RESEARCH ON DOPAMINE IN THE BRAIN: PAST, PRESENT AND FUTURE

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The number of nerve cells in the human brain is not exactly known but is estimated to be between ten and one hundred billion, that is a number exceeding the total population on this planet. Each nerve cell is in close contact with as many as thousands of other nerve cells. A fundamental problem is how the nerve cells communicate with each other. For a long time, and as late as 1960, most workers in brain research favored the view that this communication was purely electrical. Thus, just as the propagation of a nerve impulse along a nerve fiber occurs by means of electrical changes in the cell membrane, the signal transfer from one nerve cell to another was believed to be of electrical nature. This view has been dramatically changed during the last few decades. It is now generally accepted that the transfer of signals between nerve cells takes place by means of chemical substances, called neurotransmitters, which are released from the nerve endings and travel across narrow spaces to reach other nerve cells.

Research on the mode of action of the antipsychotic and antidepressant drugs, which were introduced in the 1950s, has contributed decisively to this paradigm shift. At about the same time as the introduction of these drugs European and American pharmacologists discovered the occurrence of small amounts of a number of physiologically highly active organic bases in the brain, that is the two catecholamines noradrenaline and adrenaline, and the indoleamine serotonin. Noradrenaline and adrenaline were known at this time as neurotransmitters and hormones in peripheral tissues of the body. Such a role for serotonin was not known at this time, but this substance started to attract attention following the discovery by European and American scientists that its action on peripheral organs could be antagonized by the powerful hallucinogenic agent LSD. Soon afterwards an American biochemist, the late Dr.Bernard B.Brodie, together with his colleagues discovered that the stores of serotonin in the brain and other tissues were dramatically emptied by treatment with the antipsychotic agent reserpine. This was a breakthrough by bridging the gap between neurochemistry and brain function.

I had the privilege to spend a sabbatical half-year in Dr.Brodie's laboratory in 1955-56, shortly after this discovery. I was generously introduced into the techniques recently developed in his laboratory. After returning back to Sweden I discovered, together with the late Dr.Nils-Åke Hillarp and other colleagues, that reserpine caused similar depletion of noradrenaline and adrenaline as of serotonin stores. Moreover, we could demonstrate that the most striking behavioral actions of reserpine could be linked to catecholamines rather than serotonin. Thus we found in 1957 that L-DOPA, which is a precursor of the catecholamines, could reverse the behavioral actions of reserpine and that this was due to the formation of an amine, which however,

could not be noradrenaline or adrenaline, because they did not accumulate in the brain following L-DOPA treatment. The responsible amine turned out to be dopamine, which at that time was regarded as a poorly active substance, serving merely as an intermediate in the biosynthesis of noradrenaline and adrenaline.

Moreover, in 1958-59 we discovered that dopamine occurs in the brain in much more than precursor quantities, that it was brought to disappear by reserpine treatment, and that it had a peculiar distribution in the brain, with by far the highest amounts in the basal ganglia, All this convinced us that dopamine is to be looked upon as an agonist in its own right rather than just a precursor. Furthemore, its occurrence in the basal ganglia suggested a role in motor functions. Since at that time reserpine had been found to be able to induce in patients a syndrome closely resembling Parkinson's disease, i.e. a serious and not uncommon disorder of the motor system, we proposed that this syndrome could be due to dopamine deficiency. A few years later this was confirmed in analyses of brains from deceased Parkinson patients by Dr.Oleh Hornykiewicz in Austria. Further work along this line led to the introduction of L-DOPA and other dopamine agonists in the treatment of Parkinson's disease. This treatment has dramatically improved the life quality and longevity of these patients.

These observations made me and my colleagues strong believers in neurohumoral transmission not only in the peripheral nervous system but also in the brain, but our views did not gain much acceptance to start with. However, this reluctance was largely overcome by the demonstration by our group that dopamine, and also noradrenaline and serotonin, occur in nerve cells and nerve fibers in the brain, where they show the same intraneuronal distribution pattern as in the peripheral nervous system. Here Dr.Hillarp played a decisive role by developing a method, by means of which these amines can be visualized histologically in the fluorescence microscope.

Subsequent work in our laboratory led to the conclusion that catecholamines and notably dopamine play an important role in the action of the major antipsychotic drugs, e.g. chlorpromazine and haloperidol. These remedies were found to stimulate the turnover of the catecholamines, and we proposed that this action was due to the activation of a feedback mechanism induced by blockade of so-called receptors, that is specific protein molecules mediating the signal transfer by being able to bind neurotransmitter molecules with high affinity. These observations formed the basis for the so-called dopamine hypothesis of schizophrenia, which has since then played a major role in schizophrenia research.

Pathophysiological and therapeutic strategies in schizophrenia are still largely

guided by the dopamine hypothesis. However, this hypothesis rests almost entirely on pharmacological evidence. Moreover, a fairly large percentage of schizophrenic patients are resistant to conventional treatment with dopamine-receptor antagonists. This may indicate that some patients have a different type of schizophrenia, where dopamine plays a less strategic role.

In recent work we have focused on the interaction between dopamine and other neurotransmitters, aiming to reach a deeper understanding of the mechanisms underlying higher brain functions. These studies emphasize the role of the neurotransmitter glutamate, although several other neurotransmitters, e.g. noradrenaline, serotonin and gamma-aminobutyric acid also seem to be critically involved in these interactions. These investigations open up new perspectives for the development of new remedies in psychotic conditions.

Recent postmortem observations in our laboratory support the view that schizophrenia is biochemically heterogenous. Different patterns of monoaminergic aberrations suggest the existence of two or more pathogenetic mechanisms. These aberrations encompass all the major monoamines. For example, elevations of 5-S-cysteinyl catechol adducts, i.e. a new class of catechol metabolites discovered by our group, suggest that so-called autoxidation may be enhanced, at least in a subgroup of chronic schizophrenics. This could lead to the formation of toxic catechol metabolites. Serotonergic precursor and metabolite levels may be either elevated or reduced in different subgroups, suggesting aberrations in serotonin turnover. Some of the date suggest that the primary disturbance is located outside the dopaminergic system, at least in a subgroup of schizophrenic patients.

Glutamate may be deficient and glutamate agonists therapeutically active in some cases of schizophrenia. However, more direct evidence is needed to support a "glutamate hypothesis of schizophrenia".

Research centered around dopamine and other neurotransmitters has made considerable progress in recent years and led to a deeper understanding both of normal brain function and of the mechanisms underlying a variety of mental and motor disorders. This in turn has opened up new avenues for successful treatment strategies. Future research in this area can benefit from the virtually explosive development of powerful new techniques, encompassing molecular biology, a variety of advanced neurophysiological, neurochemical and pharmacological methodologies, medicinal chemistry, modern imaging technology, and other computer-derived methods for data analysis.