IS THERE CHEMICAL TRANSMISSION AT CHEMORECEPTORS?

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I wish to comment upon the present evidence for chemical transmission of the responses initiated by oxygen want in the carotid body; but before I do, let me say a few words about the dosage of hexamethonium used in my own experiments on the problem (2). Dr. Liljestrand has reported that very high doses of hexamethonium injected locally into the carotid body region do depress the chemosensory response to oxygen want; and he has suggested that my own negative finding with hexamethonium given systemically is to be accounted for by my using comparatively low doses. I have no reason to doubt his explanation of our divergent results, but I cannot concede that the dosage which I used can be considered in any way low in a ganglion-blocking sense. On the contrary, it is much higher than that necessary to block autonomic ganglia, and the suggested similarity between autonomic synapses and carotid body "synapses" was, after all, the point being tested. In some experiments, indeed, the hexamethonium was given in such high dosage that it appeared to be approaching neuromuscular-blocking and hence near-lethal levels.

Now let me leave this particular to examine the evidence in favour of acetylcholine acting as transmitter in the carotid chemosensory path. As I see it, the body of evidence in support of acetylcholine transmission at other sites in the organism—be they autonomic ganglia or neuromuscular junctions or what you will—rests on three principal findings: 1. that acetylcholine can be recovered from the preparation during the transmission process; 2. that transmission is influenced by substances depressing the rate of acetylcholine destruction: to wit, the anticholinesterases; 3. that acetylcholine mimics the transmission process. The argument stands, as it were, like an old-fashioned stool upon three legs. Let us see now how sound are these three legs which support the argument for cholinergic transmission in the carotid body.

First we find that one leg is completely missing: acetylcholine has not been recovered from the carotid body. True, this may be due to technical difficulties consequent upon the minuteness of the carotid body, but the leg is missing nonetheless.

What of the second leg and the effect of anticholinesterases? Dr. Liljestrand has presented evidence that the anticholinesterases augment the sensory discharge from the carotid body set up by oxygen lack, but there is by no means agreement on this point. Other workers have failed to find such an effect of anticholinesterases, and to these I should add my own experience with TEPP, which injected or perfused in the carotid body region failed to reveal to me any definite effect on the normal physiologic response to oxygen lack (although the response to injected acetylcholine was greatly intensified). I would suggest that the second leg of the stool is by no means firmly attached.

What now of the third? At first it seems solid enough. Acetylcholine certainly

mimics the effect of exciting the chemoreceptors by oxygen lack, and the mimicry is sufficiently good to make it seem reasonable to assume that the afferent path activated by the two forms of stimulation is one and the same. But when we look more closely at this acetylcholine sensitivity and ask if it can be taken as reflecting in any way some specialization of the afferent path, such as we might expect if there were a peculiar cholinergic transmission of the local changes set up by oxygen lack, then we see that it cannot. In the first place, and this was an important finding in my experiments, this acetylcholine sensitivity can be abolished by hexamethonium without any depression of the carotid body response to oxygen lack. Clearly this does not fit the hypothesis, advanced by Euler, Liljestrand and Zotterman in 1939 (4), that acetylcholine stimulates by acting at some synaptic site on the afferent pathway from the oxygen sensitive elements. For to render this region insensitive to acetylcholine (which now is postulated as transmitter) would of necessity suppress the transmission of the more peripheral changes set up by oxygen lack. This point might be illustrated by reference to the neuromuscular junction or to the autonomic ganglion. One cannot render a motor endplate insensitive to acetylcholine without suppressing neuromuscular conduction, nor a ganglion cell insensitive to acetylcholine without abolishing ganglionic transmission. It seems, rather, that a better hypothesis to explain the actions of acetylcholine and hexamethonium and related drugs in this: that the carotid body afferents, in addition to being responsive to oxygen lack, possess a sensitivity to acetylcholine and similar drugs which is altogether independent of normal transmission mechanisms and which can be abolished, therefore, without detriment to the normal transmission process; a sensitivity, as it were, in parallel rather than in series with a physiological sensitivity to oxygen lack. This was the conclusion to which I was led by my experiments with hexamethonium. It should not be considered unusual or unique for a sensory mechanism to behave in this way. In 1948, Brown and Gray (1) found that nerve fibres in the cat's skin, normally excited by touch and in which there is no evidence whatever for any peripheral synapse, were excited by acetylcholine; and moreover that this sensitivity to acetylcholine could be abolished by nicotine without any apparent loss of the normal response of these fibres to mechanical stimulation. Douglas and Gray (3) extended these results and found a striking parallelism between these simple mechanical skin afferents and the chemosensory afferents of the carotid body: 1. Each was excited by acetylcholine, nicotine and lobeline. 2. In each, responsiveness to these drugs was abolished by hexamethonium. 3. Each continued to respond to its normal physiological stimulus (touch or oxygen lack) when its pharmacological sensitivity to acetylcholine-like compounds had been abolished. Now Dr. Liljestrand has likened the carotid body mechanism to the autonomic ganglion, largely on the grounds that acetylcholine and other related carotid body stimulants are ganglion excitants; but here I have described evidence that acetylcholine and similar substances stimulate afferent nerves where there is no question of there being ganglia or synapses, and other evidence of a similar sort has been presented today by other members of the symposium. So it is clear that sensitivity to such substances is a fairly wide-spread property of

afferent nerves, and we should no longer regard these drugs as specific "synaptotropic" agents. Moreover, if a comparison with other mechanisms is to be made, the carotid body afferents are more properly to be likened to those skin afferents I have described and in which abolition of acetylcholine sensitivity entails no loss of normal function. Why afferents from the carotid body should, like afferents from other regions, possess a sensitivity to acetylcholine and similar drugs is a question beyond the scope of the present discussion, but I would point out that given such a sensitivity the long recognized and striking responsiveness of carotid body mechanisms to these drugs is understandable, for the carotid body blood flow is extraordinarily high and exposure to drug action must be singularly favourable. The third leg to our stool does, then, exist, but it is a pretty hollow leg.

With one leg hollow, one wobbly and one missing, the argument that acetylcholine is involved in chemosensory transmission appears to me to stand but poorly at present; but the theory is an attractive one and we have no convincing evidence against it. Much of our pharmacological investigation and argumentation is, as I pointed out before, probably limited, by reason of extracellular distribution of our active agents, to effects exerted on the surface of the glomus cells or the adjacent nerve fibers. If chemical transmission is involved in this pathway, it is probably at the afferent nerve's very origin which is *within* the glomus cell.

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