Sympathetic postganglionic cholinergic fibres

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Commentary by

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This is one of a series of papers providing evidence for the ephemeral hypothesis that there was a cholinergic link in noradrenergic transmission, which also became known as the Burn-Rand theory, and was so indexed in the third edition (1965) of *The Pharmacological Basis of Therapeutics* by Goodman & Gilman, but has entirely disappeared from more recent additions.

My association with the late J.H. Burn and a brief account of some of the circumstances leading to the framing of the cholinergic link hypothesis has been described previously (Rand, 1993). The starting point was the demonstration that the action of tyramine and some other sympathomimetic amines was lost after depletion of noradrenaline by reserpine and that their action was restored after an infusion of noradrenaline, which was thought to replenish, at least partly, the noradrenaline stores (Burn & Rand, 1958). This gave rise to the lasting concept of indirect sympathomimetic activity, meaning action mediated by the release of noradrenaline from tissue stores. It must be borne in mind this was before noradrenaline was shown to be located in the transmitter storage vesicles of the terminal varicosities of sympathetic nerves, hence the use of the non-committal term 'tissue stores'.

The cholinergic link hypothesis was first set out in an article in *Nature* (Burn & Rand, 1959), which put together the following observations:

(i) acetylcholine has a sympathomimetic nicotinic action that is exerted at a site peripheral to sympathetic ganglia in many tissues.

(ii) this action, like that of tyramine, is lost when noradrenaline stores in the tissues were depleted by pretreatment with reserpine;

(iii) after depletion of noradrenaline stores, sympathetic nerves behave as though they are cholinergic in that stimulation produces responses resembling those to the muscarinic action of acetylcholine, being enhanced by physostigimine (eserine as it was then called) and blocked by atropine.

It follows reasonably from the first and second points above to conclude that the nicotinic sympathomimetic action of acetylcholine was indirect; that is, mediated by noradrenaline released from tissue stores. However, since there appeared to be an endogenous source of acetylcholine (the third point above), it was proposed that this acetylcholine, which we would now call 'neurogenic', acted physiologically to release noradrenaline which had the dominant action when the tissue stores were intact.

The main purpose of the work reported in the paper reproduced here was to gather further information about the presence of cholinergic sympathetic nerves to strengthen the argument for the cholinergic link in noradrenergic transmission. The procedure was firstly to deplete noradrenaline stores by pretreatment of animals with reserpine, then to observe the effects of stimulating sympathetic nerves serving various tissues (cat nictitating membrane, spleen, uterus, pilomotor muscles; rabbit ear). Findings construed as evidence for a cholinergic component were enhancement of an effect attributable to acetylcholine by physostigmine and the blockade of the effect by atropine, although in one series of experiments, efflux of acetylcholine from the rabbit perfused ear was measured by bioassay.

In the uterus and spleen, in which noradrenaline and acetylcholine, acting directly on the smooth muscle, have opposing actions (contraction and relaxation, respectively), sympathetic nerve stimulation produced a reserpine-attenuated effect that was presumed to be mediated by residual noradrenaline. The reduction of stimulation-induced contractions by physostigmine was attributed to potentiation of the counteracting effect of acetylcholine, and the enhancement by atropine was attributed to blockade of this effect of acetylcholine. In the light of present-day knowledge, the findings would be construed in terms of inhibition of noradrenergic

transmission by acetylcholine acting on prejunctional muscarinic cholinoceptors associated with noradrenergic nerve terminals, as was originally suggested by Muscholl (1980). Even so, the findings do provide evidence for the presence of neurogenic acetylcholine, which might now raise the possibility of co-transmission. However, such concepts as co-transmission and feedback modulation of transmission were well into the future, but the then heretical view of the cholinergic link may have eased the way for their introduction.

Another possibility that may explain some of the findings is that transmitters other than acetylcholine and noradrenaline were released, but in 1960 the then current dogma did not allow for other peripheral transmitters. For an account of this, see Rand & Mitchelson (1986).

What the Burn-Rand theory certainly did was to incite considerable controversy, stimulating a great deal of work purporting to confirm it, and a great deal more work seeking to refute it, quite properly carried out according to the tenets of the philosopher of science Kark Popper. Often at international conferences I meet people who tell me their first work in pharmacological research was concerned with a critical examination of an aspect of the cholinergic link hypothesis. In the event, the weight of the evidence did not support the generality of the theory. For those interested in the debate, a list of reviews concerned with critical examinations of the theory can be found in an article by Rand & Story (1991).

For my part, interest in the details of the mechanism of noradrenergic transmission led from the cholinergic link hypothesis to a study over a period of some twenty years of the prejunctional modulation of transmitter release with David Story and other colleagues. This also aroused a fair degree of controversy, but less than did the cholinergic link hypothesis, and the concept is now generally accepted. More recently, I have moved to a study of nitrergic neuroeffector transmission with younger colleagues, especially Chun Guang Li, who I think is to me what I was to Burn, when Burn was about my present age. And perhaps I am somewhat like Burn in having a penchant for controversy, since Li and I have suggested that the nitrergic transmitter is not free radical nitric oxide although transmission is absolutely dependent on the functional integrity of nitric oxide synthase (see: Rand & Li, 1995). These ventures followed logically, although the logic is somewhat tenuous, from the paper reproduced here and other work I did with Burn in Oxford nearly forty years ago.

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