead to exaggerated responses and may predispose to anxiety disorders.

NE is released in considerable amounts from the lungs to circulation as a result of sympathetic activity. The release is estimated to constitute about 18% of total NE spillover to plasma[71]. It is possible that the sympathetic supply of the lung plays the additional role of functioning as a 'hot line' between the CNS and the CVE. A more rapid switch from introversive to extroversive mode is a great advantage in terms of evolution. When a resting individual is suddenly faced with a threatening situation, the relevant neural mechanisms of course start working immediately. The organism will perform better if these mechanisms are rapidly supported by the appropriate circulating BC/EH ratio. Transfer of mediators in arterial blood is fast, and if pulmonary sympathetic fibers are involved in such mechanism, a change in the BC/EH ratio can be achieved within a very few seconds. Because of these considerations, venous blood samples taken from subjects during wakefulness may contain minimal amounts of EHs. This is particularly so because the anticipation of the needle prick and the process of withdrawing blood may markedly decrease the formation of EHs.

It should be noted that increased release of NE into circulation is more or less associated with increased secretion of EPI from the adrenal medulla. EPI is also produced in the lungs as a result of *N*-methylation of NE by NMT[91]. Since EPI is known to cause behavioral arousal, the combination of NE and EPI is thus capable

of modulating the three aspects of intro-extroversive behavior. In this way, and according to the concept of incongruity, a low NE uptake by the CVE can predispose to psychosis if associated with increased synthesis of EPI in the adrenal medulla and lungs. Glucocorticoids are known to stimulate *N*-methylation of NE in the medulla[91] and a chronic stress may thus have the potential of inducing psychosis by stimulating the synthesis of DA and EPI. This is particularly expected to occur if the CVE cells have increased D_2 receptors and/or decreased NE transporters. Unfortunately, there are no data that reflect NE uptake by the CVE or platelets in relation to behavior. In the CVE model, circulating NE and EPI play also an important role in the regulation of sleep. Their concentrations reflect the degree of involvement of the individual with the environment and their decrease seems important for sleep to occur.

Serotonin (5HT). Circulating 5HT is actively taken up by pulmonary endothelium and subsequently metabolized by MAO-A[158]. The concentration of 5HT in the CVE cells should thus depend on the regulation of these two processes. Serotonin is an important substrate and competitive inhibitor of lung NMT. In the CVE cell model, therefore, the intracellular concentration of 5HT is an important factor in modulating intro-extroversive behavior. Bufotenin is the *N*-methylated product of 5HT and an increase in its formation is supposed to be associated with an extroversive pattern of behavior. Consistent with this hypothesis is the finding that urinary bufotenin excretion in violent offenders was significantly higher than that of a control group[144].

Serotonin is a noncompetitive inhibitor of SSAO. It has been suggested that 5HT is an important endogenous regulator of this enzyme[54]. Serotonin may also compete for MAO-A with amines that are metabolized by both the A and B types of the enzyme, thus decreasing the chances of inactivating PEA by MAO-B. This suggests that the concentration of 5HT in the CVE determines the level of circulating PEA and is capable of modulating arousal as well as motivation and cognition. According to the concept of incongruity a decreased 5HT uptake by the CVE can predispose to psychosis if it is associated with increased formation of PEA and/or EPI. Both platelet 5HT uptake[100,162] and plasma SSAO[21,192] have been reported to be decreased in schizophrenic patients.

The available data suggest that the concentration of 5HT in the CVE cell may be involved in the regulation of sleep. There is a circadian rhythm in 5HT active transport in platelets where both V_x and K_m are lowest during the night[114]. At least in part, circulating melatonin seems to be responsible for this rhythm. The uptake of 5HT by platelets is significantly and inversely correlated with melatonin blood levels[114]. Melatonin induces a concentration-dependent inhibition of platelet 5HT uptake[108]. High affinity binding sites for melatonin have been described in the lungs of chicken and some other animals and it has been hypothesized that they may function as specific melatonin receptors[133]. These data suggest that the circadian changes in circulating DA and melatonin may be largely responsible for the observed diurnal changes of intro-extroversive behavior. A synergism between the effects of the two hormones on the CVE cells is quite possible.

