# Neurochemistry and Clinical Disorders: Circuitry of Some Psychiatric and Psychosomatic Syndromes

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# DEDICATION

A human being is much more than the sum of blood, bones, and viscera. In the same way, each fragment of truth in itself is a lie; therefore, the accumulation of unintegrated scientific facts does not protect us against ignorance.

In the measure that we interrelate a greater number of fragments, the closer we can come to truth, although truth as an absolute is unattainable.

We dedicate this book to those doctors and scientists who believe that the work of a good specialist or researcher must draw on the widest possible interrelated knowledge in many disciplines, in order to avoid their objective findings — clinical or experimental — being left like loose pieces of a puzzle, without universal context and lacking meaning.

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Editors

# PREFACE

Differences must be drawn at the outset between the craft of medicine and medical science. In the former, rudimentary guidelines of diagnosis and therapy, laid down by legally invested bodies, are applied by practitioners. In the latter, basic mechanisms are explored in an attempt to explain the symptoms of disease and the effect on them of therapeutic drugs. It is possible to practice medicine with only rough knowledge of the basic sciences but, as more diagnostic tools and powerful drugs are introduced, the inability to make global diagnoses increases and with it the danger of iatrogeny.

The practitioner of today grows more dependent on sophisticated diagnostic aids, he becomes tempted to forego the use of his intellect and his ability to integrate knowledge. Further, his use of pharmacotherapy in the blind fashion dictated by rigid medical school precepts, although limiting his medical efficiency, allows him to rest safely within a framework of legality, so that even when he cannot help his patient, he is protected against professional criticism, moral reproaches, and legal suits.

Ostensibly to protect the patient, such professional limitations arise from the circumstance that medical schools are aware of the poverty of the education they impart and their low level of requirements. The reduction in effort expected of the practitioner allows him more free time for personal interests.

One attempt to make up for the practitioner's partial training is team practice, compensating for the lack of individual knowledge through group cooperation. The rise of specialization and super-specialization reduces 'per capita' labor and dilutes responsibilities.

In our opinion, superspecialization has led to the mistaken concept that the practitioner need not know what lies outside his specialty because supposedly it is not his legal concern. His personal contribution grows ever narrower.

Such superspecialization has led to the mystification of new diagnostic tools. Developed by experts in physics, electronics, optics, biochemistry, pharmacology, physiology, immunology, genetics, etc., these tools bestow on the practitioner in whose hands they are used an aura of wisdom, almost of infallibility and omnipotence. The dazzling light of the new tool may obstruct a view of the global process of the disease affecting the patient. For example, when a gastroduodenal ulcer is revealed through endoscopy, the gastroenterologist will concentrate on curing the ulcer rather than the condition which caused it, like a mason plastering holes in a wall weakened by leaky plumbing. If an ulcer is produced by oversecretion of peptoacid, the specialist administers high doses of drugs to halt the secretion and allow cicatrization; there ends his job. He designs numerous double-blind tests to determine whether the H2 blockaders are more effective than the anticholinergic or prostaglandinic agonists; and once the ulcer is healed the gastroenterologist is satisfied. His fragmentary and partial training prevents him from understanding that the hypersecretion of peptic acid is the final manifestation of a chain of physiopathological events beginning in the central nervous system and that, although the ulcer may be healed, the patient is still ill. Furthermore, the gastroenterologist's scanty knowledge of the central nervous system (CNS) stands in the way of his fully understanding all the neuroendocrinal and neurochemical effects provoked by the administration of the drugs.

Anxiolytics are administered by practitioners in such prolonged and exaggerated doses that they now account for the majority of all drugs consumed. Yet how many practitioners know in what way and where the benzodiazepines act? What do they know about the GABA system, the main target of these drugs? Why do anxiolytics lose effectiveness after prolonged usage? What do their paradoxical effects mean? How does one correct the symptoms of exaggerated anxiety present in a high percentage of patients who have taken benzodiazepines for some time?

Should a practitioner be allowed to administer to his patients drugs acting on the CNS, when he has no adequate knowledge of the CNS morphology, physiology, biochemistry, and pharmacology? For example, in the case of clonidine, an $\alpha_2$-agonist whose action is fundamentally central, should this drug be handled by a practitioner ignorant of the central noradrenergic (NE) neuronal organization and the possible pre- or postsynaptic mechanisms of clonidine? How can he interpret the paradoxical effects of clonidine, which in certain patients does not provoke hypotension but rather hypertension? Similarly, how can he interpret the neuroendocrinal effects exercised by clonidine on growth hormone, cortisol, etc., or on glycemia?

We feel that the mystification of diagnosis leads the practitioner to put modern diagnostic aids foremost, relegating the patient to a subordinate or secondary plane. Thus, the lowering of blood pressure levels becomes more important than treating the patient who suffers from high blood pressure. Is the practitioner aware that drugs which lower blood pressure by inducing a depletion of central and peripheral monoamines also provoke neurochemical imbalances similar to those found in stress and depression? Is he aware of the relationship between stress, immunology, and cancer? How can the practitioner be certain that such a treatment will not predispose the patient to tumoral growth of an undiagnosed neoplasy or to an immunological deficiency which would make the patient susceptible to a latent viral infection?

We should ask, then, what is the minimum basic knowledge that a practitioner should have? Where does one specialty end and another begin? Does gatroenterology stop at the serosa of the gastrointestinal tract? Should the cardiologist and endocrinologist, who handle drugs which act on the hypothalamus, mesencephalus, mesolimbus, and cerebral cortex, also be trained in neurophysiology, neuroanatomy, and neuropharmacology? Can a team of superspecialists take the place of a practitioner who possesses adequate basic information in areas outside the field in which he was trained?

We have written this book because we believe it to be useful and necessary. Over the course of 35 years of medical practice, we have attended some 80,000 patients suffering from almost every kind of upset. In the last 2 decades we have witnessed the eruption in therapy of a vast array of psychoactive drugs, not counting those previously believed to have little effect on the CNS but which are now known to be centrally active.

Antibiotics such as penicillin, for example, have been proved to possess a GABA-antagonist effect; other antibiotics which can inhibit protein synthesis and cross the blood brain barrier are able to inhibit synthesis of the REM sleep factor. Likewise, differences have been shown between the action mechanisms of synthetic and natural steroids, because the former do not bind beyond the hypothalamus while the latter interfere powerfully in the synaptic transmission of serotonin at mesolimbus and cerebral cortex levels. (Moreover, natural steroids inhibit the hypophysis-suprarenal axis, acting preferentially at the hypothalamus level by inhibiting CRF secretion, while synthetic steroids act preferentially on the hypophysis by inhibiting secretion of ACTH).

Drugs used to halt gastric secretion (H2-antagonists, prostaglandinics, and anticholinergics), widely prescribed for treating gastroduodenal ulcers, have marked effects at the CNS level and give rise to psychoneuroendocrine alterations. Antidepressive drugs such as Doxepin and chlorimipramine have been shown to be very effective in the treatment of gastroduodenal ulcers, even when administered in small doses. Likewise, antipsychotic drugs such as thioproperazine and centrally acting, antihypertensive drugs such as clonidine, are succesfully used in treating idiopathic ulcerative rectocolitis, psychosis, and Gilles de la Tourette syndrome.

In our own experience we have found the employment of psychoactive drugs highly effective in the treatment of bronchial asthma, irritable colon, Chron's disease, rheumatoid arthritis, multiple sclerosis, female infertility, primary amenorrhea, dysthyroidism, skin allergies, and various kinds of neoplasias. With respect to neoplasias, we have been able to induce, through administration of psychoactive drugs, varying degrees of improvement in some 200 patients suffering from different kinds of cancer. Paralleling improvement in the cancerous condition of these patients was an increase in the cytotoxic activity of NK cells plus a reduction of OKT4/OKT8 ratio. This same result was obtained in rats inoculated with Walker's carcinoma.

We could extend the list of examples but those mentioned suffice to give an idea of the importance that psychoactive drugs have now and will have in the future in the treatment of so-called somatic diseases. Therefore, it becomes imperative that doctors acquire working knowledge of the anatomy, biochemistry, physiology, physiopathology, and pharmacology of the CNS.

In support of the above, the growing use of biological markers of depression and psychiatric cases in general should be noted. Such markers are of different kinds: gastrointestinal motility, hormonal, metabolic, haematic, cutaneous, pupillary, immunological, etc. Medical literature regarding immunology now abounds with experimental and clinical studies demonstrating the close relationship between the CNS and immunological activity.

Today a therapeutic arsenal of potent psychoactive drugs is available to practitioners. In view of this and the fact that many of these drugs, believed to excercise their main effect peripherally, actually cross the blood brain barrier to generate powerful central effects, the practitioner's poverty of knowledge concerning the CNS becomes not only incongruous but dangerous. Without adequate information about the drugs' numerous effects, practitioners freely administer benzodiazepines, synaptic reuptake inhibitors, MAO inhibitors, receptor agonists and antagonists (pre- and postsynaptic), inhibitors of neurotransmitter synthesis, amine depletors, antagonists of calcium channels, etc. Yet all drugs in current medical usage act on so many levels, by means of such diverse mechanisms, that it is very difficult to determine which action produces benefits and which generates iatrogeny.

No drug exists which acts on only one site through one mechanism. Like a chord played by ten fingers together, or a ray of light which diffracts on penetrating a prism, drugs act in different places in the body. Moreover, when the practitioner administers a β-receptor antagonist, a GABA mimetic, or a calcium antagonist, he cannot aim their direction to a certain central or peripheral zone. Such drugs will act on all the β-receptors, all the GABA systems, and all the cell walls in the organism. Truly specific and selective drugs have not as yet been found which would allow us to be certain they will produce a single effect and act in a single region, e.g., a β-receptor blocker which would act only in the posterior hypothalamus but not in the mesencephalus, the cardiopulmonary sphere, or the gastrointestinal tract.

One approach to minimize drug nonspecificity of action and nonselectivity of place is the use of minimum effective doses. Although it is true that drugs can have many effects at various sites, this solution has worked well for us over many years, apparently because the degree of receptivity varies in different places. As a result, the more the dosage is reduced, the greater is the drug specificity. Further, the drugs act preferentially on those receptors and mechanisms which are most activated at the moment of the drug administration. For example, when clonidine (an $\alpha_2$-agonist which inhibits the NE neurons) is administered, its effect will be registered on those NE neurons which at the time are most active. If the locus coeruleus (group A6 neurons) are most active at that moment, these are the neurons which will be inhibited by clonidine, resulting in lowered arterial pressure, an effect which is registered even when the dose of clonidine is very low. On the other hand, if large doses of clonidine are needed to provoke a hypotensor effect, this may indicate that the A6 group was not very active at the time and that the effect obtained was possibly postsynaptic (at the level of the sympathetic preganglionic neuron which is cholinergic in nature, located in the intermediolateral horn of the spinal cord and in the reticular nucleus of the medulla, in whose neurons there are $\alpha_2$-receptors.

Low doses have the advantage, besides reducing iatrogeny and side effects to a minimum, that the mechanisms of tolerance to the drug are also kept to a minimum. It is our experience that low dosage allows prolonged use of the drugs without their loss of effect with time. This phenomenon could have the following explanation: if an $\alpha_2$-agonist, for example, is administered in minimum doses, the firing of the hyperactive NE neurons could be inhibited without inducing hyperpolarization of the membrane and hyposensibilization of these receptors. Likewise, if propalanol is administered to block the β-receptors of a certain central or peripheral zone, a partial and incomplete blockade capable of reducing beta mechanisms in the target area, without suppressing them totally, might avoid the subsequent proliferation of receptors (supersensibilization) which obliges the practitioner to escalate the dosage of propalanol, at the risk of provoking its well-known and undesirable side effects.

