

CENTRAL CHOLINERGIC TRANSMISSION

By

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In spite of a large amount of work done for the last decade or so on central synaptic transmission, the problem is far from solved. Rather the problem has become more complicated. With the observation that reserpine causes release of 5-hydroxytryptamine and nor-adrenaline by Brodie and his co-workers, most of the observers have tried to implicate 5-HT and nor-adrenaline as the synaptic transmitters in the central nervous system. No one substance has been definitely identified as the chemical transmitter, but of all the substances mentioned, acetylcholine has the greatest claim (for cholinergic transmission). For non-cholinergic transmission epinephrine, non-epinephrine, 5-hydroxytryptamine, histamine, substance P and ATP have been mentioned.

It is well known that the level of acetylcholine in the brain has been shown to vary with its functional activity. Such variations have been related to physiological changes in nervous activity such as sleep or wakefulness, to the action of neuropharmacological agents, and to certain physical stimuli such as electrical stimulation. For sometime past we have been working on the effect of some of the centrally acting drugs on acetylcholine content and release in different selective areas of the mammalian brain.

In the first study the effect of some anaesthetics on the acetylcholine concentration of different areas of dog brain was seen and it was found that the acetylcholine concentration was greatest with sodium pentobarbitone, less with chloroform and least with other anaesthesia. The differences may be related to the differences in behaviour of the animals during induction of anaesthesia, in which struggling was greatest with ether, less with chloroform and least with sodium pentobarbitone.

The next study was done on effect of reserpine on acetylcholine content of different areas of dog brain and it was observed that reserpine increased the acetylcholine content of the hypothalamus. This was supposed to be in some way related to the facilitation of parasympathetic centres in hypothalamus. The acetylcholine content of the hippocampus was, however significantly reduced. Kin and Maclean, while comparing the effects of reserpine on electrical responses of limbic and neocortical structures, found that about 4 hrs. after the administration of reserpine the recordings from the hippocampus began to show much rhythmic activity at a frequency of 3.5 to 4 cycle/sec. This activity was conspicuous only in the waking

state during which neocortex showed desynchronization. The contrast between the electrical activities of the hippocampus and neocortex became even more marked 20 minutes after reserpine. The available evidence therefore suggests an important inverse relationship between the hippocampus and other areas of the brain as far as their metabolic patterns are concerned and hippocampus may play an important role in autonomic functions.

Since reserpine also has some peripheral cholinergic effects, it was considered worthwhile to see the content of acetylcholine on heart, brain and ileum. Reserpine increased acetylcholine content of all the tissues studied. The increase in the peripheral tissues was greater than in the hypothalamus. The bradycardia and the purgative effects of reserpine may be related to the increase of the acetylcholine content of sino-atrial node and the ileum.

The effect of intra (cerebro) ventricular reserpine on the acetylcholine content of heart, ileum and hypothalamus of the dog was studied and it was found that the increase in the peripheral tissues was greater than in the hypothalamus and the increase in the acetylcholine content was not quantitatively related to the other effects of reserpine. The increase in acetylcholine content of the sino-atrial node and the ileum and also the peripheral effects observed can be attributed to its central action.

In further study the effect of reserpine the acetylcholine concentration in hypothalamus, ileum and heart of the dog after bilateral vagotomy and ganglionic blockade was studied. Animal which received pentolinium tartarate showed no significant change from the controls in the acetylcholine level of tissues and the group which received pentolinium and reserpine showed a statistically significant increase in the acetylcholine level of the hypothalamus alone there was also sedation but no other general effects. The animals which had bilateral vagotomy did not show any significant change from the controls in the acetylcholine levels or other general effects, but the group which had bilateral vagotomy and reserpine, showed a significant increase in the acetylcholine content of the hypothalamus alone, there was sedation, miosis and salivation but no other general effects. These findings suggest that the peripheral parasympathetic effects of reserpine are due to central nervous actions.

We thought it worthwhile to see the effect of tranquillizer belonging to other groups on the acetylcholine content of different areas of dog brain. With chlorpromazine there was significant increase in the acetylcholine content of the frontal cortex. It has been suggested that chlorpromazine exerts depressant effects on the medial ascending reticular activating system through cholinergic blockade. It has also been observed that in rabbits the depressant effect of chlorpromazine on "arousal" responses could be reversed by physostigmine but not by amphetamine, serotonin, epinephrine. Chlorpromazine is known to exert its peripheral and central acetylcholine action. It is quite possible that it might have a similar central action.

The effect of Meprobamate on acetylcholine content of dog's brain has also been studied. There was a significant increase in the acetylcholine content of the hypothalamus and the hippocampus after meprobamate, while in other areas of brain studied the changes were insignificant though there was a slight reduction.

It was considered that the measurement of content of acetylcholine may not throw the same light on the effect of psychopharmacological agents as the release of acetylcholine from the brain. The following study was done on the release of acetylcholine.

Effect of ether and sodium pentobarbitone on the release of acetylcholine:—It was seen that the release of acetylcholine by a push pull cannula technique is greater with pentobarbitone than with ether anaesthesia probably acetylcholine is being removed as soon as synthesized.

In further study, it was found that the release of acetylcholine after reserpine under sodium pentobarbitone anaesthesia is more than under ether anaesthesia. However, the percentage increase in acetylcholine released by reserpine is not greater under pentobarbitone. In this connection it is interesting to note that Giarman and Pepeu while studying the effects of drug induced changes in brain acetylcholine, reported that the most striking aspect of increase in the levels of acetylcholine after certain central depressants may be related to a depression of synthetic process by acetylcholine itself. It appears that the sodium pentobarbitone does not allow the brain content of acetylcholine to go beyond a certain level, so that excessive acetylcholine formed under this anaesthetic alone, as well as under reserpine is released.