The use of desipramine in studies of noradrenergic nerve function

Desipramine is frequently used in investigations of noradrenergic nerve function to prevent the re-uptake of released noradrenaline. This may involve an assumption that desipramine affects only the uptake$_1$ process and does not interfere with other systems involved in noradrenergic nerve function. The evidence presented below indicates that such an assumption may not be valid in all circumstances.

Vasa deferentia from mice or guinea-pigs were set up in isolated tissue baths (20 ml) in McEwen solution (McEwen, 1956), gassed with 5% carbon dioxide in oxygen and maintained at 37°. Changes in length of the tissues in response to exogenous (—)-noradrenaline were recorded using an isotonic transducer (load 200 to 500 mg) and were displayed on a Heathkit chart recorder. Tissues responded with submaximal contractions when exposed to (—)-noradrenaline ($1 - 3 \times 10^{-5}$ M) and equi-effective doses were determined in the absence of drugs and in the presence of either cocaine (3×10^{-5} M) or desipramine (8×10^{-6} M). The equi-effective dose ratios calculated from these determinations are shown in Table 1. Clearly, cocaine potentiated the response to noradrenaline in both mouse and guinea-pig vasa deferentia, about 1/10th of the concentration of noradrenaline being required to elicit the same response in the presence of cocaine as in its absence. Desipramine potentiated the response in the guinea-pig vas deferens to a similar extent but antagonized the response of the mouse vas deferens, the concentration of noradrenaline having to be approximately doubled in order to maintain the same response in the presence of desipramine.

The inability of desipramine to potentiate the response of the mouse vas deferens to noradrenaline could be explained by a variety of mechanisms of which two seemed most likely. Firstly, that desipramine fails to block the noradrenaline uptake$_1$ process in mouse vas deferens and/or secondly, the α-adrenoceptor blocking activity known to be possessed by desipramine (Brodie, Dick & others, 1961; Türker & Khairallah, 1967) is much more marked in the mouse than in the guinea-pig.

To test the first of these possibilities (the inability of desipramine to block noradrenaline uptake) mouse vasa deferentia were incubated for 20 min at 37° in McEwen solution containing ascorbic acid (1×10^{-4} M) and [^{3}H](—)-noradrenaline ($1{\cdot}5 \times 10^{-5}$ M; 13·0 Ci mol^{-1}). Tritium uptake, as determined by combustion followed by liquid scintillation counting, was 926 ± 33 d min^{-1} mg^{-1} of tissue (mean ± s.e.; 10 tissues) while in the presence of desipramine (8×10^{-6} M) these figures were reduced by about 75% to 238 ± 8 d min^{-1} mg^{-1} of tissue. Thus desipramine is capable of blocking the uptake of noradrenaline into the mouse vas deferens under these conditions.

Testing the second possibility (α-adrenoceptor blockade) is complicated by the noradrenaline uptake blocking properties of desipramine which will tend to potentiate the response and thus interfere with quantitation of α-adrenoceptor blocking activity.

Table 1. *Showing equi-effective dose ratios (mean ± s.e.; number of experiments in parentheses) determined for cocaine and desipramine in guinea-pig and mouse vas deferens.* The equi-effective dose ratio is taken as the dose of noradrenaline required to produce a response of a given size in the presence of the drug divided by the dose required to produce the same sized response in the absence of the drug.

Drug	Equi-effective dose ratio in Mouse	Guinea-pig
Cocaine (3×10^{-5} M)	0·14 ± 0·01 (10)	0·09 ± 0·02 (5)
Desipramine (8×10^{-6} M)	2·41 ± 0·28 (5)	0·12 ± 0·03 (5)

To overcome this problem, pA_2 values for desipramine (contact time 2 min) against noradrenaline were determined by the method of Schild (1947) in the presence of cocaine (3×10^{-5} M). It seems likely that this concentration of cocaine is maximally effective against noradrenaline uptake since there was no further potentiation of the response to noradrenaline in vasa deferentia from either species when the concentration of cocaine was increased from 3 to 6×10^{-5} M. In guinea-pig vas deferens a pA_2 value of $5{\cdot}95 \pm 0{\cdot}11$ (mean $\pm$ s.e.; 7 experiments) was obtained, while in mouse vas deferens the corresponding figures were $8{\cdot}95 \pm 0{\cdot}32$ reflecting a greatly increased blocking activity for desipramine in mouse tissues. The blocking action was reversed on washing the tissues with desipramine-free McEwen solution and cannot be due to non-specific depression of smooth muscle since, at concentrations which were effective against noradrenaline, desipramine did not depress the submaximal response of the vas deferens to barium chloride ($0{\cdot}6 - 1{\cdot}2 \times 10^{-3}$ M).

It appears therefore that the net effect of desipramine on the response to noradrenaline in guinea-pig and mouse vasa deferentia is a balance between potentiation due to uptake blockade and antagonism due to α-adrenoceptor blockade. At 8×10^{-6} M, desipramine is highly effective as an α-adrenoceptor blocking agent in mouse vas deferens and this action over-rides the potentiation due to uptake blockade; thus a net reduction in the response is seen. In guinea-pig vas deferens, however, the lower α-adrenoceptor blocking activity of desipramine enables a net potentiation to be produced.

These results have implications for the use of desipramine as a tool to block noradrenaline uptake in investigations of the nature of the control over the release of noradrenaline. In addition to α-adrenoceptors mediating the contractile response to noradrenaline, one of the servo-loop mechanisms thought to be involved in the control of noradrenaline release may also be mediated through α-adrenoceptors (Enero, Langer & others, 1972; Stjärne, 1973; Vizi, Somogyi & others, 1973). If these are identical to those involved in the production of the contractile response then the use of desipramine to block noradrenaline uptake (usually in concentrations of 10^{-8} to 10^{-6} M) may also co-incidentally interfere with the control of noradrenaline release as well as the production of the contractile response.

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