In our opinion, drugs are employed in unnecessarily heavy doses, leading to counterproductive results in the medium and long term. The widespread use of large doses derives from the mistaken assumption that human dosage can be extrapolated from experiments on rats, and that double-blind studies on large groups of patients can establish accurately the minimum dose effective for a single patient. We arrive at the minimum effective dose through adjustments after frequent communication with the patient. In our experience, when large doses of a drug are needed to suppress a symptom, then the chosen drug is not the right one and it is better to use another.

Benzodiazepine is commonly administered as an anxiolytic. Yet, benzodiazepine drugs are GABA-mimetics which act on all neurological circuits, among which the GABA system is just one. Although these drugs stimulate the GABA system responsible for blocking monoaminergic neurotransmissions generating anxiety, their prolonged administration can stimulate other GABA systems and block other monoaminergic circuits. As a result, benzodiazepine drugs can throw a patient from a state of anxiety into a depressive or even psychotic state. Sadly, this phenomenon is a daily occurrence.

In this book we have gathered enough information to propose a model for the anxiety circuit. A considerable body of clinical and experimental research supports the NE, dopaminergic (DA), and serotonergic (5HT) mechanisms believed to be involved in anxiety. Whether or not our proposed model is simplistic, incomplete, or topographically inexact, it has the virtue of allowing a therapeutic approach broad enough to cover, besides the benzodiazepines, a whole range of other anxiolytic drugs (5HT antagonists, DA blockers, $\alpha$-antagonists, $\beta$-antagonists, dopamine liberators, etc.). Our therapeutic approach, and the small doses we employ, have led us to surprising findings, widening our practical knowledge to the point where we can formulate hypotheses and propose model circuits, some of which are put forward in this book.

Perhaps the most important conclusion we have derived from our work with drugs is that, in the face of neuropharmacological advances, it is no longer possible to continue authorizing the practitioner to administer powerful psychoactive drugs if he is unprepared in the anatomy, biochemistry, physiology, physiopathology, and pharmacology of the central autonomous nervous system (ANS). No matter what his specialty, the practitioner should be required to know with some degree of accuracy what is the effect on the organism of the powerful drugs he administers. He should not handle such drugs according to the rough rules set out by the legal medical authorities which make the physician into a simple medical artisan. A deeper level of knowledge in the scientific areas composing modern medicine should be required of the practitioners of today.

In his book, *Structure of Scientific Revolutions*, Khun puts forward the eternal confrontation between what is accepted as the offical truth and new findings which must struggle for a place within the old structures of "paradigms". He also speaks of the phenomenon of scientific revolution which, once accepted officially, becomes paradigmatic, resisting changes brought by new scientific knowledge. The only logical conclusion to be drawn from this cycle is an acceptance of continuous revolution, in accordance with the one constant of our universe: change.

Poets dream, philosophers reflect and spin hypotheses, scientists test these hypotheses, and artisans apply the new knowledge. The practitioner belongs in the last category and therefore mocks the poet, denies the philosopher, and attempts to ignore the scientist while glorifying his own craft although, without the preceding links, his craft would not exist. When a medical specialist applies diagnostic or therapeutic innovations, in his skill he often overlooks the debt he owes to those who first dreamed of the technique or tool, others who conceived it, later tested it, and finally produced it.

In the field of medicine it is difficult if not impossible to determine where science ends and craft begins. Over the centuries, the interdisciplinary nature of medicine has led to close cooperation by chemists, physicists, mathematicians, biologists, and other scientists with the physicians directly concerned with people's health. This has given rise to areas of convergence such as physiology, physiopathology, pharmacology, genetics, immunology, etc., and, as if this were not complex enough, psychology and psychiatry call in all the above scientists and philosophers, sociologists, and writers as well.

However, the interdisciplines are so numerous in medicine today they are no longer able to intercommunicate. Like the biblical Tower of Babel, the higher the specialization, the deeper the cracks in communication. With few exceptions, the superspecialist has become the purest craftsman of the entire medical community. In the end he can only communicate with the few who are perched on his peak and so affords a typical example of what conceptual philosopher Ernesto Lechín calls "tunnel vision" as opposed to "peripheral vision". Only through the latter is it possible to maintain an overall view of knowledge, avoiding the risk of its psychotic fragmentation. By way of illustration, the author and thinker contrast the inhabitant of an island or a valley who regards his limited surroundings as his universe with the passenger on a space ship whose view of the planet makes him see the need to integrate knowledge. Naturally, neither of the two positions can stand alone since knowledge is an infinite succession of analyses and syntheses.

Empirical knowledge leads to lineal thinking or, in other words, A leads to B. In order to form hypotheses and then build models, systemic thinking is required in which each point is related to all others. Instead of a straight line, the association of more than two variables leads to polyhedra of three, four, five, or six sides and more, ad infinitum. Scientific knowledge must have recourse to systemic thinking in order to approach the absolute truth, even though the absolute is unobtainable, of course. All truths known and accepted as such are conventions and therefore are constants, each forming one of the infinite tangents of a circle, the only form which can adequately represent systemic thinking.

In current biomedical research, fragmentary and partial experimental knowledge predominates in chains of lineal thinking. Some researchers have reached the extreme of saying, "I do not think, I investigate." Such an attitude arose as a defense against the speculative tendency derived from Cartesian rationalism. Scientific journals oblige researchers who sumbit articles for publication to limit discussion of their results and rule out inferences, or have their work rejected. Therefore, when a researcher has a great deal of interdisciplinary information to which he could relate his study and he is cut short in his capacity to report it, his readers are denied this wide and potentially useful context.

In this way, scientific literature accumulates an enormous body of new, fragmentary knowledge which in the long run is underused. Further, the superspecialist all too often lacks information from areas other than his own and so remains unaware that his personal ocean is, in fact, a pond. Countless specialized "oceans", deprived of intercommunication, become sterile in the end. Those of us who read medical journals widely are constantly astonished by the great number of closely related studies whose authors are apparently ignorant of similar research, despite journal indexing and the development of information technology. Fragmentation, when combined with poor communication and the superspecialist's restricted knowledge, leads to costly repetition of research and a continual "rediscovery of the wheel".

Review articles are published with the aim of fitting together loose pieces in the jigsaw puzzle of experimental research. But it is our observation that most such reviews are timid attempts at integration which do not risk making structures of any complexity or proposing true models.

The inability of modern medicine to solve human health problems, despite vast resources and efforts invested in cures, appears to justify our Tower of Babel simile, our fears of the failure of the ambitious project of medicine to reach heaven. Karl Popper, Ph.Sc., states that no scientist can extend the bounds of knowledge unless he has complete knowledge of the work of previous scientists. Although empirical science struggles to make knowledge as objective as possible, uncontaminated by subjective speculation, thinkers and philosophers teach us that this is not possible. Albert Einstein in his *Theory of Relativity* and Werner Heisenberg in his *Uncertainty Principle* assert the impossibility of avoiding interaction between the observer (subject) and the observed (object), which are the two main structural components of the scientific method.

In this book, when we launch a hypothesis and propose models of greater or lesser complexity (which are certainly simplistic in the description of real structures or behaviors), we are not concerned that our models may describe the mechanisms, say of mamalian brain function, less than perfectly. Our view is pragmatic; what counts is the soundness and broad base of information on which our models are based, and the direct usefulness of the model in therapy for our patients. We know that we can never own the truth and that we must conform our goals to approximate or even probable truths. Neither are we worried that future models may substitute ours; we believe we must work on the basis of theoretical models which can be tested by experimentation. Karl Popper states that a theory is scientific if its set of propositions has a logical/rational structure permitting it to be compared with reality, and that a scientific theory does not attempt to explain all the facts deriving from an experience. Popper accepts that in order to refute a scientific theory experimental findings must contradict the hypothetical postulations. Finally, as the criterion of validity, Popper replaces "empirical verification of scientific hypothesis" with his thesis of "empirical refutation of scientific hypothesis".

Rudolph Carnap and Werner Heisenberg believe that contemporary science should substitute "probable predictive hypothesis" in place of the conventional "exact predictive hypothesis" which presupposes control of all variables intervening in the empirical phenomenon of observation or experimentation. If we take into account the thinking of Einstein, Popper, and Heisenberg that empirical data arising from observation may be subjective and that, vice versa, rational hypotheses may be objective, it becomes impossible to attain control of all variables.

Mario Bunge, Ph.Sc., says that today scientific progress is measured more by theoretical progress than by the accumulation of data. For this author, contemporary science should offer something beyond experience: theory, to which is added experience — planned, directed, and understood in the light of hypotheses. He believes that theoretical models can and should be represented in the form of mathematical models, and that reality is better represented through theoretical models than empirical data. Bunge concludes that a scientific prediction is one in which experimental data, obtained by the scientific method, are integrated to formulate a set of hypotheses or a theory. This is what we have attempted to do in the present book.

According to Bunge, no theory which has survived examination of its rational construction can be entirely false, while no theory is totally true even when it has triumphed in the test of experimentation. Bunge believes that science does not require absolute certainty but rather the possibility of correction and that, further, although one or several of the hypotheses making up a theoretical model may be refuted, the general theory may still stand.

Popper, like Bunge, is of the opinion that the process of scientific research begins by posing problems within the body of theoretical scientific knowlege already acquired. To carry out research, therefore, one must read widely and gather full and up-to-date information.

Ernesto Lechín postulates that it is impossible to be aware without conceiving; the two processes of perception and conception are inseparable. Yet the current of empiricism in biomedical research of today to a certain extent restricts and even prohibits conception. The introduction of ideas in the discussion of a scientific paper is usually criticized and rejected by the referees appointed by editors of the scientific journals on the grounds of "unscientific speculation". In fact, present biomedical science is almost totally immersed in the positivist theory of Ernst Mach that "sensations" (the observable) are the only means of perceiving reality. Marshall McLuhan says that the tools of empirical research are just extensions of our five senses. Yet, since the discovery of invisible phenomena such as atoms and the unconscious, the positivist theory must be considered obsolete.

This book may not meet great acceptance among the positivists because our models are based on ideas as well as observation.

The book is organized into six chapters covering (1) neuroanatomical basis, (2) anxiety-like syndrome, (3) depressive syndromes, (4) psychotic syndromes, (5) blood pressure regulation, and (6) biological markers.

Chapter 1 reviews information on morphology, electrophysiology, histochemistry, and neurochemistry in general which contribute direct and indirect evidence of the existence of neuronal nuclei, their areas of projection, and their interconnections. Although all this information is found in hundreds of specialized papers, as far as I know it has not been previously gathered, ordered, or assembled into book form. Until now, this information has been the exclusive property of superspecialists, beyond the reach of most practitioners who therefore were totally cut off from a possible understanding of psychoneuropharmacology and psychoneuroendocrinology. This chapter, in essence "positivist", is in no way controversial since it draws only on data from proven experimental findings and we have abstained from conceptual or hypothetical considerations.

In Chapter 2 a model is proposed for the monoaminergic circuits involved in this syndrome. The model is based on hundreds of experimental and clinical findings demonstrating that there are NE, 5HT, and DA nuclei which are activated during the appearance of the syndrome, and which, at the same time, are believed to inhibit other monoaminergic nuclei. This model has led the authors to a succesful therapeutic approach which goes beyond the simple use of drugs known as anxiolytics. The chapter also proposes connections between anxiety manifestations coexisting with certain types of depressive syndromes.