According to the CVE model, the goal of drug therapy of schizophrenia is to balance the relationship between cognition and arousal along the intro-extroversive dimension. In both cases it is not required for the drug to cross the BBB. For example, a D_2 antagonist that does not cross into the brain should also be effective. The idea of a conservational treatment of schizophrenia by drugs that do not cross readily into the brain is indeed exciting. If a behavioral characteristic can be manipulated through the natural hormonal components, why should we impose unnecessary drugs on the sensitive structure of the brain? The treatment of psychiatric disorders may require long periods of time and the harmful effects of these drugs on the brain is sometimes greater than that of the original functional disturbance.

Alcoholism. The use of the method of quantitative trait locus mapping led to the interesting finding of an association between the polymorphic allele at the D_2 receptor locus and alcoholism[127,137]. Subcutaneous injections of D_2 agonists were found to cause a decrease in alcohol drinking in rats[50,145]. These data suggest that the D_2 receptor density may be lower in individuals who are genetically predisposed to alcoholism. Low density of D_2 receptors is expected to lead to an enhanced appetite and to a high BC/EH ratio; both factors may play a role in the predisposition to alcoholism. In support of the idea that a high BC/EH ratio predisposes to alcoholism, treating rats with intraventricular infusions of the BCs, harman and tetrahydronorharman, induced a significant preference for ethanol in a dose-dependent manner[153]. If decreased formation of EHs is important in the predisposition to alcoholism, one should expect also the involvement of lung NMT. Interestingly, when the activities of NMT in dialyzed platelets from psychotics and normals were studied[199], a group of chronic alcoholics was included as a hospitalized control group. Platelet NMT activities in alcoholics were the lowest among the tested groups. Although the difference between alcoholics and normals was not statistically significant (small sample), a trend toward a lower activity was obvious.

However, chronic exposure to alcohol is reported to decrease the activity of methionine synthase[18], a rate-limiting enzyme in the synthesis of SAM and also the principal consumer of MTHF[14]. Giving rats ethanol for a period of four weeks produced a hepatic accumulation of MTHF[19]. In the CVE cell, alcoholism may lead thus

to more synthesis of BCs. In other words, alcoholism may amplify the same problem that motivates the abuse, and inhibition of methionine synthase by alcohol may thus be responsible for the loss of control that characterizes the disorder. It is interesting in this regard that Rommelspacher and associates have found that the blood concentrations of norharman (β-carboline) in chronic alcoholics are more than three times that in nonalcoholics[155].

Conceivably, low concentrations or activities of both NMT and MAO in the CVE cell can lead to a greater formation of BCs. This may explain the finding of low platelet MAO-B activity in individuals who are genetically predisposed to alcoholism[46].

Affective and sexual behavior

It seems that regulation of sleep is closely related to regulation of affective and sexual behavior. There is a significant decrease in platelet 5HT uptake during the premenstrual phase in patients diagnosed with premenstrual syndrome compared to control subjects[4]. The symptoms of the premenstrual syndrome include depression, irritability, and suicidal tendencies[4]. In perfused lungs of female rats, 5HT uptake is highest during pro-estrus[11]. In pro-estrus, female rats exhibit sexual behavior and one may postulate that they have better mood at that time. This may suggest that 5HT uptake by platelets and the CVE cells is regulated similarly and that a decrease in uptake is associated with a negative affect and diminished libido. There are other data that support this idea. The β-adrenergic antagonist, propranolol, inhibits 5HT uptake by pulmonary endothelial cells in culture[94] and propranolol is known to cause depression and decreased libido[138]. Nitrites stimulate serotonin uptake in platelets[99] and inhaled nitrites are known as mood elevators and aphrodisiacs[92].

