Chemical Transmission in the Brain: The Role of Amines, Amino Acids and Peptides

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published in
Progress in Brain Research
1982

Preface

In the stately headquarters of the Royal Netherlands Academy of Sciences, located in the heart of Amsterdam, where the 12th International Summer School of Brain Research on Chemical Transmission in the Brain was held in 1981, it was relatively easy to let one's mind wander back to the 1901 meeting in Paris, of the International Association of Academies, where the anatomist Wilhelm His proposed that research into the nervous system should be placed on an international footing. Three years later this suggestion resulted in the formation of the International Academies Committee and, another five years later, in the foundation of the Netherlands Central Institute of Brain Research. This was the first in a series of similar institutes that were soon to form a worldwide chain. Shortly after its installation, the committee pointed out that "the time is not far distant when the study of the millions of brain cells will have to be divided amongst researchers in the way astronomers have been obliged to divide the millions of stars into various groups".

Eighty years later, astronomy is still far ahead. Human brains have meanwhile developed the technology for launching into space sophisticated satellites for telecommunication, still without any knowledge of the chemical compounds and mechanisms that these same brains are using for their *own* internal intercommunication. Our ignorance about the latter topic is gradually diminishing nowadays by the rapidly increasing number of substances that are found to take part in the process of neurotransmission. Following in the footsteps of the classical biogenic amines, and a growing list of amino acids, an increasing number of peptides are now thought to be involved in neurotransmission. Historically, only acetylcholine was considered as a "true neurotransmitter", although this has only been proved unequivocally for the neuromuscular junction, and not for the the central nervous system. The monoamines (and centainly the peptides) are approached more cautiously by naming them "neuromodulators", although nobody knows exactly (or everybody has his own ideas about) what is meant by this term.

From the finding of all these new substances it is becoming more and more clear that the brain is built with an enormous diversity of neurons and networks. The lateral septum, for example, receives inputs from a wide variety of brain structures, each of which has neurons containing specific neurotransmitters: dopamine-, noradrenaline- and serotonin-containing fibers originating from the brain stem; vasopressin, somatostatin, LH-RH, α-MSH and TRH fibers are derived from the hypothalamus; glutamate from the hippocampus and GABA, substance P or enkephalin fibers from interneurons or other as yet unknown sources.

What message lies concealed in the enormous diversity of transmitters? Is this diversity meant to enable a neuron to discriminate among the various inputs it receives simultaneously? If so, a neuron must have some means of discriminating among the various transmitters that act on its cell body or processes. In addition to the diversity in the site on the neuron where the input is received, also the binding of the transmitter to its receptor can be "translated" in various ways, not only by different influences on the membrane properties, but also via indirect mechanisms, such as adenylate or guanylate cyclase, which influence membrane properties via protein kinases. Another possible difference is the route via which the transmitter might reach the neuron; this is supposed to take place either via a highly controlled synaptic release, or via a diffusion from fiber varicosities or the bloodstream and to distant receptors.

The necessity emerges of a detailed description of the anatomy of the various transmitter systems, where they come from, what their target structures are, and what can be derived about their possible function in the brain. One could also wonder whether the fact that the same transmitter is released in the brain and into the bloodstream would mean that the central and peripheral (endocrine) actions are coupled. These are the issues in the first part of the book.

Another important aspect of these neurotransmitters is the question of the mechanisms by which their release is controlled, how and where they are released, what the probabilities and possibilities are for non-synaptic release, how general dendritic release is, and what the morphology of the structures involved in release is. These are the questions that are dealt with in the second part of the book.

The issue of the third part of the book is the action of these transmitters after they have been released and the possible role of glial cells in this process. The binding to receptors is described, and what will be the result, depending on site and binding properties, in biochemical and electrical changes of the membrane. Techniques which can visualize the influence of neurotransmitters in local brain activity are currently applicable to patients and will probably cause a major improvement in our knowledge on the functioning of the human brain in the near future. Another central question in this section of the book is whether peptides can be considered as modulators of the "superior" functions of the classical transmitters — the amines and amino acids — or even the reverse might be true; probably it will appear that all three groups are similarly effective and important. Finally, one might find an answer to the question if the mammalian brain is too complicated to allow a fundamental study of transmitter actions, and if we shall have to look for more simple systems, or whether comparative neurobiologists have in fact already solved questions that are asked by the mammalian neurobiologists.

Ultimately, stimuli from the periphery, body and brain result in an integrated neuronal response and so, in changes in transmitter release. Consequently, information about how an imbalance of certain transmitters becomes expressed in changed behavioral output is another way of gaining an insight into a function of such transmitter systems under normal conditions. As usual, the clinic does not wait until a full understanding of fundamental mechanisms has been accomplished, but supplies information itself. Thus, an answer can be found if administration of transmitters or analogues indeed compensates a paucity of endogenous substances, e.g. in mental disease and, if so, for what reasons then do we have neurons that are supposed to integrate information. A recent alternative for substitution of transmitters, viz. transplantation of neuronal systems, is also dealt with in the final part of this book.

Around these topics this Summer School was organized, in an attempt not so much to answer the question whether one ought to call a substance a neuromodulator, but rather to gain a better insight into the similarities and differences among the three types of transmitters, i.e. amines, amino acids and peptides, with respect to their distribution, release, action and function. Thus, a start has been made, on the basis of a comparison of the many different properties of these substances, towards a better understanding of the questions that we have to ask ourselves about our brain.

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Amsterdam, December, 1981