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).

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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

least 90% of the transmitter, and Uptake$_2$ can remove up to 75% when Uptake$_1$ is blocked. The combined effects of these two processes probably serve to inactivate slightly more than 90% of the transmitter under physiological conditions. These conclusions are based on the assumption that the drug effects are solely due to the inhibition of the respective uptake processes, and that the outflow, in the presence of both drugs, represents the total transmitter release.

Normetanephrine, which blocks Uptake$_2$, enhances the neuronal uptake of ^{3}H-NA in the rat vas deferens (Iversen, Fischer & Axelrod, 1966). This observation supports the results presented here.

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Amine uptake characteristics of the guinea-pig Auerbach plexus

P. A. SHORE and M. F. SUGRUE*†

Department of Pharmacology, University of Texas Southwestern Medical School, Dallas, Texas 75235, USA

Noradrenaline (NA) uptake is a Na^+ dependent phenomenon, and in a study of the Na^+-dependent uptake of the NA analogue (—)-metaraminol {(—)-MA} by rabbit heart slices we have shown that the amine transport system appears to be coupled, rather than an allosteric, type of Na^+-dependency. Thus, lowering (Na^+) resulted in a decreased V_{max} with an unchanged apparent K_m (Sugrue & Shore, 1969a). Such a kinetic pattern is consistent with sugar uptake in the rabbit ileum (Goldner, Schultz & Curran, 1969). In other species, however, altered (Na^+) is associated with a decrease in the apparent K_m of sugar uptake and no change in V_{max} (Crane, 1968). We decided, therefore, to study (—)-MA uptake kinetics in another species and selected the isolated longitudinal muscle-Auerbach plexus of the guinea-pig, since this preparation has an extremely efficient amine concentrating mechanism (Govier, Sugrue & Shore, 1969). We have also reported the presence, in rabbit heart, of a Na^+-dependent, optically specific and reserpine-sensitive amine carrier mechanism which is distinct from the main, relatively non-specific, reserpine-insensitive membrane amine carrier system (Sugrue & Shore, 1969a) and a study was made to determine if such a system exists in the guinea-pig Auerbach plexus.

Kinetic studies revealed that alterations in (Na^+) left the apparent K_m of (—)-MA uptake unaltered but did effect a change in V_{max}. Incubating the Auerbach plexus in the presence of a high (K^+) also lowered V_{max} while leaving the apparent K_m unaltered, thus agreeing with our rabbit heart findings (Sugrue & Shore, 1969b). Hence, a striking similarity exists in the amine uptake characteristics of rabbit heart and the Auerbach plexus of the guinea-pig, indicating that our hypothesis for the role of Na^+ in the rabbit applies to another species.

A plot of (+)-MA uptake versus (Na^+) showed that (+)-MA uptake was a single

†Present address: Department of Pharmacology, Organon Laboratories Ltd., Newhouse, Lanarkshire.