Serotonin uptake by platelets is reported to be decreased in depression[76] and increased in mania[111]. Positive response to antidepressant treatment is associated with increased platelet 5HT uptake[76]. Because of this association, neuroscientists mistakenly thought that regulation of 5HT uptake by platelets may parallel that of serotonergic neurons. However, a considerable amount of data shows that this is not the case. In the animal model of depression, platelet 5HT uptake was decreased but synaptosomal uptake was increased[76]. In rats, paroxetine-binding to serotonin transporter sites was decreased in both hippocampus and cerebral cortex by chronic antidepressant treatment[194]. Long term administration of antidepressants also decreases 5HT transporter mRNA steady-state concentrations in rat brain[95]. Furthermore, a decreased 5HT uptake in the brain is likely to result in a higher concentration of 5HT which conflicts with the serotonin hypothesis of depression[112].

In developing the CVE model, thus, we need to explain these findings about 5HT uptake and affective behavior. Are there certain hormonal connections between the CVE and the brain that are responsible for modulating affective and sexual behavior? How can 5HT uptake by the CVE cells affect such connections?

The PEA/EPI connection. As discussed earlier, the level of circulating PEA depends on the concentration of 5HT in the CVE. The amphetamine-like effects of PEA and the finding that its plasma or urine concentrations are decreased in depression and increased in mania led Sabelli and associates to the phenylethylamine hypothesis of affective disorders[163,164]. Although EPI and PEA are similar in that both seem to be involved in modulating arousal, EPI seems to have a negative effect on mood. When adrenaline infusions are given in small doses, the subjects report feeling restless, tense and apprehensive[60]. The ratio PEA/EPI may thus be involved in modulating the affective status of the individual.

The tryptoline connection. The synthesis of methoxyindolamines in the retina and pineal gland is regulated by daylight, and it seems that these hormones and their derivatives signal the light status of the world. 5MoTR is synthesized in the pineal gland, the gastrointestinal tract and elsewhere[143]. It is a substrate for the 5HT transporter[197] and is a candidate for condensation and formation of the β-carboline derivative 5-methoxytryptoline (Pinoline). Decreased activity or density of the 5HT transporter may thus lead to decreased formation of pinoline. The hydroxyl group of the β-carboline derivative of 5HT is expected to impede its passage to the brain. Pinoline is a 5HT uptake inhibitor and it has been suggested that it may subserve a role as a hormone that modulates 5HT uptake in the brain and may be involved in the pathogenesis of depression[93]. Pinoline produces behavioral stimulation manifested by an increase in exploratory and locomotor activity[126], a profile that agrees with a positive affect. A decreased formation of pinoline by the CVE during depression can explain not only the low 5HT concentration in the brains of suicidal depressives but also the observed disparity in the regulation of 5HT uptake in platelets and serotonergic neurons. There is a day-night rhythmicity in the concentration of pineal 5MoTR. The rhythm is reciprocal with melatonin so that there is an increased formation of 5MoTR during day time[62]. It should be noted that 5HT is an important competitive inhibitor of lung NMT. An increase in 5HT uptake by the CVE cell may thus divert 5MoTR from *N*-methylation to β-carboline formation. The ratio of pinoline to tryptoline and/or norharman may be responsible for the regulation of affective behavior during the extroversive mode of behavior. It has been reported that the accumulation of tryptophan in the platelets is significantly greater in acutely depressed patients than in the control

group[198]. The ratio of plasma tryptophan to other amino acids was also significantly decreased in depressed patients[45]. These data suggest that the decreased plasma tryptophan in depressed patients may be a result of an increased uptake of tryptophan into the CVE. Formation of β-carbolines that arise from TR (like tryptoline and norharman) may thus be enhanced. Norharman is the most potent pro-conflict-producing agent, and high affinity binding sites has been described for this β-carboline in the rat brain[141]. Obviously, studying the regulation of tryptamine in the CVE is very important.

The pineal gland is an important but not the only source of 5MoTR. In tissues other than the brain, the distribution of 5MoTR parallels that of 5HT[134]. Although the gastrointestinal tract of the rat contains a 300 times lower concentration than the pineal gland[134], its size makes it a significant source. Studying the formation of 5MoTR in the gut is thus important because it may contribute to the regulation of affective behavior.