In Chapter 3 we have tried to avoid being trapped by the numerous classifications used in the area of depressive syndromes. We have attempted to simplify the definitions and limits of depressive syndromes which are in truth rather imprecise. The considerable confusion and disagreement surrounding these definitions are aggravated by similar symptoms shown by subjects during certain stages of stress.

Some models of animal depression which have been employed in neurochemical investigations and later extrapolated for human study are reviewed in this chapter, as are some of the biological markers used in diagnosis or classification of depressive syndromes. Largely because our therapeutic methodology is based on the use of psychoactive drugs in much smaller doses than those conventionally employed, we have been able to establish subtle differences between antidepressive drugs which potentiate the NE and 5HT systems. We have become convinced that the size of the dose employed not only allows a different therapeutic approach but also a more accurate diagnosis.

Our definition of depressive syndrome is based on two types: (1) anxious depression and (2) anergic depression. The former is accompanied by peripheral sympathoexcitation (sympathoexcitatory side effects), while the latter coexists with peripheral sympathoinhibition. We accept that, rather than two types of depression, the conditions are really alternating states of the same syndrome. Naturally, there are subjects in whom one of the two states predominates in intensity and frequency. Our theoretical standpoint is reinforced by the practical results emanating from treatment of hundreds of patients. We have drawn useful conclusions from our therapeutic successes but more so from our failures, for these have led to successful reformulation of therapies. Although we have published our findings in some specialized journals, these papers far from reflect the store of information we have accumulated through years of day-to-day individual treatment of patients. By comparison, we feel that double-blind studies are clumsy tools of clinical research which exclude the other, more profound side of medical practice — that direct knowledge which every physician takes to his grave, too often without transmitting it to his colleagues.

Psychotic syndromes, perhaps the area in which we have greatest clinical and therapeutical experience, is discussed in Chapter 4. Based on this experience and on an exhaustive review of published information, we classify psychotic syndromes according to two large groups: schizophrenics and schizoaffectives. The first are psychotic patients characterized by a lack of libido and affectiveness (weak affections and libido), dangerous aggressive conduct, and a history in which truly normal periods are absent. In contrast, schizoaffectives include psychotic patients showing an excess of affectivity and libido, pseudo-aggressive behavior (more apparent than real), and a history of long periods of normal family life. Schizoaffectives treat their partners and children with affection and enjoy positive, aggreable social activity. While the schizophrenic, even in his "normal" periods, appears cold, unaffectionate, different from others, it is hard to distinguish a schizoaffective patient from other people during periods of normalcy. We believe we have achieved an effective therapy for these patients, superior to any we have seen reported in medical literature. Our therapy differs from the conventional approaches and for many years we have lamented that our papers published on the subject in different scientific journals have not drawn adequate attention to the benefits of effective pharmacotherapy. We therefore continue our work without attempting to convince others of the usefulness of our physiopathological and therapeutical approach.

The section discussing aggressive behavior analyzes results of numerous experimental studies provoking aggressive behavior in animals, in particular the muricidal behavior experimental model. Also discussed are findings of studies on humans showing homicidal and suicidal behavior, with special reference to biochemical analyses of the cerebrospinal fluid *in vivo*, and postmortem brain studies of suicide victims. We also present the indirect evidence arising from therapeutic trials.

The section on manic syndrome is defined by the symptoms which, according to the DSM III, are the indispensable requisites for labeling a syndrome as manic. This is a section which sparks controversy among the various schools of psychiatry. However, it is not our intention to endorse any particular current or to enter discussions on diagnostic criteria; for this reason we have adhered to the DSM III convention. We simply offer possible anatomical and physiological bases for the symptoms accepted as making up the manic syndrome. As in earlier and later chapters, our theoretical work is reinforced by considerable therapeutic experience in the use of psychoactive drugs on patients, in this case manic subjects.

In Chapter 5 the possible mechanisms involved in blood pressure regulation puts forward an excellent model of what in our opinion should be considered a psychosomatic disorder, high blood pressure. We attempt to show that the so-called psychosomatic illnesses may operate through neuronal circuits similar to those involved in psychiatric syndromes. The fact that these neurochemical disorders produce in certain subjects only somatic manifestations, with little or no psychic alteration, obliges us to seek additional physiopathological factors at work, possibly genetic ones. Nevertheless, we believe that the imbalance in neuronal circuits could be the point where somatic and psychosomatic illnesses converge.

In this chapter on blood pressure regulation we wish to draw attention to the fact that a majority of scientists involved in neurochemical research fall into the error of treating the autonomous CNS as a homogeneous system whose only differentiation is in the type of neurotransmitter or modulator which is synthetized or released. In fact, each of the neuroautonomic systems is composed of antagonic pairs and we place great emphasis on presenting the exhaustive information now demonstrating this. For example, there are sympathoexcitatory and sympathoinhibitory NE systems. There are 5HT systems which are active during wakefulness and others which are active during sleep. Further, there are DA systems favoring motor activity and others paralyzing motor activity. Although this antagonic pairing is familiar to all who seriously read scientific literature dealing with this matter, it is not yet taken into account by most neurochemical researchers and much less by practitioners.

In Chapter 6 we focus on the two biological markers we employ in our search for a diagnostic approach to psychosomatic syndromes: (1) intestinal pharmacomanometry and (2) intramuscular clonidine test.

The introduction to the chapter is a summary of the anatomical and functional interactions among components of the ANS: NE, DA, 5HT, and acetylcholinergic (ACh) systems. How the drugs (agonists and/or antagonists to these systems) modify distal colon motility (DCM) and how we draw inferences from these drug-induced changes are discussed.

In the section discussing procedure, we give details of intestinal pharmacomanometric methodology, the significance of the two components of DCM — intestinal tone (IT) and phasic activity (PA) or waves, the influence of emotional factors on DCM, and the effects of different psychoactive drugs.

We put forward experimental and clinical evidence supporting the hypothesis that drug-induced DCM changes are central and not peripheral effects.

We also discuss the difference between sigmoidal and rectal responses to drugs.

In other sections we summarize the results obtained in treatment of psychotic, affective, and psychosomatic disturbances.

Pharmacomanometric, metabolic, hormonal, and neurochemical evidence strongly suggesting the existence of two antagonistic DAs is also provided. This first line of research supporting a DA-antagonistic receptor hypothesis (1981), has been reinforced by other evidence. However, the new findings are less impressive than those drawn from intestinal pharmacomanometry.

Lastly, we describe how intestinal pharmacomanometry is used to guide psychoactive drug therapy of psychotic and depressive syndromes. These two examples are used to illustrate the procedures we follow for psychosomatic syndromes.

In the section discussing intramuscular clonidine test, we present the results obtained with the test in three groups of subjects: normal, depressed, and severely ill. Although response of plasmatic growth hormone (GH) levels to intravenous clonidine injection is widely used as a biological marker of depressive syndromes, intramuscular clonidine testing (introduced by us) offers some advantages over the former. Intramuscular administration of the drug is a weaker stimulus to $\alpha_2$-anterior hypothalamic receptors, hence this test gains in sensitivity. On the other hand, differentiation of depressive patients into two groups, (1) low-IT + high NE plasma levels and (2) high-IT + low NE plasma levels, which show different responses to clonidine challenge, constitutes a valuable biological marker. In addition, intramuscular clonidine test performed according to our methodology introduced three other parameters of evaluation: (1) plasma cortisol response, (2) plasma NE response, and (3) diastolic blood pressure (DBP) response. This trio, in addition to GH responses, allows us to evaluate not only depressive syndromes but exacerbation of chronic illnesses. The fact that during exacerbation periods clonidine-induced responses are similar to those obtained during experimental stress situations leads us to postulate that stress plays some role in triggering such exacerbation periods in severely diseased patients.

Finally, the authors of this book ask those who do not agree with our point of view to allow us the recognition due to professionals who have worked unceasingly for many years. We know it is improbable, even impossible, to "sell" our viewpoint to the majority. However, this does not detract from the value of the vast bibliographic review gathered here for use by the reader; we believe, like Popper and Bunge, that in order to begin research, the investigator must obtain as much information as available. Perhaps our most important message is that those who intend to begin diagnosis or therapy in the areas of psychoneuropharmacology and psychoneuroendocrinology should have a prior theoretical model which can be rectified or ratified with use.

Science, according to Bunge, does not consist of accumulating experimental data but in the interpretation of the findings. Men have always observed the sun rising in the east and setting in the west, yet it took a scientist to interpret the fact as due to the rotation of the earth around the sun.

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Chapter 1

# NEUROANATOMICAL BASIS

**Fuad Lechin, Bertha van der Dijs, José Amat, and Marcel Lechin**

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# I. THE NORADRENERGIC SYSTEM

Noradrenergic (NE) neurons are confined to three groups in the pons and medulla oblongata (see Figure 1): (1) the well-defined locus coeruleus (LC) or A6 cell group, (2) a more diffuse but continuous lateral and ventral group that arches through the pons and medulla, and (3) a third dorsal medullary group known as A2 cell group, centered in the dorsal motor nucleus of the vagus. NE-LC or A6 nucleus and NE-A2 nucleus are dorsally located in the tegmental area, whereas the lateral groups are ventrally located with respect to the former and include A7, A5, and A1 cell groups. NE-A1 cells are the most caudally located in ventrolateral medulla oblongata. The LC (A6) with approximately 1600 neurons (in the rat) and the A5 with approximately 340 neurons are the largest in size of all NE cell groups.

There is general agreement that the basic organization of the central catecholaminergic (CA) system consists of cell bodies located in caudal brain stem that give rise to ascending and descending fiber systems terminating in widespread areas of the brain. However, substantial areas of disagreement still exist in results obtained with different methods and by different investigators as to precise pathways and functions.

The NE brain stem cell groups (except LC) do not form compact nuclei but are dispersed among non-NE cells. However, they send axons which terminate in a larger number of apparent pericellular arrays, particularly in certain cranial motor nuclei where they are capable of exerting direct, potent control on neuronal postsynaptic activity. LC innervation, affecting only sensory and association nuclei (in the brain stem), also sends profuse innervation to telencephalic and diencepalic structures. In these projection areas, LC axons terminate in a uniform, sparse to moderately dense plexus which may contribute modulatory control over other neuronal input here.

Three NE pathways are known to project rostrally: (1) dorsal NE bundle (DNB) or dorsal tegmental tract, originating in LC; (2) ventral NE bundle (VNB) or ventral tegmental tract which collects fibers from A1, A2, A5, and A7 cell groups, plus some fibers arising from LC and NE cells lying ventral to LC (subcoeruleus group); and (3) dorsal periventricular tract originating in A2 cell group which collects fibers from NE cells of LC and subcoeruleus areas.

The DNB projects mainly to brain cortex, dorsal hippocampus, striatum, and some mesolimbic and hypothalamic structures. The VNB projects mainly to hypothalamus and some mesolimbic structures; its axons never reach hippocampus or brain cortex. The dorsal periventricular tract projects mainly to central gray or periventricular area (see Figures 1 to 3).

NE-LC (A6) efferent projections are found in brain cortex, putamen-caudate, globus pallidus, amygdala, hippocampus, septum, olfactory tubercles, nucleus accumbens, posterior hypothalamus, mediobasal hypothalamus (nucleus arcuate, nucleus ventromedial and nucleus paraventricular), and median eminence of hypothalamus (outside the blood brain barrier, bbb). Profuse projections to the brain stem structures (sensory and association but not motor nuclei) have also been demonstrated, as well as a clearly defined projection to the ventral spinal horn (see Figure 4).

