Transmitter Biochemistry of Human Brain Tissue

Edited by
Peter Riederer
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TRANSMITTER BIOCHEMISTRY OF HUMAN BRAIN TISSUE

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Preface

Research using human post-mortem brain tissue is performed in a number of scientific centers in the world; many find such research not only necessary but also invaluable to answer questions not only of basic neurochemistry but also of applied biochemistry, biochemical pharmacology and drug treatment.

The possibilities and limitations of neurochemical research using human brain tissue have not been discussed previously *in extenso*; a number of questions are still unresolved. Although there has recently been a 'Workshop on Dissection of Human Brain Tissue' (Vienna, 1979), a conference where research groups working in the fields of neurochemistry and pharmacology of the human brain exchanged results and techniques had not been organized prior to the 1980 CINP Congress in Göteborg, Sweden. At that meeting, there was a Symposium on Transmitter Biochemistry of Human Brain Tissue, with discussion extended to the molecular level for diseases of the central nervous system.

Methods are discussed in this volume for biochemical analyses using post-mortem brain tissue, including how subcellular fractions (mitochondria, synaptosomes, membranes, etc.) behave in unfrozen tissue in comparison to frozen tissue and how post-mortem time, age, disease, therapy, preparation of homogenates, storage conditions, etc. influence results. Such methodological questions need to be discussed in the light of comparison between neuropathology and neurochemistry. Studies on uptake, release and receptor binding are also covered. Comparisons are made of data obtained with human brain tissue with data from animal experiments.

Animal models have their limitations in simulating psychiatric and neurological disorders; studies on schizophrenia, Parkinson's Disease, Huntington's Disease, senile dementia of Alzheimer's type, and problems of the aging brain contribute to a better understanding of the underlying pathomechanisms of such disorders and may help in developing new therapeutic strategies.

This interchange of ideas and experience by international experts allows us to take stock of knowledge on the neurochemistry of human brain tissue. We hope this important information will stimulate basic research as well as applied pharmacology.

It is now 20 years since, as a consequence of analyses of human brain tissue, a therapy was found for a neurological disease: L-Dopa therapy for Parkinson's Disease. We are happy that Dr Birkmayer and Dr Hornykiewicz, both responsible for opening this door to human brain biochemistry and pharmacology, have accepted our invitation to contribute to this Symposium.

Peter Riederer, Earl Usdin

Abbreviations

ACE, angiotensin converting enzyme
ADTN, 2-amino-6, 7-dihydroxy-1, 2,3,4-tetrahydronaphthalene
AMP, adenosine monophosphate
ATD, Alzheimer's-type dementia
ATPase, adenosine triphosphatase
BBB, blood–brain barrier
BGP, brain gastric peptide
CA, catecholamine(s)
cAMP, cyclic AMP
CAT, choline acetyltransferase
CBF, cerebral blood flow
CCK, cholecystokinin
CNS, central nervous system
COMT, catechol *O*-methyltransferase
CSF *or* c.s.f., cerebrospinal fluid
DA, dopamine
DBH, dopamine β-hydroxylase
DHEC, dihydroergocryptine
DNA, deoxyribonucleic acid
Dopa *or* dopa *or* DOPA, dihydroxyphenylalanine
DOPAC, dihydroxyphenylacetic acid
EDTA, ethylenediamine tetraacetic acid
GABA, γ-aminobutyric acid
GABA-T, GABA transaminase
GAD, glutamic acid decarboxylase
GC, gas chromatography
GRH, gonadotropin-releasing hormone
H.D., Huntington's Disease
5-HIAA, 5-hydroxyindole acetic acid
HPLC, high performance (*or* pressure) liquid chromatography
^{3}HSP, ^{3}H-spiroperidol
5-HT *or* HT, serotonin
5-HTP, 5-hydroxytryptophan
HVA, homovanillic acid
KYN, kynurenine
MAO, monoamine oxidase
MC, magnocellular
met, methionine
MHPG, 3-methoxy-4-hydroxyphenylalanine
NA, noradrenaline (*or* norepinephrine)
NM, normetanephrine
NTR, neurotransmitter receptor
pat., patients
PC, parvocellular
rCBF, regional CBF
RN, red nucleus
RNA, ribonucleic acid
SN, substantia nigra
TH, tyrosine hydroxylase
TRP, tryptophan
TRP-OH, TRP hydroxylase
TYR, tyrosine
TYR-OH, TYR hydroxylase
VAL, valine
VIP, vasoactive intestinal polypeptide

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Section I
Behavior and Biochemistry: An Introductory Essay

Behavior and Biochemistry: An Introductory Essay

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It is questionable whether someone with next-to-no understanding of the content of this book should be permitted to write its preface. I can only justify this introduction by saying that one can well estimate the importance of a new research field and its results if one is able to assess the gap in our present knowledge which they help to bridge.