In a simple metazoan, like an earthworm, the gastrointestinal tract may be more capable of reflecting the positive aspects of the environment. A gut filled with the appropriate nutrients means that environmental conditions are favorable and the organism has a good chance for growth and reproduction. If the cells of the gut could signal information about the availability of nutrients through a hormone similar to 5MoTR, the controlling endothelial cells can use this signal to direct the activities of the organism towards growth and reproduction. On the other hand, the nervous system of a simple metazoan seems more capable of signaling the adverse conditions of the environment. This can be useful in directing the resources of the organism toward defense and homeostasis. Undoubtedly, through evolution the nervous system became very efficient in expressing both the positive as well as the negative aspects of the environment. However, new characteristics tend to be built on old ones, and the early gut hormones probably became the mediators of information whether they were derived from the gut or the nervous system.

There seem to be two distinct groups of hormonal inputs to the CVE that are particularly important to the regulation of affective and sexual behavior. The first is the gut group, that is, 5HT, PEA and 5MoTR. The second is the catecholamine group, that is, NE, EPI and DA. There is an interesting parallel between the members of the two groups in the CVE model. Both 5HT and NE are important inhibitors of NMT; both PEA and EPI are involved in modulating arousal; and both 5MoTR and DA reflect respectively the favorable and unfavorable conditions of the environment. The affective behavior of the individual is expected to depend on the relative contribution of each group as an input to the CVE, and also on the densities or concentrations of the corresponding receptors, transport mechanisms, etc.

The 5MoDMT/DMT connection. Although 5MoDMT and DMT are known as hallucinogens, one should expect them to have different physiological roles. Both pinoline and 5MoDMT are synthesized from 5MoTR and both tryptoline and DMT are synthesized from TR. This may suggest that the 5MoDMT/DMT ratio is involved in the modulation of affective behavior through the introversive mode. 5MoDMT acts on the $5HT_2$ receptor as an agonist but DMT acts on that receptor like an antagonist or a weak partial agonist[44]. Administration of ketanserin, a selective $5HT_2$ receptor antagonist, to pro-estrus rats completely blocks ovulation but coadministration of 5MoDMT with ketanserin reverses the induced inhibition of ovulation[187]. An intraperitoneal dose of 5MoDMT given to male rats causes ejaculation and the effect is blocked by a $5HT_2$ receptor antagonist[147].

There is an association between sexual and introversive behaviors. Sexual activities usually occur during times of relaxation and before sleep. Nocturnal erections and ejaculations are regular physiological phenomena. The sexual drive is strong in day and night dreaming. This suggests that the ratio 5MoDMT/DMT may be particularly high during sleep and day dreaming. It also suggests that a circadian rhythm may be more marked for circulating 5MoDMT than for circulating DMT.

This association between the regulation of sexual and introversive behaviors in the CVE cell model is reminiscent of Freud's great work *The Interpretation of Dreams*. The idea that hormones responsible for modulating cognition are involved in regulating sexual activities supports Freud's theory in that the sexual drive plays a principal role in the cognitive process. Pinoline may also play a role in regulating sexual activities by stimulating social behavior and making the individual more daring. It is likely that the mechanisms of modulating cognition and social activities are evolutionarily derived from the mechanism of regulating sexual behavior. The mechanism that brings the opposite sexes together probably became more complex, involving care for their offspring and other beings. Thus, the word 'love' is used in several different contexts.

As discussed before, melatonin may be involved in the regulation of sleep by inhibiting the uptake of 5HT to the CVE. This should also lead to a decrease in 5MoTR uptake which seems to contradict the assumption of a nocturnal increase in the formation of 5MoDMT. However, melatonin enters all body tissues and can be metabolized into 5MoTR[74]. Melatonin may thus serve as the main source of 5MoTR during the evening and the night. One may assume that the physiological role of melatonin in relation to behavior is to induce an introversive mode of behavior without altering, and possibly even improving, the affective status of the individual.