The following areas are known to receive NE-A5 axons, based on unilateral decreases in NE levels following A5 nucleus lesion: caudate nucleus, piriform cortex, interstitialis nucleus stria terminalis, medial forebrain bundle, medial preoptic nucleus in anterior hypothalamus, and median eminence. NE-A5 neurons send also axons to pons, medulla oblongata, and spinal cord. With respect to this, NE-A5 axons constitute the main innervation of sympathetic preganglionic cells located in the intermediolateral (IML) spinal horn, in the rat (see Figure 5).

NE-A1 efferent projections send axons to the hypothalamus (n. paraventricularis, n. ventromedial, n. arcuate, anterior preoptic area, etc.), septum, and other mesolimbic structures. The axons do not reach the hippocampus and brain cortex. Pons, medulla oblongata, and spinal cord receive NE-A1 efferents. Important NE-A1 fibers also reach NE-LC and NE-A2 cell groups (see Figure 6).

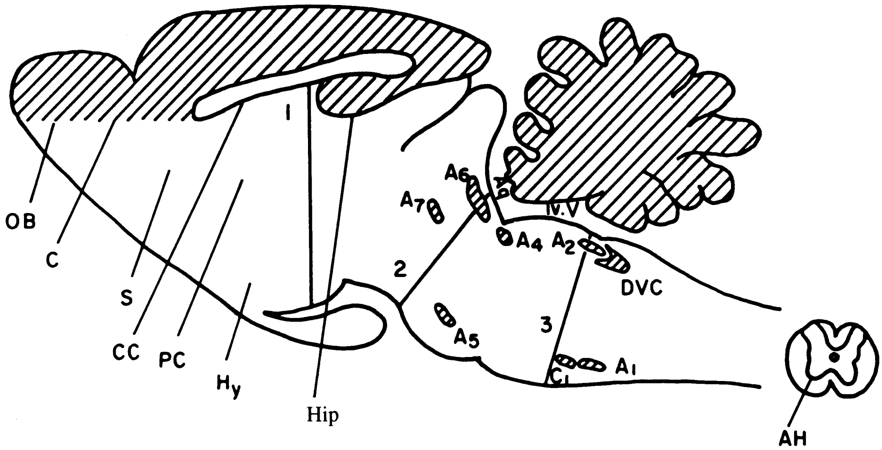


FIGURE 1. Sagittal section of the rat brain showing the dorsoventral and rostrocaudal location of the noradrenergic cell groups. (1) Divisory line between diencephalon and mesencephalon, (2) divisory line between mesencephalon and pontis, and (3) divisory line between pontis and medulla oblongata. OB = olfactory bulb, C = cortex, S = septum, CC = corpus callosum, Hy = hypothalamus, Aq = aqueduct, IV V = fourth ventricle, DVC = dorsal vagal complex, AH = anterior spinal horn, and Hip = hippocampus.

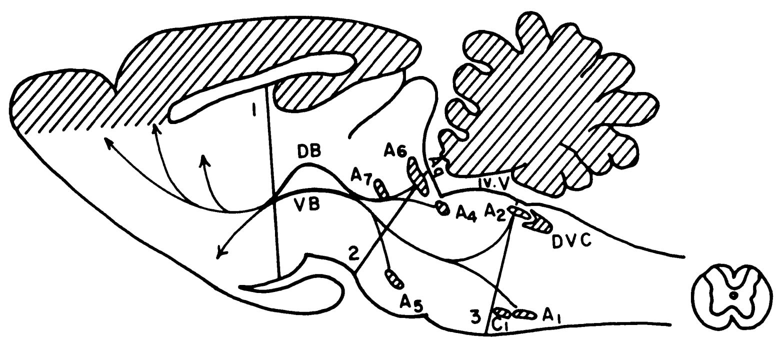


FIGURE 2. Sagittal section of the rat brain sources and projections of the dorsal and ventral noradrenergic bundles (DB and VB).

The NE-A2 efferents cell group sends its axons to the same central nervous system (CNS) areas as the NE-A1 cell group. A2 efferents also reach parasympathetic and sympathetic preganglionic cells. Parasympathetic preganglionic cells are located in nucleus ambiguus and n. dorsal motor vagii, and are also dispersed in the reticular formation. Sympathetic preganglionic cells are found in the lateral reticular formation, nucleus reticularis lateralis, IML spinal horn, etc. (see Figure 7).

### A. Neuroanatomical Connections between Noradrenergic Cell Groups

The different methodologies employed in numerous investigations of the neuroanatomical connections between NE cell groups have given rise to some disagreements. Not surprisingly, some discrepancies occur because of the different animal species studied; others are due to the fact that the NE cell groups can interact not only through direct monosynaptic but also polysynaptic mechanisms.

The LC complex (A6 + subcoeruleus cell area + the caudally located A4 cell group)

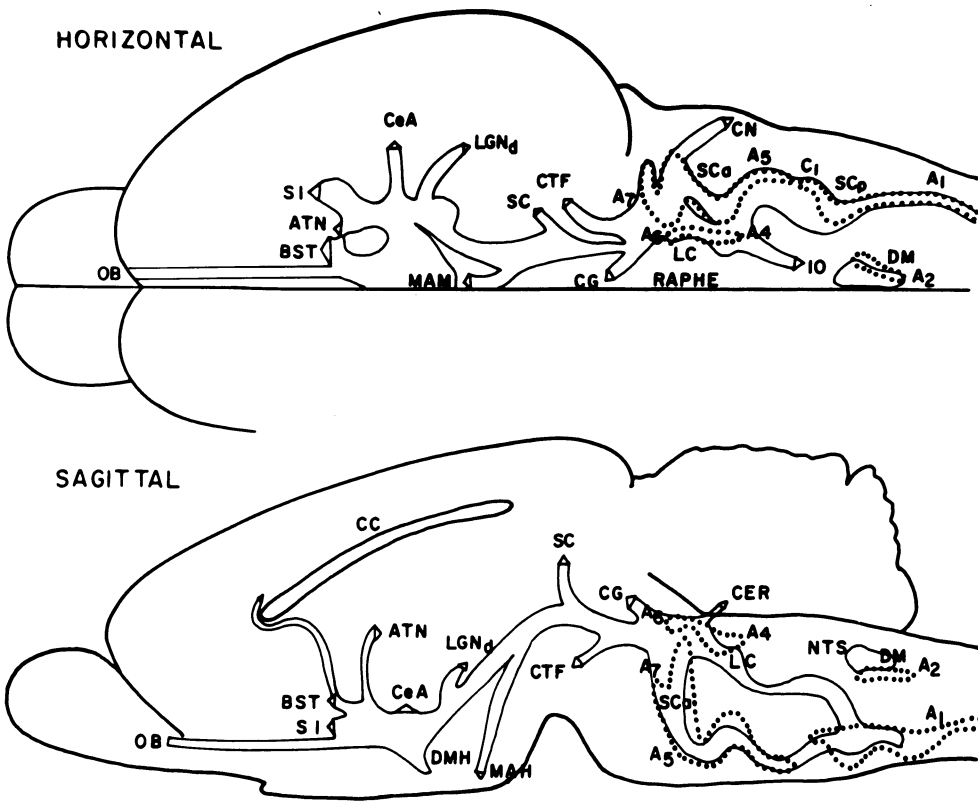


FIGURE 3. Drawings of horizontal and sagittal projections of the rat brain showing the location of adrenergic cell groups (dotted lines), the principal adrenergic fiber bundles, and major terminal field.

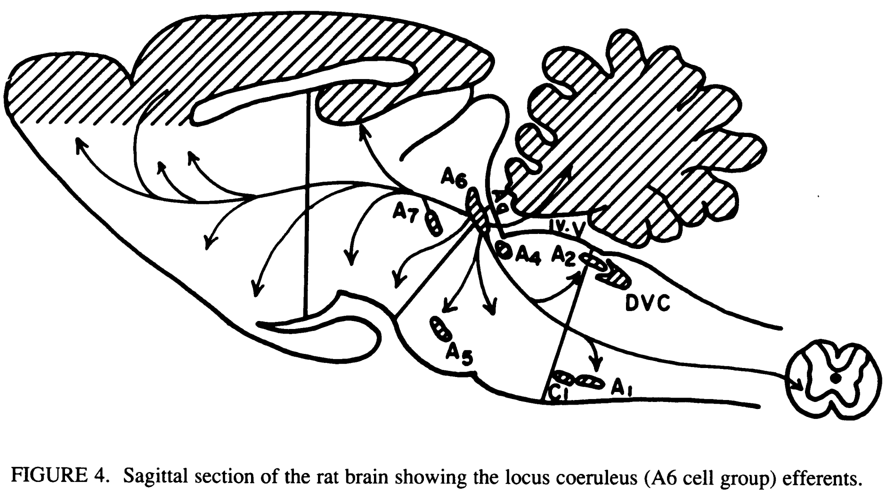


FIGURE 4. Sagittal section of the rat brain showing the locus coeruleus (A6 cell group) efferents.

innervates primary sensory and association brain stem nuclei located in the pontine gray and medullary reticular formation. It does not contribute innervation to somatic motor nuclei or discrete visceral motor nuclei of the brain stem. However, many physiological studies provide evidence that the LC has a central role in peripheral pressor, depressor, micturition, respiration, and other mechanisms which involve brain stem reticular formation (see Figure 8).

The lateral tegmental NE cell groups (A7, A5, A1) and the dorsal paramedian NE-A2 cell

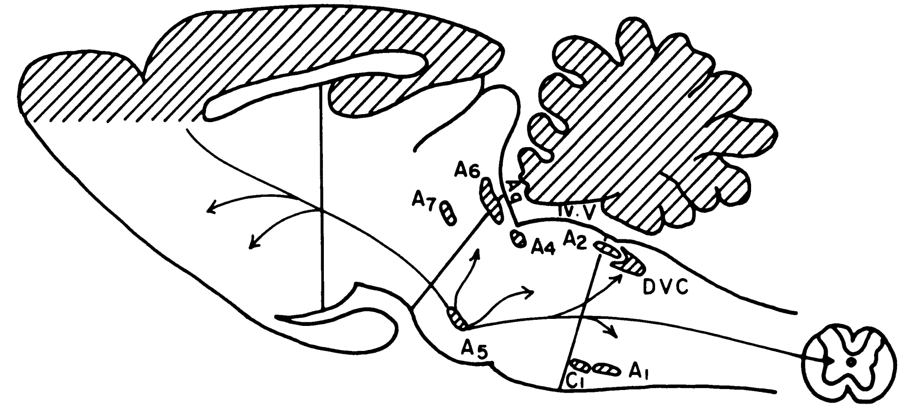


FIGURE 5. Sagittal section of the rat brain showing A5 cell group efferents.

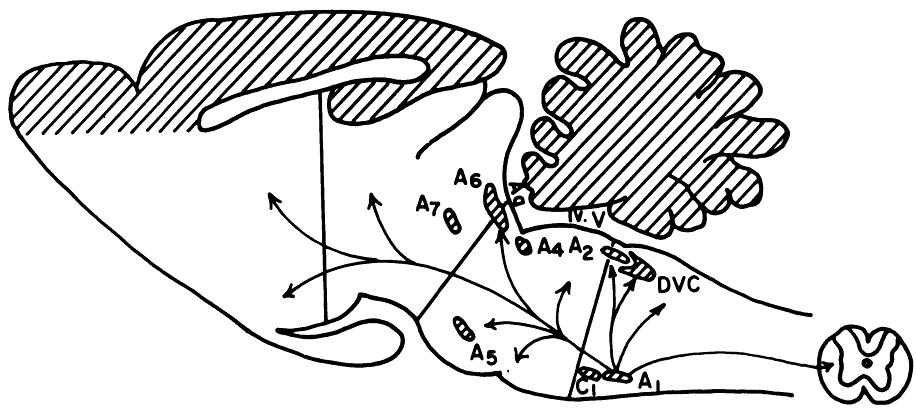


FIGURE 6. Sagittal section of the rat brain showing A1 cell group efferents.

