Unexplained inhibitory action of D-lysergic acid diethylamide (LSD) on postganglionic motor transmission in the guinea-pig vas deferens

N. AMBACHE, LINDA P. DUNK*, P. MIALL and M. ABOO ZAR
Medical Research Council, Department of Physiology, Royal College of Surgeons of England, Lincoln's Inn Fields WC2A 3PN

Desheathed vas deferens preparations were stimulated every minute with one–fourteen pulses (0·1–2 ms duration; 10 Hz; constant voltage) and the tension was recorded isometrically; other experimental conditions were as described by Ambache & Zar (1971).

LSD tartrate, $0{\cdot}5–10 \times 10^{-7}$ g/ml, produced a reduction in tension response which was the more marked the fewer the number of pulses per train; for example 96% for five-pulse trains but only 49% for fourteen pulse trains (Fig. 1, curves A and B, obtained 42 min apart). The corresponding curve (C, simultaneous with B) obtained after the 42 min interval from the contralateral, untreated vas deferens did not differ by more than 5% from its original curve (simultaneous with curve A; not shown).

Non-specific smooth muscle depression by LSD was excluded by tests with acetylcholine or noradrenaline, the effects of which were potentiated.

This inhibitory action of LSD, obtained also in other species, is not related to its ability to antagonize 5-hydroxytryptamine (5-HT), because: (1) 5-HT, 1–10 μg/ml fails to contract the vas deferens; (2) the inhibitory action on the vas deferens of other, more powerful 5-HT antagonists was either considerably weaker than that of LSD, for example, 2-bromolysergic acid diethylamide hydrogen tartrate (BOL; curve D) or virtually absent, for example, methysergide bimaleate. Thus 2-bromo substitution or

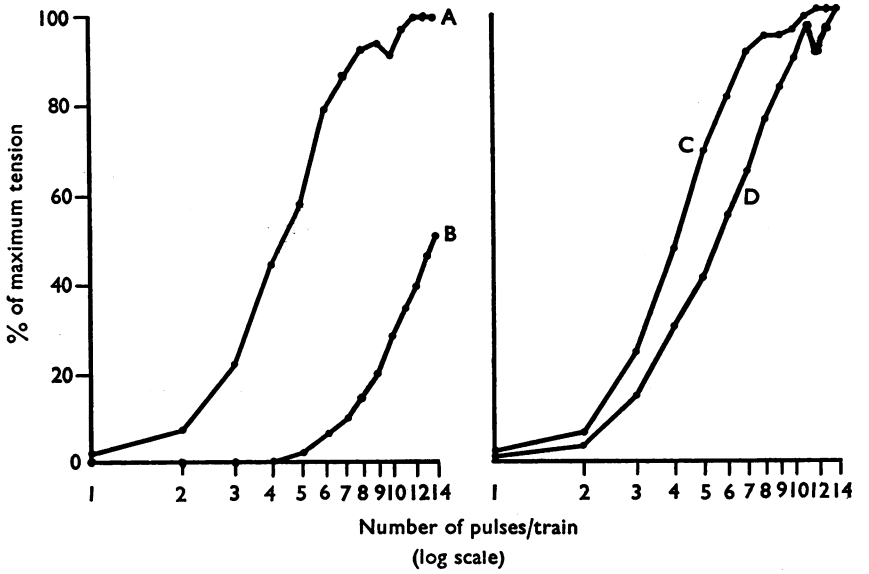

FIG. 1. LSD inhibition of postganglionic transmission in the desheathed guinea-pig vas deferens. Parallel preparations from the same animal; 35°C. Field stimulation with trains of 2 ms pulses (10 Hz). Maximum tensions developed: left vas, 6·7 g; right vas, 6·5 g (muscle weights: left, 51·8 mg; right, 47·3 mg).
Left vas deferens: curve A, obtained before and B, during exposures to LSD, 5×10^{-7} g/ml.
Right vas deferens: curve C, obtained simultaneously with B, before BOL; and D, during exposure to BOL, 5×10^{-7} g/ml.

N-methylation of the indole ring drastically reduces the effectiveness of LSD, as it does for its central actions.

The inhibitory action of LSD on the vas deferens does not appear to be due to antagonism of the unknown postganglionic motor transmitter at the muscle-receptor level because after the maximum inhibition was obtained with 10^{-6} g/ml of LSD it was not possible to extinguish the responses to six–fourteen pulses even with 10^{-5} g/ml.

The inhibitory action of LSD was unaffected by reserpine and was antagonized by phentolamine (10^{-6} g/ml).

REFERENCE

AMBACHE, N. & ZAR, M. ABOO. (1971). Some physiological and pharmacological characteristics of the motor transmission in the guinea-pig vas deferens. *J. Physiol, Lond.*, **212**, 15–16*P*.

Evaluation of neuronal and extraneuronal uptake mechanisms during adrenergic nerve stimulation

J. HUGHES
Department of Pharmacology, University of Aberdeen, Scotland

Iversen & Salt (1970) have found that corticosterone is a selective inhibitor of $Uptake_2$ (Iversen, 1965) in the rat heart. If corticosterone enhances noradrenaline overflow during sympathetic nerve stimulation, this would provide additional evidence for $Uptake_2$ playing a role in the inactivation of the sympathetic transmitter. This possibility has now been examined in the rabbit vas deferens.

The vas deferens was incubated in a 2·5 ml donor bath containing Krebs solution at 37°C. The intramural nerves were excited by electrical field stimulation (1 ms duration, 240 pulses at 2 or 16 Hz, supramaximal stimuli). Noradrenaline overflow was measured by transferring the donor fluid to a cascade system where the transmitter was assayed on superfused preparations of the rabbit aorta and iliac artery (Hughes, 1970).

In the untreated vas deferens, corticosterone (20 μg/ml) caused a 1·36-fold mean increase in noradrenaline overflow (S.E.M. $\pm$0·04, n=6). Higher concentrations of corticosterone had no further potentiating effect. In tissues treated with cocaine (5 μg/ml), corticosterone increased noradrenaline overflow 3·9-fold (S.E.M. $\pm$0·22, n=6), a significantly greater effect than in untreated tissues. The increase in outflow was reversed on washing out the corticosterone. Cocaine alone caused a 4·4-fold, increase in noradrenaline overflow (S.E.M. $\pm$0·2, n=7). However, pretreatment of the tissue with corticosterone resulted in a 13-fold increase in outflow on addition of cocaine (S.E.M. $\pm$0·4, n=3). Thus there was a mutual interaction between these two drugs. Further experiments established that the effect of cocaine was maximal at 2–4 μg/ml; therefore, this interaction was unlikely to be due to an additive effect on the same process.

One explanation of these results is that there is normally a balance between neuronal and extraneuronal inactivation. When one of these mechanisms is blocked, more noradrenaline becomes available to the remaining process and its relative importance increases. Thus, treatment of the tissue with corticosterone will divert transmitter, normally removed by $Uptake_2$, to $Uptake_1$. It follows, therefore, that it is impossible to estimate the contribution which each of the two uptake processes makes to the inactivation of the transmitter under normal physiological conditions. It can be calculated, however, that when $Uptake_2$ is blocked $Uptake_1$ is capable of removing at