Regulation of 5HT uptake in the CVE cell. According to the developing model, the uptake of 5HT by the CVE

influences affective behavior. It is important thus to examine the regulation of the 5HT transporter of the CVE cell. A study of platelet 5HT uptake in monozygotic twins suggested that the V_{max} of 5HT uptake is, in part, heritable[113]. The human brain and platelet 5HT transporters were found to be identical, indicating that both proteins are encoded by the same single-copy gene. This makes it likely that the 5HT transporter of the CVE cell is also encoded by that gene. The transporter contains two consensus phosphorylation sites for cyclic AMP-dependent protein kinase A (PKA) and three potential phosphorylation sites for protein kinase C (PKC), suggesting a role for both kinases in the regulation of 5HT uptake[96]. Activation of PKC in platelets[2], in cultured endothelial cells[121] and in perfused rat lung[196] inhibits extraction of 5HT. The effect of cyclic AMP (cAMP) on 5HT uptake has not been studied in the lung but the 5HT trasporter expressed in a human placental choriocarcinoma cell line is activated by cAMP[41]. This indicates that 5HT uptake by the CVE is under reciprocal control by PKA and PKC. According to the one cell model, thus, activation of PKA and PKC via the corresponding receptors should lead to opposite effects and the interplay between these two groups of receptors should affect the position of the individual on the mood dimension.

The receptors of the CVE cells have not been studied in relation to affective behavior. However, blood cells share the same environment with the CVE cells and one can examine the available data about platelet and lymphocyte receptors to see to what extent they conform with the model.

Activation of both platelet $5HT_2$ and α_2 adrenergic receptors increases phosphoinositide hydrolysis[148] and consequently leads to activation of PKC. As expected, platelet 5HT uptake is decreased by activation of PKC[2]. In support of the model, there is a significant increase in $5HT_2$ receptor density in platelets of depressed and suicidal patients[26,27,28]. There is also a higher density of α_2 receptors in depressed, dysthymic patients[84] and in women with dysphoric premenstrual syndrome[73]. Furthermore, thrombin receptors mediate activation of PKC[12] and thrombin-stimulated intracellular calcium in platelets was significantly higher in depressed patients[49]. β-adrenoceptors are known to mediate their effects through activation of the cAMP-dependent PKA, and as expected from the model their activation should lead to increased 5HT uptake and a positive affect. In support of the model, the density of lymphocyte β-adrenoceptors have been found to be decreased in patients with major depression[37], and β-adrenergic-mediated cAMP accumulation was reduced in lymphocytes obtained from depressed patients[51].

If both α_2 and β-adrenergic receptors are expressed on the CVE cells as suggested, then the effect of norepinephrine, for instance, on mood may depend on inter-individual differences in the α_2/β-adrenergic ratio and not just on the concentration of norepinephrine. The CVE cells may respond to stress by modifying this ratio. This applies also to other receptors that affect 5HT uptake reciprocally. Measurements of the relations between the relevant CVE elements are thus much more important and informative than separate measurements.

As discussed before, an increase in circulating DA may lead to a decrease in the concentration of MTA (methylthioadenosine) in the CVE cell. It is interesting that MTA was found to be an inhibitor of cAMP phosphodiesterase[149]. This suggests that the introversive mode of behavior induced by an increase in circulating DA is expected to be associated with a decrease in 5HT uptake and a negative mood. While this effect supports the idea of synergism between the roles of melatonin and DA in the regulation of sleep, it also suggests that the affective status during sleep will depend on the relative contribution of each hormone in that regulation.

One of the important factors that may be involved in the modulation of affective behavior is the intracellular pH (pH_i) of the CVE. A decrease in pH_i of platelets is reported to enhance the activation of PKC[101]. This suggests that pH_i regulates 5HT uptake into the CVE. A high pH_i is usually associated with favorable conditions and is required for cell proliferation[72]. On the other hand, a low pH_i may reflect certain stresses, e.g. hypoxia. This is particularly important in invertebrates where the CVE is not associated with lungs or gills. Interestingly, it has been reported that activation of D_2 receptors induces an intracellular acidification by inhibiting the Na^+/H^+ exchanger[63]. This suggests that pH_i operates as an important second messenger.