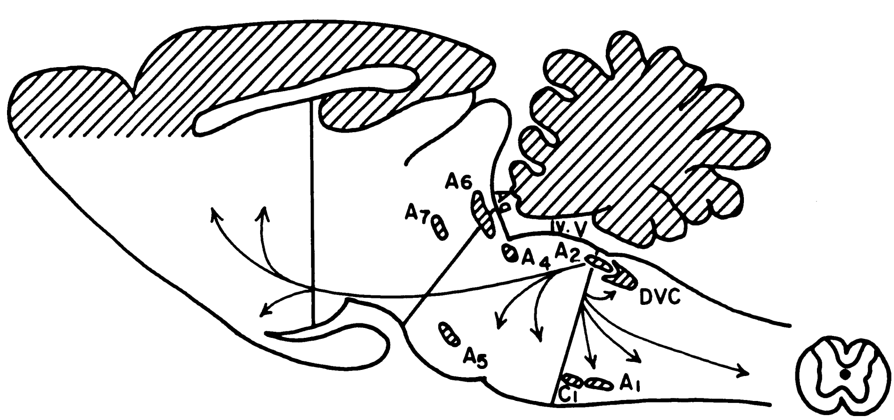


FIGURE 7. Sagittal section of the rat brain showing A2 cell group efferents.

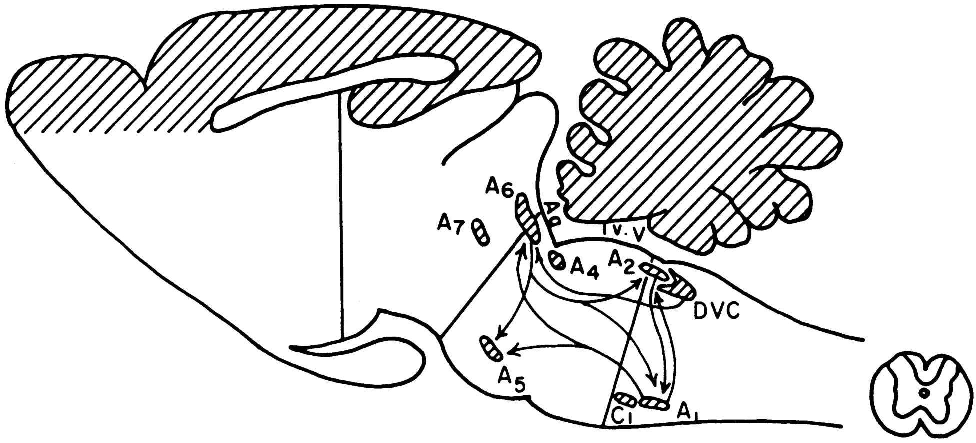


FIGURE 8. Sagittal section of the rat brain showing interconnections among noradrenergic cell groups.

group densely innervate the somatic motor and visceral motor nuclei. It is of note that innervation of the hypothalamus also arises mainly from these groups, suggesting that they may have a general function in regulating autonomic, visceral, and neuroendocrine activity.

The NE-A6 (LC) cell group sends axons to A5, A2, and A1 cell groups. In turn, NE-A1 group densely innervates A6, A5, and A2 groups. NE-A2 neurons send a well-defined innervation to NE-A1 group which, however, is not NE in nature.

A study of inputs to antidromically identified neurons of the LC has shown that stimulation of the vagus nerve produces inhibition of LC neurons, an inhibition followed by excitation, while stimulation of the splacnic nerve and sciatic nerve produces excitation of LC neurons. These findings suggest that afferent projections to LC arise from the dorsal vagal complex in which are included NE-A2 neurons. This connection, however, does not emanate from the NE-A2 neurons but from the nucleus of the solitary tract (NTS) which is the principal recipient of first order vagal afferent input. The NTS projects to preganglionic cell groups of both divisions of the autonomic nervous system — sympathetic and parasympathetic, a series of relay nuclei in the brain stem, and a number of cell groups in the hypothalamus and limbic region of the telencephalon which control autonomic, neuroendocrine, and regulatory behavioral responses. Because cell groups receiving direct NTS inputs project back to this region and/or the vagal motor nuclei (dorsal motor nucleus of the vagus and nucleus ambiguus), they are therefore in a position to influence vagal motor outflow. Such vagal motor outflow is also under the influence of the NE-A2 and NE-A5 neurons which send important projections to vagal motor nuclei (see Figure 8).

## B. Neuroanatomical Connections between Noradrenergic Nuclei and Other Monoaminergic Nuclei

Although a great bulk of evidence demonstrates direct monosynaptic pathways between NE and serotonergic (5HT) or dopaminergic (DA) neurons, some of these pathways are inferred from pharmacological, biochemical, and behavioral evidence. Frequently the various monoaminergic brain stem nuclei are so closely joined that electrophysiological and microinjection studies are difficult to perform and produce conflicting and even contradictory results. However, as the new methodology develops, results obtained will be more precise. Below, we summarize the most convincing evidence supporting our postulations. Our propositions, however, undergo continuous revision and rectification.

### *1. Neuroanatomical Connections between Noradrenergic and Serotonergic Systems*

Fuxe demonstrated fine CA terminals within the dorsal raphe (DR) 5HT nucleus (see Figure

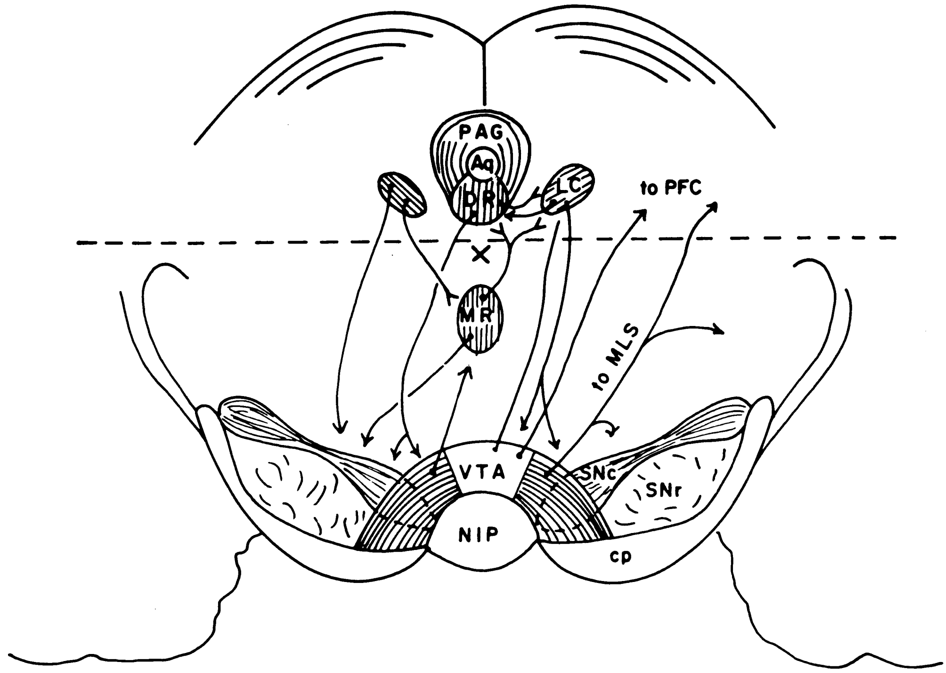


FIGURE 9. Two transverse sections of mesencephalic (bottom) and pontis (top) levels. Interconnections between NE locus coeruleus (LC) nucleus, 5HT dorsal raphe (DR) nucleus, 5HT median raphe (MR) nucleus, DA ventral tegmental area (VTA) and DA substantia nigra (SN) nucleus. PFC = prefrontal cortex, NIP = interpeduncular nucleus, MLS = mesolimbic structures, CP = cerebral peduncle, PAG = periaqueductal gray, and Aq = aqueductus.

9); Loizou reported that some of these terminals disappear following lesions of the LC; Baraban et al. demonstrated recently NE-LC innervation of 5HT neurons in the DR. These anatomical findings are supported by others showing that NE innervation of the DR is not exclusively provided by LC neurons since lesioning of LC nucleus does not eliminate the NE content of DR, which is among the richest brain stem nuclei. Furthermore, Roizen and Jacobowitz reported that VNB contributes most NE input to the raphe area. Finally, Gallager and Aghajanian demonstrated that complete transection at the pontine reticular formation level, separating the lower brain stem from the raphe area, abolishes the depressant effects on raphe firing of antipsychotic agents, piperoxane, and other $\alpha_2$-antagonists. This finding may be interpreted as the well-known inhibition of 5HT neurons exerted by NE innervation through $\alpha_2$- adrenoceptors; this inhibition arises at least partially from caudal brain stem NE nuclei. According to the above, NE innervation arising from LC (A6) nucleus would excite 5HT-DR neurons through $\alpha_1$-adrenoceptors, while non-A6 NE innervation would inhibit 5HT-DR neurons through $\alpha_2$-adrenoceptors.

It is well known that the largest 5HT content of LC is significantly reduced after DR lesioning (86.7%). Experimental findings also show that LC receives dense innervation from DR. These DR axons are proven to be 5HT and to exert an inhibitory role on NE neurons of the LC, since lesioning the DR results in an increase in tyrosine hydroxylase activity of LC neurons. However, it should be noted that 5HT axons arising from the median raphe (MR) nucleus also innervate the LC with inhibitory fibers; destruction of MR produces a long-lasting stimulation of NE-LC neurons.

We know that MR receives important NE innervation from LC and lateral tegmental NE nuclei (non-A6 nuclei) because LC lesions produce only partial reduction of MR norepinephrine content. In contrast with well-established excitatory effects of NE on 5HT-DR neurons, NE innervation exerts an inhibitory effect on 5HT-MR neurons. This effect is mediated through $\alpha_1$-adrenoceptors. In effect, both microinjection of $\alpha_1$-agonists and lesioning of the MR decrease

5-HIAA in those forebrain structures innervated by 5HT-MR axons. This NE-5HT antagonism between NA and MR-5HT systems would explain the increased 5HT turnover observed following administration of the CA-specific neurotoxin 6-OHDA, of the tyrosine hydroxylase inhibitor α-methyl-*p*-tyrosine, and of dopamine-β-hydroxylase inhibitors. Furthermore, marked increases in serotonin synthesis in the telencephalon are produced by lesioning the rostral third of LC, a fact consistent with the existence of an LC-MR inhibitory fiber system.

CA = NE + DA are present in varying amounts in all raphe nuclei. Their activity in these areas is found to be of the same order of magnitude as that of tryptophane hydroxylase, an enzyme responsible for the formation of serotonin. Whereas administration of dopamine-β-hydroxylase inhibitor results in over 90% depletion of NE according to recent experiments, 5HT levels are not significantly changed except in raphe magnus (RMg) and MR nuclei, where 5HT concentrations significantly increased. No change is seen in 5HT levels in DR nucleus. This finding would ratify the fact that NE input exerts an inhibitory effect on MR and RMg nuclei.

Other studies demonstrate that 5HT-MR neurons send prominent innervation to LC and that this 5HT input inhibits NE neurons. In effect, destruction of MR system produces a long-lasting stimulation of NE neurons and a significant rise in the LC concentration of tyrosine hydroxylase (see Figure 9).

