RECENT TRENDS IN NEUROCHEMISTRY

By

G. P. TALWAR

All-India Institute of Medical Sciences, New Delhi

When Prof. Arora asked me to present the "Recent trends in Neurochemistry" in a span of 10 minutes, I felt faced with a Herculian task. I will not claim to do justice the many developments in the vast field of neurochemistry, but will confine my remarks to a few observations.

First of all we notice that a very evident fact, that of the morphological heterogenity of the brain, is being translated consciously on a biochemical level. Attempts have been made to decipher the differential chemial architecture of the various areas of the brain. Such studies, though unsuccessful so far, intend to chracterise the specific function of different regions in terms of their peculiar chemical make-up. The concentration of various neurohumours has been reported to be different in different areas of the brain, as established by the work of Feldberg, Marthe Vogt, Macleans & others. Similarly the activity of several enzymes is not alike in all areas of the brain. We will be presenting elsewhere in this conference the results we have obtained as regards the respiratory activity of some areas of the brain. Broadly it may be summarised that the oxygen uptake of tissue slices from the neocortical regions is higher than that of the limbic areas of the brain. Conversely the tolerance to hypoxia of neocortical portion of the brain should be lower than that of the visceral brain. In our studies QO_2 for cerebellum was significantly low. The hexokinase activity paralleled the oxygen uptake capacity of various regions. The differences observed are quantitative but not qualitative. It is, however, likely that the quantitative metabolic pattern of a region may be so determined as to suit best the particular function of that region. A purine deaminating enzyme guanase has been observed by us to be present in the brain at a higher level of activity than any other tissue of the body. Its concentration is particularly high in the thalamus and relatively low in the cerebellum. The exact role of this enzyme is at the moment not known.

Lowry and his colleagues in U. S. A. and Holger Hyden in Sweden have developed beautiful microchemical techniques whereby it has been possible to study single cell bodies, such as a neuron or a glia in isolation. From these studies glia have been found to contain an extensive enzymatic equipment Their morphological disposition in between the blood vessels and the neurons, and the observed absence of interstitial fluid around the neuron has led to the opinion that the glia cells may be playing an important role in the nutrition of the neuron. Lumsden has demonstrated the phenomenon of pinocytosis through the forked ends of the fiber. The neuron and the glia are supposed to constitute together a functional unit. In other studies involving micro-chemical techniques dendrites have been seen to contain an abundance of mitochondria, so much so that some workers are speaking of the existence of a "dendrite metabolism."

Brain has also been studied in vivo as a whole organ by the methods developed by Ketty et al. This approach, while yielding useful information on the broad pattern of physico-chemical data, in conditions of rest, mental activity or disease process, has occluded certain salient features of cerebral function. It was for example taken as established that carbohydrates were the sole fuel of brain, as analysis of arterial and venous blood from the brain revealed essentially an uptake of glucose and oxygen, and a release of the breakdown products of glucose metabolism. Further support was lent to this belief from the value of the respiratory quotient of the brain which was found to be near to unity. Furthermore the neurotropic viruses, as well as certain vitamin deficiencies giving rise to neurological symptoms, were seen to cause "biochemical lesions" in one or more of the reactions encountered commonly in the carbohydrate metabolism. Studies of Gerard, later confirmed and elaborated by Alexander Geiger seem to challenge such a conception. They have found that cereberal function could be maintained for prolonged periods with glucose free perfusions. Pyrimidine compounds like uridine and cytidine enhanced the effectiveness of the perfusion fluid. The sole dependance of the brain tissue on glucose supply has thus become questionable. Similarly the notion of the blood-brain barrier, as being impermeable or very slightly permeable to non-carbohydrate substances needs revision. Waelsch & his associates have demonstrated an active uptake of glutamine. Most of other amino acids though synthesised in the brain, are in active equilibrium with the nitrogen pool of the blood. Brain possesses a substantial amino acid pool, the concentration of somo like glutamic acid being several times higher in this tissue than elsewhere in the body. Amino acids injected intrathecally undergo a very rapid turnover. Gaitonde and Richter have worked with methionine. Their observations have been broadly corroborated by Waelsh & colleagues using lysine.

It has been seen that a rapid production of RNA, protiens and lipids accompanies neuronal activity. Attardi found the Purkinje cells to respond with a RNA increase per cell. Edstrom and Eichner studied the ganglion cells of the supraoptical nucleus after stimulation with sodium chloride. The amount of RNA in the cytoplasm increased by 80%. The RNA concentration of the nucleoli however showed a significant decrease. The view has been expressed that large differences in the RNA and proteins of the individual nerve cells might reflect differences in their functional state. Micro and macrochemical bulk analysis show that there is a high RNA and protein production and metabolism in the nerve cells increasing with functional demands.

A particular feature of the nerve cell is its capacity to store impressions and the ability to recall them. How could this task be performed in terms of biochemical parameters? Holger Hyden has advanced an extremely interesting hypothesis. According to him a "thought" is received as a frequency modulation by the sensory cells. This modulated frequency, as an electrical pattern, affects the ionic equilibrium of the cytoplasm and changes the stability of one or more of the four bases of the RNA molecule at certain sites. The split bases are replaced. The excitation thus alters the sequence of bases in the RNA of the nerve cell. This "specification" of the RNA induces the formation of an altered protein in combination with it. The information thus is stored in the cell in form of a ribonucleoprotein complex. When the neurons in this already established memory trace are activated, the nucleoprotein complex specific to the exciting modulated frequency breaks releasing this transmitter substance which in turn excites the postsynaptic structure. The number of permutations possible in the RNA molecule by alterations in the sequence of bases has been calculated to equal 10^{15} arrangements—a number large enough to contain adequate items of information. Some experimental data is in support of such a hypothesis. Geiger has shown that stimulation of the brain cortex for 20 seconds causes a decrease of the nucleic acids from the cortical area with an increase of the amino nitrogen content. These changes were reversible at rest after five minutes. Geiger has also found that stimulation for 30 seconds changed the composition of RNA in the cortex. The cytidine and adenine content of the nucleic acids increased, that of uridine and guanine remaining constant. Isotope studies have also demonstrated a high metabolic rate of intracellular proteins. Our knowledge of the stereostructure of nucleic acids is yet fragmentary. It is therefore difficult to make precise or understand at the moment how changes in the biological properties of these macromolecules are brought about by minor variations of the structure. Further work on the nucleoproteinic constituents of the brain may throw more light on the intricacies of the neural function.