Regulation of MAO-A. MAO-A is the enzyme that inactivates 5MoTR and 5HT and is involved in regulating the concentrations of these two amines in the CVE cell. Here, we shall discuss some regulators of this important enzyme.

Harman (1-methyl-β-carboline). Harman binds reversibly to the active site of MAO-A in vivo and it has been postulated that it operates as a natural inhibitor of MAO-A in mammals[156]. Harman and its precursor have been identified and quantified in the rat lung[31,32]. Thus, increased concentrations of harman within the CVE cells may lead to a positive mood. The initial step in the formation of harman is thought to be through the condensation of tryptamine with pyruvic acid[156]. This seems to be an important step in the regulation of affective and sexual behavior. As mentioned before, more tryptamine in the CVE cell is supposed to favor the synthesis of tryptoline and norharman, both of which have negative effects on mood. Through condensation with tryptamine, pyruvic acid can lead instead to the formation of an agent that has the opposite effect, i.e. harman. Thus, the concentration of pyruvic acid in

the CVE may modulate affective and sexual behavior. Conceivably, an increased concentration of pyruvic acid indicates an adequate supply of oxygen and glucose. In a simple metazoan, it reflects good chances for growth and reproduction. In the case of hypoxia, for instance, lactic acid accumulates, leading to a decrease in pH_i which in turn inhibits 6-phosphofructo-1-kinase, the rate-limiting enzyme in the glycolytic pathway[75]. This leads to a low concentration of pyruvic acid. Thus, a low pH_i in the CVE can lead to a negative mood by decreasing the concentration of pyruvic acid. Although mediation of stress in a mammal evolved into a complex process it may still be based on the same old mechanism. For example, stress or administration of dexamethasone increases the rate of lactate production in lymphocytes[172]. This suggests that glucocorticoids or stress can lead to activation of MAO-A by decreasing the synthesis of harman. Studying the regulation of pH_i and glycolysis in the CVE cell may therefore be important for understanding the physiology of affective behavior. The relationship between pH_i and harman may explain why depressed persons may feel as if they are choking. Such a relationship between emotions and respiration that seems to have evolutionary roots is probably behind the notion that the chest is a seat of emotions and control.

Rommelspacher and associates found a time-dependent increase in harman in the erythrocytes of normal subjects after the intake of ethanol. The concentrations of ethanol, acetaldehyde and erythrocyte-harman showed a parallel trend over time[154]. It was suggested that acetaldehyde leads to an increased formation of harman by inhibiting the pyruvate dehydrogenase enzyme complex, favoring a higher intracellular concentration of pyruvic acid[156]. Considering the role of harman as an endogenous inhibitor of MAO-A, this finding can explain the euphoric effect of ethanol. The concentration of harman in the brain seems to be too low to suggest a significant role in inhibiting MAO-A in that organ[156]. In the CVE cell model, harman is not considered as a circulating hormone.

Steroids. The effects of steroid hormones on MAO activity have been studied in the endothelial and chromaffin cells of bovine adrenal medulla. MAO-A activity was found in the endothelial but not in the chromaffin cells[201]. The endothelial MAO-A was stimulated by hydrocortisone and dexamethasone. It is possible that a decreased formation of harman is involved in this stimulation. This effect of glucocorticoids on MAO-A might explain the observed relationship between an overdrive of the hypothalamic pituitary adrenal axis (HPA) and psychotic depression[160]. In addition to the effects on MAO-A, an overdrive of HPA axis may lead to hallucinations and delusions by increasing the relative concentrations of DA and EPI. Plasma DA is reported to be increased in psychotic depression[160]. This relationship between the HPA axis and MAO-A could also explain the reported antidepressant effects of ACE inhibitors. As mentioned before, circulating AngII stimulates the secretion of corticotrophin-releasing hormone from the hypothalamus.

In the same study, estradiol was found to inhibit MAO-A, but progesterone stimulated it. This helps in explaining the regulation of sexual behavior. It can also help in explaining the mood changes of premenstrual syndrome and involutional melancholia.