*2. Neuroanatomical Connections between Noradrenergic and Dopaminergic Systems*

Neurons of LC and non-LC NE systems send and receive axons to and from the two brain stem DA systems: the substantia nigra (SN) = A8 + A9 cell groups, and the ventral tegmental area (VTA) = A10 cell group. Moreover, NE and DA axons frequently converge on the same CNS areas populated by various types of postsynaptic NE and DA receptors. Furthermore, NE terminals have been shown to possess inhibitory DA receptors, while DA terminals possess excitatory $\alpha_2$ adrenoceptors. All these findings show that NE-DA interactions are complex and difficult to determine precisely. This complexity is accentuated by the existence of polysynaptic pathways which permit indirectly exerted influences between both systems.

There are NE terminals in the SN and VTA nuclei (see Figure 9). The NE in the SN seems to exert an excitatory effect, since lesions of NE cell bodies in LC produce increased sensitivity of striatal postsynaptic DA receptors on the operated side (in turning experiments), perhaps due to interruption of NE neurons from LC which normally facilitate the nerve impulse flow in nigrostriatal DA neurons. However, other NE influences exert inhibitory effects on the nigrostriatal system. In effect, lesion of VNB increases nigrostriatal activity. In our opinion, this finding might be due to a direct inhibitory effect by NE axons arising from NE-LC neurons which are facilitatory on the nigrostriatal DA system. With respect to this, it has been shown that lesioning the VNB provokes increase of DA activity in the nucleus accumbens along with reduction of DA activity in the prefrontal cortex. Other experiments show that NE innervation of VTA exerts an inhibitory influence on DA mesolimbic system, as reflected by a decreased DA turnover in the olfactory tubercles after microinjection of NE in the VTA DA area. This apparent inhibitory NE-DA interaction has been suggested in a variety of experimental studies. The NE innervation of VTA region, which exerts an inhibitory influence on DA mesolimbic system, originates in the LC. However, this same LC-VTA NE fiber system has been proven to exert an excitatory influence on DA mesocortical system. This DA system consists of DA neurons located in the median and anterior parts of VTA region whose axons terminate in the deepest layers of the prefrontal cortex. The DA neurons innervating subcortical mesolimbic structures are located in the lateral and posterior parts of VTA (see Figures 9 to 11).

Further experimental studies demonstrate that lesions of VNB produce opposite effects to the above mentioned lesions of NE-LC neurons. In effect, VNB lesions do not decrease prefrontal cortical DA activity but, paradoxically, increase dopamine at this cortical level by as much as 40%. This opposite effect gives rise to the often-suggested hypothesis that LC and non-LC NE systems behave as two opposing NE systems. The fact that cortical prefrontal and mesolimbic subcortical DA systems are able to inhibit each other, through direct and indirect pathways, fits

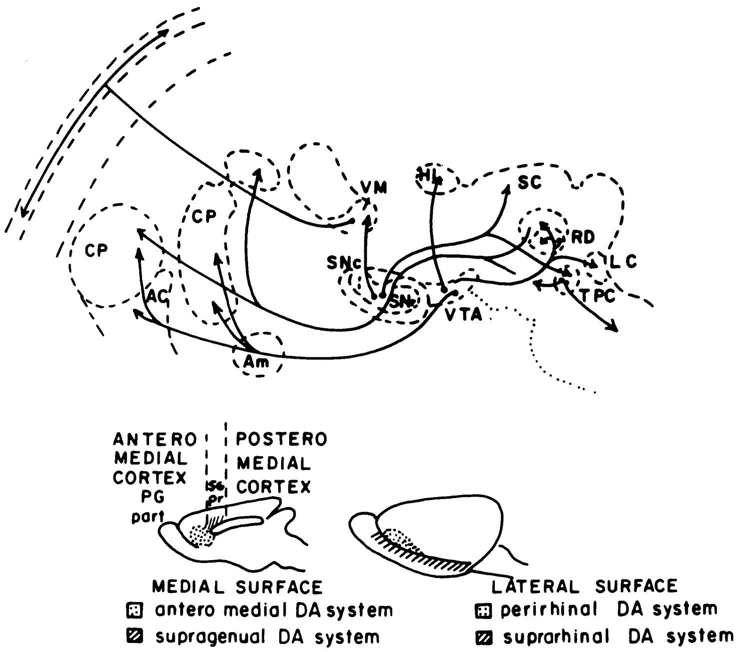


FIGURE 10. Top: diagrammatic representation of the efferent relationships of the pars compacta (SNc), pars reticulata (SNr), and ventral tegmental area (VTA). Bottom: schematic representation of the distribution of the mesocortical DA systems. Not included in the diagram are the DA VTA projections to the prefrontal cortex and entorhinal cortex. AC = nucleus accumbens, LC = locus coeruleus, RD = dorsal raphe, Am = amygdala, CP = caudate putamen, HL = lateral habenular nucleus, SC = superior colliculis, SNc = substantia nigra compacta, and SNr = Substantia nigra reticulata.

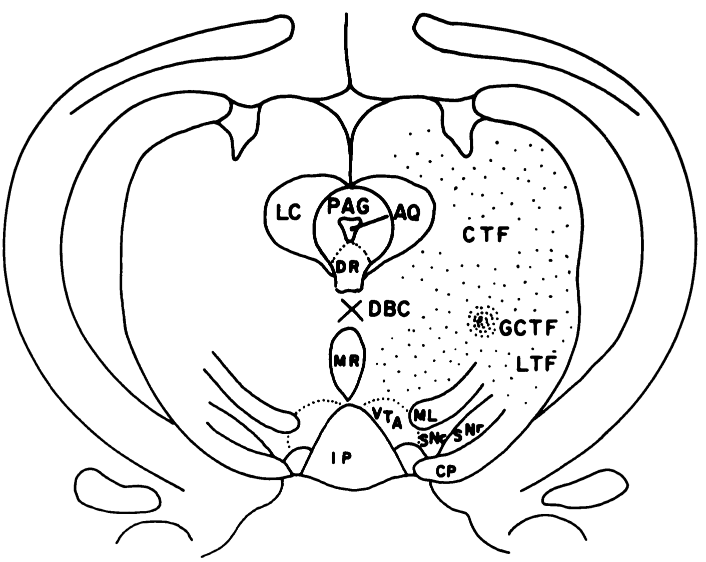


FIGURE 11. Transverse section of the rat brain at the mesencephalic level. LC = locus coeruleus, PAG = periaqueductal gray, AQ = aqueductus, DR = dorsal raphe, DBC = decussatio brachium conjunctive, MR = median raphe, VTA = ventral tegmental area, IP = interpeduncular nucleus, SNc = substantia nigra compacta, SNr = substantia nigra reticulata, CTF = central tegmental field, LTF = lateral tegmental field, GCTF = nucleus giganto cellularis tegmental field, ML = medial lemniscus, and CP = caudate putamen.

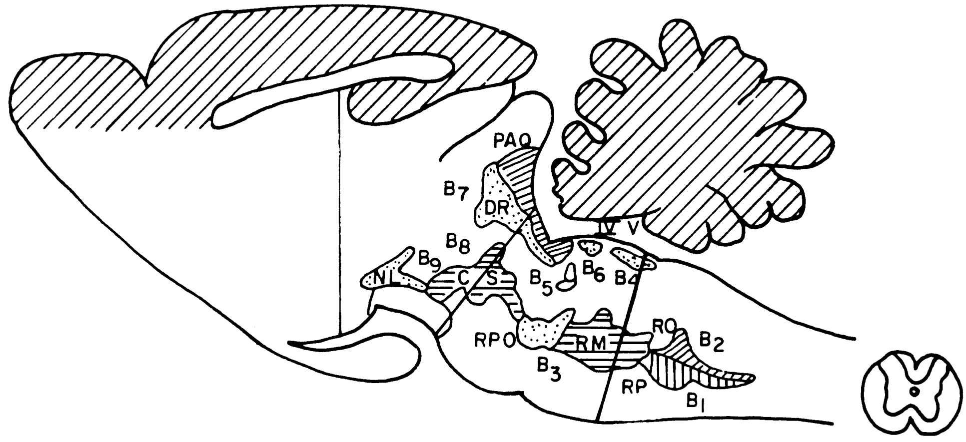


FIGURE 12. Sagittal section of the rat brain showing the dorsoventral and rostrocaudal location of the serotonergic cell groups.

well with the postulation of two opposing DA systems. This matter will be discussed in other chapters.

Many findings show that SN and VTA DA neurons send efferent projections to LC and other NE nuclei located in the brain stem reticular formation, thus giving anatomical support to the above hypothesis postulating the existence of two opposite NE-DA systems. One of them would be constituted by the NE-LC and DA-SN + DA mesocortical, whereas the other, operating antagonistically to the former, would be constituted by the NE-non-LC system and the DA-mesolimbic system (see Figure 9).

## II. THE SEROTONERGIC SYSTEM

The 5HT neurons are grouped in nuclei located along the midline (raphe) of the brain stem. There are two chains of 5HT raphe nuclei, one dorsal, the other ventral. The most rostral nucleus of the former chain is the DR nucleus or B7 cell group. DR limits with the aqueduct and possesses rostral (mesencephalic) and caudal (pontine) parts. The raphe pontine B6 and B5 cell groups and the raphe pontine-medullary B4 cell group constitute the three other 5HT components of the dorsal chain.

The most rostral nucleus of the ventrally located raphe chain is the nucleus linearis (B9 cell group) which is located in the mesencephalon. The nucleus centralis superioris or MR nucleus (B8 cell group) is caudal to the former and possesses a mesencephalic and a pontine part. MR nucleus is ventral to DR and is separated by the decussation of brachii conjunctivi. Caudally to MR are located the pontine nucleus raphe pontis oralis (RPO) and the pontine-medullary RMg nucleus. RPO + RMg constitute the B3 cell group. The medullary raphe obscurus (RO) = B2 and raphe pallidus (RP) = B1 cell groups are the most caudally located 5HT nuclei integrating the ventral 5HT chain (see Figures 11 and 12).

The lateral and dorsal parts of the aqueduct are occupied by 5HT neurons composing the periaqueductal gray system (PAG). Yet another 5HT system has been postulated with neurons located at hypothalamic level.

The mesencephalic and pontine 5HT neurons innervate the anterior regions of the CNS: the telencephalon, diencephalon, and mesolimbic structures, whereas pontine and medullary-5HT neurons innervate pontine, medullary, and spinal structures. PAG-5HT system innervates anterior brain stem and some telencephalic-diencephalic structures. Rostral 5HT nuclei are interconnected with caudal 5HT nuclei (see Figure 13).

DR projects to brain cortex, mainly in the temporoparietal area, as well as to the striatum,

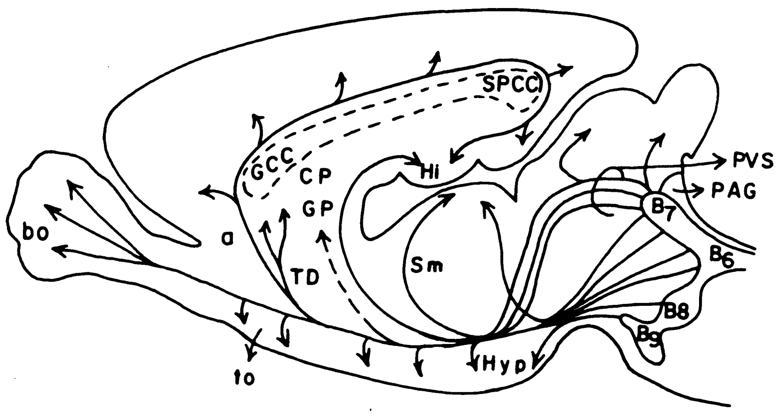


FIGURE 13. Schematic representation of the major organizational features of the ascending 5HT systems of adult rat brain, as revealed by light microscope radioautography after intraventricular administraton of [$^3$H] 5HT. bo = bundle olfactorius, to = tractus opticus, a = nucleus accumbens, GCC = genu corporis callosi, SPCC = splenium corporis callosi, CP = caudate putamen, TD = tractus diagonalis (broca), GP = globus pallidus, Sm = stria medullaris thalami, Hyp = hypothalamus, Hi = hippocampus, PVS = periventricular system, and PAG = periaqueductal gray.

amygdala, nucleus accumbens, lateral septum and hypothalamus (ventromedial mainly). The median eminence, outside the blood brain barrier, is also innervated by DR axons. Some DR axons project to dorsal hippocampus and brain stem reticular formation.

