On the blockade of neural and exogenous noradrenaline

It is generally accepted that higher doses of α-adrenoceptor blocking agents are required to block effector responses to noradrenaline released from local neural sources than those to noradrenaline that enter from outside the tissue. Wyse & Beck (1972) presented experimental results which they considered questioned the applicability of this principle to vascular tissue. Since evidence based on studies of two very different types of blood vessels confirming this principle has been published (Ljung, 1969; Bevan & Su, 1971), there is a need to resolve the discrepancy.

The original experimental observation was made by Dale (1906). He observed *in vivo* that when *equal*, presumably *submaximal*, responses to sympathetic nerve stimulation and sympathomimetic amines were compared, a given dose of an ergot preparation reduced the neural response less than the other. The results of Wyse & Beck (see Fig. 2) looked at in these terms tend to support rather than refute the classical position. They found that before exposure to the blocking drug, phenoxybenzamine, tissue responses to noradrenaline (10^{-7} g ml^{-1}) and sympathetic stimulation at 10 Hz were comparable. After partial blockade, the numerical mean of the responses to noradrenaline (10^{-7} g ml^{-1}) were lower than that to stimulation at 10 Hz. Although these were not significantly different when compared as groups, a comparison of the same data as paired observations (which minimizes differences due to individual variation), may have shown the difference between the two groups of responses to be significant. Wyse & Beck's Fig. 2 indicates that at least twice the dose of noradrenaline would have been needed to match the neural response after blockade than before.

Bevan & Su (1971) proposed the "distribution hypothesis" to explain the comparative resistance to blockade of the neural response in large blood vessels where there is no true adrenergic synapse. In the rabbit pulmonary artery for example, the closest neuromuscular distance is several μm (Verity & Bevan, 1966). Adrenergic nerves in blood vessels surround the media, the muscle coat, like a sleeve. Transmitter (noradrenaline) on release moves into the media following its concentration gradient. In the steady state, there is a concentration gradient of noradrenaline in the media, highest in the region of the nerve endings at the outer surface of the media and lowest at the inner or intimal surface (Bevan & Osher, 1970). In contrast, exogenous noradrenaline is evenly distributed through the thickness of the media. Thus the distribution of noradrenaline in the vessel in the two circumstances is dissimilar. To elicit equivalent responses, the peak concentration of neural noradrenaline in the media must be higher than the level of exogenous amine. It was proposed that the neural response was harder to block because of this higher concentration of noradrenaline.

Ljung (1969) utilizing the rat portal vein obtained experimental findings consistent with the classical concept. The neuromuscular cleft in the rat portal vein is as narrow as 100 nm (Booz, 1971), and there is highly suggestive evidence that the α-adrenoceptors in this tissue are restricted to the cells closest to the innervation (Johansson 1970). High intrasynaptic transmitter concentrations are likely in this vessel as a consequence of the narrow cleft (Johansson & others, 1972). Thus, the "intimate relationship hypothesis", first advanced by Dale & Gaddum (1930) to explain certain phenomena in the cholinergic synapse may well apply to this situation. Bevan & Su (1971) and Johansson & others (1972) have discussed the significence of the temporal distribution of the transmitter. In the vessel with a narrow cleft there are transient high transmitter concentration peaks within the synapse corresponding to each quantum of transmitter release. In contrast, the temporal distribution of

exogenous noradrenaline at the steady state is uniform. It is our opinion that the smaller the blood vessel, and therefore presumably the smaller the size of the neuromuscular cleft, the less important is the transmural distribution of noradrenaline and the more important are the "intimate relationship" effect and the temporal variation in transmitter concentration in determining the resistance of neurogenic excitation to blockade.

In experiments designed to test the relative resistance of neural and exogenous noradrenaline responses, the procedures employed must ensure excitation of *all* nerve endings, if these results are to be valid. Wyse & Beck employed pulses of 75V for stimulating bath-immersed tissues. The important feature in *in vitro* experiments is not the nominal voltage setting of the stimulator, but that supramaximal parameters be selected. The latter parameters were utilized by Su & Bevan (1970) using superfused tissues but the same voltage in bath-immersed tissues did not stimulate all nerve fibres. After treatment with phenoxybenzamine, a drug that not only blocks the α-adrenoceptor but also the neural re-uptake of noradrenaline, tissues were stimulated for 6 min at different frequencies. It is our consistent experience that when the re-uptake is blocked the transmitter falls off within several min of stimulation (Su & Bevan, 1970). Thus to obtain a maximum neural response each tissue should be stimulated only once at one frequency, and then discarded. Since only one comparatively low concentration of phenoxybenzamine was tested by Wyse & Beck, their findings in this matter are restricted.

In the light of the points made we consider that the questions raised by Wyse & Beck are seriously weakened. Alternative interpretations or experimental results require to take into account, as does the distribution hypothesis, the stratification of nerve and muscle elements in most blood vessels.

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