Many neurophysiologists and behaviorists underestimate the width of the abyss which lies between our knowledge of behavior and its underlying neurophysiology. Even if one believes in the outmoded idea that the "reflex" is the basic element of all animal and human behavior, and even if one thinks that "the nervous system of animals is nothing else but an organ for the processing and transport of information" (Neureiter, 1974) a tremendious cleft still remains between the action of a single neural element and the behavior of the whole organism. We have learnt from Erich von Holst, Kenneth Roeder and others that the neuron itself, indeed even an axon, has a complex and comprehensive inventory of spontaneous behavior. We know, too, that the reaction of an effector cell to a stimulus is described not by a single impulse but by a modulation of the frequency of continuously and spontaneously emitted impulses. As there is so much complexity at even this "simple" level, the gap between the behavior of an organism and that of its constituent elements appears much greater. Thus the research strategy of our best neuroethologists (such as F. Huber, and W.Heiligenberg) is to study relatively simple behavior in relatively simple organisms. The gap between our present understanding of elementary neuronal and sensory functions and our ability to interpret animal and human behavior is tremendous, but it must be emphasized that it can, in principle, be bridged by the knowledge of the functions of elements and of the s t r u c t u r e s into which they are combined.

There is, however, another "hiatus" - as Nicolai Hartmann has described it. It is the inability, in our present way of thinking to overcome the basic problem of the body-mind relationship. This is in principle insoluble since the relationship between the physiological and the subjective event is, as expressed by Max Hartmann, alogical. We know that some physiological processes are generally accompanied by certain subjective phenomena, while other such processes are not consciously experienced. This relation of the physiological with the subjective is not correlated with the complexity of the process. Some simple events, such as the inflammation of tooth-pulp, have an intense subjective parallel, while some highly complex phenomena, for example computations performed by our Gestalt perception, are not only unconscious but not even accessible to introspection. Thus the old idea that simple neurosensory processes are "merely" physiological, while higher, more complex events are better explained psychologically (found in the otherwise excellent animal psychology textbook by Hempelmann) is totally false.

Provided one assumes the inherent insolubility of the body-mind problem, there are three possible attitudes that can be taken with regard to it. Firstly, one may assume a reciprocal interaction between the physiological processes and the concomittant subjected experiences. This I refuse to accept because it postulates a non-physical causation of physical events. The second assumption is that a prestabilized harmony or a parallel exists between psychological and physiological events. There are, however, limitations to "psycho-physiological parallels", since there are so very many neuro-physiological functions which do not have any subjective parallels. The third assumption is that body and mind are only two different aspects of the same reality, each defined by a different cognitive apparatus of our brain. This "identity doctrine" meets the same difficulties as that of parallelism. There is no doubt that only a few particular neurological events are accompanied by objective phenomena. They rise above the threshold of our consciousness as does the tip of an iceberg, while its greater part remains below the surface.

In spite of this difficulty I adhere to it for the simple reason that the cognitive structures of every normal human being are dictating it. When I assert that my fried B.is sitting beside me, I mean neither the presence of his physical system accessible to physiological research, nor do I mean the unity of all his undisputed mind and his subjective phenomena, so similar to my own. What I mean is quite exactly the unity of both.

One can step aside from this problem by neglecting subjective reaction and by examining only objectively measurable animal behavior. This is the approach of the large American school of behaviorism. This narrowing of interest is justifiable when studying either simple organisms or specific and relatively simple learning mechanisms. However, in the case of man and the higher animals this exclusion of subjective experience is the greatest sin in our search for truth: as it means the refusal to accept perfectly accessible knowledge.

If one is convinced of the fundamental unity of the organisms, then it is justifiable to correlate qualitative experience with neurophysiological action. Of course, the reverse is not necessarily true. But every experience, even the most transient dream, correlates with a physiological event. There are no miracles! Even when this assertion is more religious than scientific it is nevertheless the basis of the scientific study of man.

Thus it is perhaps justifiable to say that the nervous system is more than just an organ for the processing and transport of information. Indeed, since "I" am my own nervous system, I contradict with greatest possible assurance the statement that I am "nothing else but an information processing and transport system".

Both complex and basic processes of our brain are accompanied by subjective experience. Indeed, regulatory processes occuring in the brain are able to influence our psyche to a great extent. This is important in relation to this publication, as without the observation of subjective phenomena (so despised by behaviorists) it would hardly have been possible to have advanced so far in our understanding of the biochemical function of the brain stem. It raises our confidence in that such observation of subjective phenomena may be a reliable indicator of the excess as well as of the deficiency of certain biochemical transmitter substances, in particular in brain stem regions. The importance of this has been illustrated by the fact that through such observations and subsequent research it has been possible to correct abnormally functioning regulatory mechanisms by chemotherapy.

If it is at all possible to bridge the gap between biochemical function and behavior, then the work on transmitter abnormalities in the brain stem will be seen to be a vital contribution.