Pharmacotherapy of affective disorders. Recent reports suggest that the molecular locus of anti-depressant action resides at the stimulatory GTP-binding protein. Antidepressants thus lead to an increase in adenylate cyclase activity[132]. This means that anti-depressant drugs act by enhancing the formation of cAMP, a finding that is consistent with the model. Lithium inhibits adrenergically activated adenylate cyclase function[107] and also inhibits activation of PKC after chronic treatment[193]. These effects of lithium suggest that Li^+ can limit both the increase and the decrease in 5HT uptake by CVE cells. This may explain the therapeutic and prophylactic actions of lithium towards both mania and depression.

According to the CVE cell model, inhibition of the $5HT_2$ receptors in the brain has a negative effect on mood but their inhibition in the CVE has a positive effect. If this is the case, which drug should we use in the treatment of depression, a $5HT_2$ agonist or antagonist? In reality, $5HT_2$ antagonists are used in the treatment of depression, but as with other antidepressants there is a time lag of weeks between the start of treatment and improvement. One way to explain this lag is that it is the time required to resolve this conflict. While the $5HT_2$ antagonists are supposed to correct the disturbed regulation of mood in the CVE they also oppose the effects of this correction in the brain. Time is thus needed to overcome this opposition through modifying the density of brain receptors, uptake mechanisms, etc. One of the important predictions of the CVE cell model is that conservational antidepressants that do not cross the BBB can bring a faster and more efficient improvement than those that cross readily into the brain. A conservational ACE inhibitor, for instance, would be expected to be a very useful antidepressant, particularly in psychotic depression and melancholia. It has the potential of correcting both the affective and psychotic aspects of the disease.

An overview of the CVE cell model

The concepts of control as expressed in this work do not contradict any established knowledge from the field of neuroscience. They are intended to enrich and systematize this knowledge. The new concepts should stimulate the study of the control relationships within the

nervous system. The idea that the highest level of control lies in the CVE does not imply that research in the field of neuroscience is less important than before. That parliaments constitute the highest level of control in political systems does not mean that the roles played by presidents, prime ministers and ministers are less important than the roles played by parliamentary members.

According to the CVE cell model of control, however, studying the nervous system is not enough to explain its processes. On the other hand, satisfying explanations of how the nervous system is controlled by the CVE require study of the various control processes occurring within the nervous system down to the molecular level. If we investigate, for instance, how circulating psychoactive hormones modulate cognition and affect, we can develop neurobiological models for these processes and its control within the nervous system. This principle should also apply to other organs. We can thus improve our understanding of the function of organs by studying how these functions are controlled by the CVE. As we have noticed in the model, important psychological processes that occur in the brain are integrated and controlled by the CVE. We noticed that the elements that are involved in the control of these processes are also involved in the control of blood pressure. Knowledge of this kind will not be missed if organ functions are studied in relation to the CVE.

However, the structure and function of the CVE cells should also change during certain physiopathological conditions. This means that our knowledge of the functions of organs can still be enhanced by studying how the CVE cell is controlled by its genome. The idea that organ function should be studied with reference to the highest level of control in the body is not new. It is a Hippocratic concept.

If the model is principally correct, then its medical importance is great. It should help in all fields of medicine. If we can explain, for instance, inter-individual differences in immunity in terms of differences in the CVE cells, i.e. in terms of differences in their concentrations of enzymes, receptors and transport mechanisms, then we may be able to develop more successful and at the same time more conservational treatments for a number of diseases.

There are important philosophical implications of the CVE cell model. For example, the problem of the 'self' that is usually misnamed the 'mind-body problem' is about identifying a central controlling entity that endures the changes of the body. One usually denotes such entity by the term 'I.' It is interesting that the brain, a seat of cognition, has the notion that the self is located in the chest. This notion, that has been utilized in formulating the theory of the naive, is also revealed when one points with a finger to the chest to indicate one's 'self.'

It remains to be said that the CVE cell model is just a model derived from many hypotheses. Some of these may survive and many will turn to be wrong. What is important is that they can be put to the test and can thus be very helpful in developing a better model.

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