MR projects to brain cortex, mainly the prefrontal, hippocampus, septum, and other mesolimbic structures. The anterior preoptic hypothalamic area is selectively innervated by MR axons. Further, MR innervates brain stem reticular formation and DR nucleus.

The RPO nucleus sends axons to anterior spinal motor neurons and to preganglionic sympathetic neurons located in the IML spinal horn. These 5HT projections exert an excitatory influence in both spinal regions.

A 5HT nucleus which is closely involved in nociceptive functions, the nucleus RMg sends its axons to the spinal cord dorsal horn. This sensory area in turn sends projections to the RMg. All medullary 5HT nuclei send axons to all medullary non-5HT nuclei and to brain stem reticular formation. RMg nucleus sends projections to hypothalamus.

Although PAG-5HT system is preferentially interconnected with brain stem structures, it also interconnects with some mesolimbic and hypothalamic structures (see Figures 12 and 13).

### A. Neuroanatomical Connections between the Different Serotonergic Systems

Although there is no direct projection from DR to MR, the latter sends axons to the former. Since serotonin iontophoretically injected on 5HT DR-perikarya exerts an inhibitory effect on the firing rate of these neurons, the MR to DR fiber system would represent an inhibitory control of MR over DR. There is also evidence of anatomical connections between PAG and DR, PAG and MR, and MR with raphe pontine nuclei (RPO and RMg). Indeed, caudal 5HT nuclei are considered to constitute true relay stations to rostral 5HT nuclei.

One of the best established connections linking 5HT nuclei is the excitatory input of PAG on RMg. Supposedly mediated through glutamate or aspartate fibers, this pathway would be involved in analgesic mechanisms depending on opiates to release PAG activity from a GABA inhibitory neuron (see Figures 9 and 13).

### B. Neuroanatomical Connections between Serotonergic and Noradrenergic Nuclei

It is well established that DR sends axons to LC and receives afferents from LC and non-LC NE nuclei. MR and PAG nuclei also receive afferent projections from NE systems. In turn, MR sends axons to both NE systems. However, 5HT fibers innervating NE-A2 nucleus arise from medullar 5HT nuclei, preferentially (B4 cell group) (see Figures 9 to 11).

Intermingled 5HT and NE axons frequently innervate the same central areas. Both types of terminals possess $\alpha_2$-presynaptic receptors capable of exerting a modulatory effect at those central projection areas (see Figure 9).

**C. Neuroanatomical Connections between Serotonergic and Dopaminergic Nuclei**

The DR is proven to send axons to both SN and VTA. The resulting inhibitory effect would be exerted by serotonin through 5HT receptors located on DA neurons. However, evidence exists that DR bridles only DA neurons of the lateral regions of VTA, sparing DA neurons of the anterior VTA nucleus. Lateral VTA neurons send axons to subcortical mesolimbic structures, while anterior VTA-DA neurons provide axons composing the mesocortical DA fiber system which innervates the deepest layers of the prefrontal cortex.

Both DR and MR 5HT nuclei send axons to VTA DA region. These 5HT fiber systems exert an inhibitory effect on DA mesocortical system. In turn, there are clearly established DA afferents to MR arising from VTA, which give an excitatory input (see Figures 9 to 11).

Abundant evidence demonstrates that MR innervates the SN. Although this 5HT input to SN is inhibitory, it would have a different functional role to that displayed by 5HT input arising from DR. In effect, while the latter 5HT input is associated with punishment behavior, suppression of MR input to SN fails to modify this behavior (see Figure 9).

**D. Neuroanatomical Connections between Serotonergic Nuclei and Brain Stem Reticular Formation**

The nuclei of brain stem reticular formation (BSRF) all contain about the same amount of 5HT. Excitatory and oscillatory as well as inhibitory responses to raphe stimulation have been found in BSRF neurons. However, although BSRF is densely charged with serotonin, there is only a scattered 5HT input to BSRF neurons. Despite the fact that both the sensory and motor cranial nerve nuclei receive 5HT innervation, motor nerve nuclei seem to contain more of the amine than do sensory nuclei.

Evidence suggests that DR receives an important cholinergic input. Since microinjection of acetylcholine in DR induces synchronization, it is logical to assume that this ACh input to DR exerts an inhibitory inflluence (see Figures 9 and 13).

## III. THE DOPAMINERGIC SYSTEM

Two well-defined DA cell groups are found in the mesencephalon: the SN = A8 + A9 cell groups, and the adjacent VTA = A10 cell group. VTA nucleus is medially located and posterior to SN. Pars compacta of the SN = SNc sends axons to the striatum whereas pars reticulata (SNr), besides its striatal axons, sends projections to the thalamus, tectum, and pontomesencephalic tegmentum. Pars compacta (SNc) also sends axons to DR, MR, and hypothalamus, both inside and outside the blood brain barrier (see Figures 10 and 11).

The VTA nucleus sends axons to ventromedial striatum, nucleus accumbens, olfactory tubercles, thalamus, habenula, amygdala, posterior hypothalamus, lateral hypothalamus, anterior hypothalamus, lateral septum, prefrontal cortex, enthorhinal cortex, DR, MR, and LC. It has been found that VTA is composed of two different groups of DA cells, those located in its lateral and posterior regions and those located in the anterior and medial regions. The former group known as DA mesolimbic system, provides the axons which innervate subcortical mesolimbic structures, whereas the second group of cells, the DA mesocortical system, gives rise to axons innervating the prefrontal cortex (see Figure 10).

DA cells are also differentiated according to their electrophysiological characteristics. Thus, mesocortical DA cells possess a much faster firing rate ($9.3 \pm 0.6$ per second) than mesolimbic DA cells ($5.9 \pm 0.5$ per second) and mesostriatal DA cells ($3.1 \pm 0.5$ per second).

Most DA cells of the SN-striatum system receive an inhibitory GABA-afferent loop from the striatum, emanating from DA-innervated area. Such a loop has not been demonstrated for DA cells of VTA region although GABA is present within this VTA area.

DA neurons contain their own transmitter in their dendrites. When dopamine is applied iontophoretically in the vicinity of DA cell bodies, it provokes an inhibition of DA neuronal activity. Evidence suggests that this somatodendritic inhibitory mechanism is more important for DA-VTA neurons than DA-SN neurons. For instance, whereas systemic picrotoxin, a GABA antagonist, reverses the depressant effects of systemic D-amphetamine on DA-A9 impulse flow, it does not reverse this effect on DA-A10 impulse flow. This would indicate that the inhibition of A10 activity may be more strongly influenced by dendritic release of DA, which would stimulate autoreceptors located on the somatodendritic areas. However, if we accept recent evidence that mesocortical DA neurons lack autoreceptors, then inhibitory mechanisms for these neurons would depend on other mechanisms. With respect to this, an effective inhibitory mechanism of further synthesis and release has been found in the reuptake of dopamine by DA terminals in the transmitter released at synaptic level (see Figure 10).

### A. Neuroanatomical Connections between Substantia Nigra and Ventral Tegmental Area Dopaminergic Nuclei

The term SN refers to a complex structure lying immediately dorsal to the cerebral peduncle, composed largely of medium-sized cells of a fairly uniform type. Such cells appear in Nissl material to be more darkly stained and more closely spaced in the dorsal area called SNc, than in the larger subjacent SNr. As demonstrated through histofluorescence, SNc is composed largely, if not entirely, of DA neurons while most but not all SNr cells are not dopaminergic. The same technique reveals that, in the rat at least, SNc = A9 cell group of Dahlström and Fuxe does not have the flat dorsal border traditionally ascribed to it, but instead emits a pair of large dorsal excrescences lacking the dense cell packing of SNc. The larger medial one of these protruding cell masses, dopamine cell group A10, extends dorsomedially into the VTA, while the smaller, more caudal and lateral extrusion, dopamine cell group A8, invades a ventrolateral region near the SN caudal pole. At caudal levels of the SN, cell groups A10 and A8 are interconnected by an irregular array of cells that extends transversely over the dorsal border of the medial lemniscus; many of these cells synthetize dopamine (supralemniscal cell group, retrorubral nucleus) (see Figure 10).

DA-VTA cells send axons to the ipsilateral SN through which they are distributed over the entire rostrocaudal extent of SNc, and in lesser number to the most dorsal zone of SNr. This rather homogenous distribution suggests a termination of VTA efferents in contact with either somata of compacta neurons, or compacta dendrites oriented parallel to the dorsal border of SN (see Figures 9 and 10).

### B. Neuroanatomical Connections between Dopaminergic and Noradrenergic Brain Stem Nuclei

VTA but not SN sends axons to LC; however, LC sends axons to both SN and VTA-DA nuclei. There is evidence showing that the VNB which collects axons from non-LC NE neurons, preferentially, innervates VTA. On the other hand, the DA-A10 cells (VTA) send projections to both types of NE nuclei (coeruleus and noncoeruleus).

Interactions between NE and DA systems are complex and both cooperation and antagonism can be observed. This phenomenon is found not only at cell body level but also at terminal level (see Figure 9).

### C. Neuroanatomical Connections between Dopaminergic and Serotonergic Brain Stem Nuclei

SNc sends efferents to both DR and MR-5HT nuclei. The SNc projections exert an inhibitory influence on 5HT neurons. In turn, both 5HT nuclei inhibit SNc-DA neurons through DR and

MR efferents. Similarly, DA-A10 cell group interchanges axons with DR and MR-5HT neurons and, again in these cases, DA and 5HT influences are inhibitory. There is also strong evidence showing that DR projects to and inhibits mesolimbic DA cells, while MR projects to and inhibits mesocortical DA cells (see Figure 9).

## IV. THE CHOLINERGIC SYSTEM

Cholinergic neurons are so widely diffused throughout the CNS that it is difficult, if not impossible, to group these dispersed neurons into one or several systems functioning as units. An attempt to transfer to the CNS the peripheral autonomic model of two sides, one sympathetic and the other parasympathetic, according to the corresponding norepinephrine or acetylcholine neurotransmitters, is fruitless because the activity of certain central cholinergic pathways may lead to peripheral sympathetic hyperactivity, while the activity of some central catecholaminergic pathways may lead to reduced peripheral sympathetic activity and consequently predominance of the peripheral parasympathetic system. Despite such objections, there are sufficient experimental findings to document concrete proposals concerning the existence of central cholinergic pathways. We mention here the most significant results of such research.

Injection of physostigmine, a cholinesterase inhibitor, either i.v. or into the cerebral ventricles (icv) and specific brain regions, evokes a centrally mediated rise in arterial blood pressure. This response requires functional brain acetylcholinesterase and brain acetylcholine (ACh). The blood pressure rise is mediated peripherally through an increase of sympathetic activity. The icv injection of various ACh agonists in dogs and rats, or into specific brain areas of rats, also raises blood pressure. Recent evidence from several laboratories suggests that brain ACh is involved in the elevated blood pressure observed in spontaneous hypertensive rats. Moreover, cholinergic substances also appear to influence spinal autonomic mechanisms and sympathetic reflexes.

Electrical stimulation of pontine NE cell nucleus, LC, increases the turnover of peripheral norepinephrine via the sympathetic system. For this reason it has been suggested that LC acts as a sympathetic nucleus situated in the brain with extensive parts of the CNS as its target regions. The LC receives rich ACh input and the activity of NE-LC cells is enhanced by microinjection of ACh agonists.

The posterior hypothalamus appears to be an intermediate link in the neural pathway mediating sympathetic responses to LC stimulation since destruction of posterior hypothalamus significantly inhibits such sympathetic responses. Further, LC has been shown to be a major source of NE innervation of the posterior hypothalamus. Superfusion of this area with ACh and carbachol (an ACh agonist) induces increased peripheral sympathetic activity.

Stimulation of the so-called medullary reticular pressor area with nicotinic but not with muscarinic agonists provokes increased peripheral sympathetic activity. The lateral reticular nucleus is the area of medullary reticular formation most related to sympathetic activation.

Besides the above central areas in which cholinergic mechanisms are associated with vasopressor responses and thus with peripheral sympathetic hyperactivity, there are other central regions in which cholinergic mechanisms elicit vasodepressor responses supposedly mediated through reduction in peripheral sympathetic activity. For example, while ACh agonists evoke hypertensive response when injected in posterior hypothalamus, injections of these agents into dorsomedial and anterior hypothalamus of rats result in hypotension. Similarly, areas of medullary reticular formation such as the nucleus tractus solitarius (NTS) and paramedian reticular formation behave as vasodepressor regions when stimulated with ACh agonists.

The NTS is the primary termination site of afferent fibers of cranial nerves IX and X including those arising from arterial and cardiopulmonary mechanoreceptors (see Figures 14 and 15). As such, NTS plays a critical role in integrating the cardiovascular reflexes arising from those

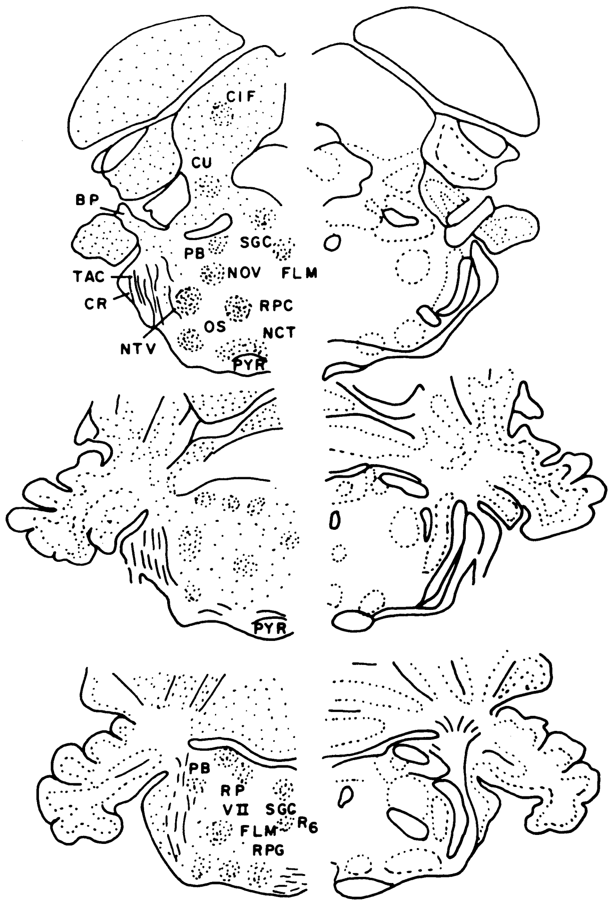


FIGURE 14. Coronal sections (transverse sections) of adult rat brain at 3 different levels (pontis and medullary). CIF = collicular inferior, CU = area cuneiformes, BP = brachium pontis, SGC = striatum griseum centrale, NOV = nucleus originis nervi trigemini, FLM = fasciculus longitudinalis medialis, RPC = nucleus reticularis pontis caudalis, OS = oliva superior, NTV = nucleus terminationis nervi trigemini, NCT = nucleus corpus trapezoides, Pyr = pyramidis, RG = nucleus reticularis gigantocellularis, RPG = nucleus reticularis giganto paracellularis, and V II = nervus fascialis.

receptors. Injections of ACh lower blood pressure and heart rate, depending where the injection is applied. This cardiovascular response is elicited from the intermediate one third of NTS, termination site of baroreceptor afferents. A pressor response has been observed after injections outside the NTS. Such findings suggest that activation of different populations of neurons produces differing cardiovascular responses.

Hypotensive response to ACh is blocked by administration of ACh antagonists such as atropine, but not hexamethonium. This observation itself implies that the action of ACh agonists released in NTS results directly from activation of cholinergic muscarinic receptors, not cholinergic nicotinic receptors.

As implied by the conflicting responses to centrally administered ACh mentioned earlier, cholinergic systems elsewhere in the CNS may have opposite effects on the peripheral autonomic nervous system. Sympathetic activity arises following activation of cholinergic mechanisms in posterior hypothalamus, lateral reticular formation, and poorly defined areas

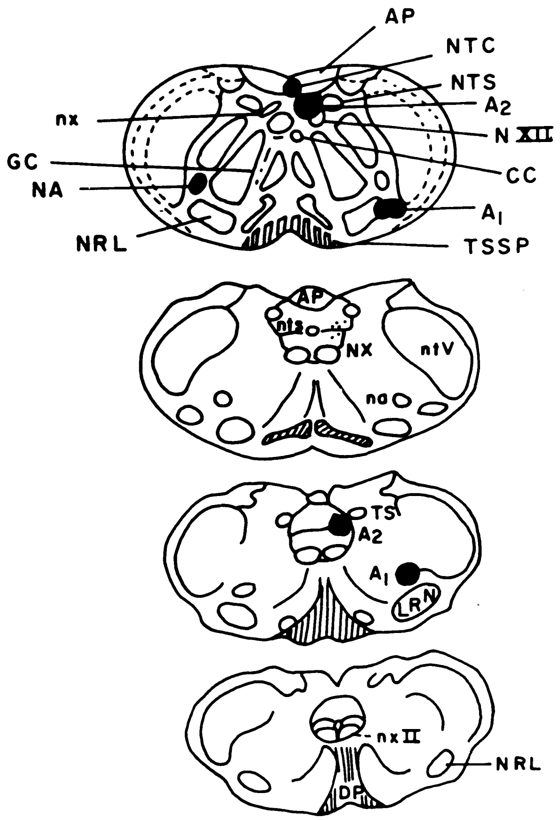


FIGURE 15. Sections at different levels of the rat brain stem from 0.6 mm of the spinal cord-medulla border (bottom) until 2 mm of the spinal cord-medulla border (top). AP = area postrema, NTC = nucleus tractus commisuralis, NTS = nucleus tractus solitarii, NX = nucleus originis dorsalis vagi, nx II = nucleus originis nervi hypoglossi, CC = central canal, NA = nucleus ambiguus, NRL = nucleus reticularis lateralis, DP = decussatio pyramidis, ntV = nucleus of the spinal tract of the trigeminal nerve, TS = tractus solitarius, and GC = nucleus reticularis giganto cellularis.

around the fourth ventricle. On the other hand, sympathetic activity declines upon activation of cholinergic mechanisms in some other hypothalamic areas and some paramedian reticular medullary areas.

In order to explain the existence of opposing central ACh mechanisms, we suggest that these paradoxical effects would depend on the postsynaptic neuron being activated by the cholinergic neuron. Hence, activation of sympathetic preganglionic neurons, which are cholinergic in nature, results in peripheral sympathetic hyperactivity, while activation of parasympathetic preganglionic neurons, also cholinergic like the parasympathetic postganglionic neurons, results in a diminished peripheral sympathetic activity and in peripheral parasympathetic predominance.

Cholinergic neurons are widely disseminated in most CNS structures: the cerebral cortex, hippocampus, striatum, septum, hypothalamus, and other brain areas (see Figures 14 and 15). All these cholinergic interneurons receive heavy input from ACh system disseminated along the BSRF. The BSRF projects to cholinergic preganglionic sympathetic and parasympathetic neurons. In turn, preganglionic neurons make contact with and stimulate postganglionic sympathetic and parasympathetic neurons, respectively.

One of the most thoroughly studied cholinergic projections in the CNS emanates from the septum to the hippocampal formation. This septal-hippocampal pathway has been related to analepsis. In effect, activation of this pathway increases EEG synchrony and theta activity in the hippocampus.

There is also evidence that BSRF activates cerebral cortex cholinergic interactions. It is probable that ACh is indeed the final mediator at the cerebral cortex level, responsible for behavioral and EEG arousal subsequent to BSRF activation.

Although it is now widely accepted that ACh may be a synaptic transmitter in the cerebral cortex, its precise role has not been clearly defined and pathways which mediate impulses via cholinergic synapses have as yet not been identified. A number of studies suggest that cholinergic cortical endings transmit input from mesencephalic reticular formation to cortex. Systemic application of ACh produces behavioral and EEG arousal similar to that elicited by electrical stimulation of BSRF. In contrast, systemically applied atropine induces slow waves in EEG and increases the threshold for EEG stimulation, probably by acting not only on BSRF but also on the cortex. The hypothesis that ACh participates in cortical arousal is supported by numerous investigations showing that the ACh release rate from the cortical surface increases during spontaneous or induced periods of alertness and EEG desynchronization. Furthermore, histochemical studies have demonstrated that ACh-esterase-containing fiber systems to the cortex probably arise in various subcortical structures which may serve as relayers for the BSRF activating system.

The effect of ACh on single neurons in the cerebral cortex has been studied using multibarreled micropipettes. These studies show two kinds of responses depending on the cortical area investigated. In the visual cortex, for instance, an excitatory response is observed which mimics the excitatory effect of stimulating BSRF. On the other hand, prominent depressant effects of ACh are observed on neurons in the pericruciate cortex and other cortical areas. In theses studies strychnine and muscarinic and nicotinic cholinolytics were found to block depressant effects produced both by ACh and by synaptic stimulation of cortical surface, pyramidal tract, lateral hypothalamus, and BSRF. Hence, ACh is postulated as a transmitter for those inhibitory cortical interneurons involved in responses. Effects of reticular stimulation on single neurons of the pericruciate cortex have been reported variously to be predominantly inhibitory, excitatory or mixed.

Although ACh neurons are spread widely along BSRF, they are also found in some groups of nuclei, i.e., nucleus reticularis lateralis (NRL), nucleus reticularis pontis caudalis (RPC), and nucleus gigantocellularis (NGC). BSRF cells receive diffuse endings from the various NE, 5HT, and DA brain stem nuclei (see Figures 14 and 15). In turn, BSRF cells send axons to those monoaminergic nuclei. The two pontine reticular nuclei, RPC and GC, receive afferent projections only within or caudally to the pons medulla; they receive no afferents from structures rostral to the pons. Such afferent cholinergic projections are compatible with the proposal that both RPC and GC nuclei may serve as connections within the brain stem for an ascending system. In addition, two cholinergic nuclei send efferent projections to brain stem 5HT raphe nuclei, from which they receive afferent projections.

BSRF cells have extensive ascending and descending projections. Golgi studies in rodents indicate that a considerable number of reticular neurons give off an axon which dichotomizes and has a long ascending branch and a long descending branch. The number of reticular cells with ascending projections diminishes towards the caudal area. The relative sparsity of reticular projetions ascending from medulla oblongata to midbrain or beyond in rats is in keeping with data on mammals (see Figures 11, 14, and 15)

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