Noradrenergic influences on dopamine-dependent behaviour in rats

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It is difficult to assess the precise neurotransmitter roles of noradrenaline in the brain. It has been suggested that noradrenaline may play a modulator role in the control of motor activity (Andén & Strömbom, 1974), and its action may be facilitation of the nigro-neostriatal dopaminergic system of the brain (Pycock, Donaldson & Marsden, 1975). However, it has been demonstrated that a noradrenergic component is apparently not important for the production of amphetamine-induced locomotor activity (Roberts, Zis & Fibiger, 1975) or stereotyped behaviour (Creese & Iversen, 1975) in rats, although an intact dopamine system is necessary (Creese & Iversen, 1974). Work described here has utilized two animal models with lowered cerebral noradrenaline levels to study the effect on behaviour in rats characteristically observed after dopamine receptor stimulation and dopamine receptor blockade.

Depletion of cerebral noradrenaline was achieved in two separate groups of rats by (i) injection of 6-hydroxydopamine at birth, and (ii) bilateral electrolesions placed in the region of the locus coeruleus in adult rats. When both groups, plus an additional litter-mate control group, had reached adult stage, the intensity of catalepsy induced by the dopamine receptor blocking agent haloperidol (range 0.1–2 mg/kg) was observed. A month later, the stereotyped behaviour induced by both directly and indirectly acting dopamine receptor agonists (apomorphine, 0.1–5 mg/kg s.c., and amphetamine, 0.1–10 mg/kg i.p.) was compared in the 3 animal groups. After a further month, animals were killed for determination of forebrain monoamine levels.

Both 6-hydroxydopamine at birth and bilateral locus coeruleus lesions specifically harmed the dorsal noradrenergic bundle innervation of forebrain structures. Dopamine and 5-hydroxytryptamine levels were not changed. Cortical noradrenaline levels fell to between 40–50% of control levels ($P < 0.001$) for both types of lesions.

Cerebral noradrenaline depletion had no effect on stereotyped behaviour induced by either apomorphine or amphetamine, but it did significantly enhance both the time to onset and intensity of catalepsy induced by haloperidol at all doses used.

It is difficult to comment on the mechanism by which lowered central noradrenaline levels modifies catalepsy, due to apparent dopamine receptor blockade, but does not influence stereotypy resulting from dopamine receptor stimulation. It is possible that two different populations of dopamine receptor are responsible for the two types of behaviour, and that each is modified by different noradrenergic mechanisms.

(C.P. is a Fellow of the Parkinson's Disease Society.)

References

ANDEN, N-E. & STRÖMBOM, U. (1974). Adrenergic receptor blocking agents: effects on central noradrenaline and dopamine receptors and on motor activity. *Psychopharmac. (Berl.)*, **38**, 91–103.

CREESE, I. & IVERSEN, S.D. (1974). The role of forebrain dopamine systems in amphetamine-induced stereotyped behaviour in the rat. *Psychopharmac. (Berl.)*, **39**, 345–357.

CREESE, I. & IVERSEN, S.D. (1975). The pharmacological and anatomical substrates of the amphetamine response in the rat. *Brain Res.*, **83**, 419–436.

PYCOCK, C.J., DONALDSON, I.MacG. & MARSDEN, C.D. (1975). Circling behaviour produced by unilateral lesions in the region of the locus coeruleus in rats. *Brain Res.*, **97**, 317–329.

ROBERTS, D.C.S., ZIS, A.P. & FIBIGER, H.C. (1975). Ascending catecholamine pathways and amphetamine-induced locomotor activity: importance of dopamine and apparent non-involvement of norepinephrine. *Brain Res.*, **93**, 441–454.

Paradoxical aversive property of dexamphetamine

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The intravenous self-administration of dexamphetamine shows that it can serve as a reinforcer in rats (Pickens & Thompson, 1971) but a paradoxical, aversive property has been observed with oral self-administration (Le Magnen, 1969; Stolerman, Kumar & Steinberg, 1971). Rats have also been shown to reject distinctively flavoured solutions when their previous consumption was followed by intraperitoneal dexamphetamine (Cappell & LeBlanc, 1971), and a modified procedure involving discrimination between two flavours has been used to analyse further the aversive action of the drug.

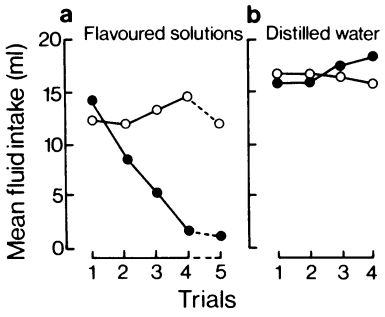

Figure 1 Aversive conditioning with dexamphetamine (1.0 mg/kg) in rats ($n=8$). (a) The mean consumption in 15 min of flavoured solutions paired with dexamphetamine (1.0 mg/kg i.p.) fell progressively (●, $P<0.001$), whereas the consumption of the control flavour was relatively constant (○). (b) There was a small but significant ($P<0.001$) compensatory increase in the mean 15 min water intake on the days after drug administrations (●), as compared with the days after intraperitoneal saline (○). The vertical bars indicate s.e. mean.

Solutions with synthetic 'chicken' and 'lemon' flavours were modified from Lovett & Booth (1970). After rats were adapted to restricted access to water, a flavour was presented for 15 min on every second day. Immediately afterwards, either dexamphetamine sulphate or saline was injected intraperitoneally. Thus, for half of the rats in an experiment, 'chicken' was repeatedly paired with dexamphetamine and 'lemon' with saline, and *vice versa* for the remaining rats. Water was available for restricted periods between flavour presentations.

The conditioning of flavour aversion with dexamphetamine (1.0 mg/kg) is shown in Figure 1 (trials 1–4). The aversion, which was confirmed when both flavours were presented simultaneously (trial 5), was not affected by delaying injections until 45 min after flavour presentations, or by providing spatial as well as flavour cues. Lower doses of dexamphetamine (0.10–0.32 mg/kg) yielded weaker aversions, but even smaller doses (0.025–0.05 mg/kg) did not enhance flavour intake. Severe deprivation combined with highly palatable flavours may have precluded any further enhancement by the drug. However, manipulations of palatability and deprivation also failed to reveal enhanced intake. The apparent aversive property of dexamphetamine has therefore proved robust to several variations in procedure and it appears to date that neither the dose level nor a 'ceiling' effect can account for the absence of a positive reinforcing action in this type of experiment.

References

CAPPELL, H. & LeBLANC, A.E. (1971). Conditioned aversion to saccharin by single administrations of mescaline and (+)-amphetamine. *Psychopharmacologia*, **22**, 352–356.

LE MAGNEN, J. (1969). Peripheral and systemic actions of food in the caloric regulation of intake. *Ann. N.Y. Acad. Sci.*, **157**, 1126–1156.

LOVETT, D. & BOOTH, D.A. (1970). Four effects of exogenous insulin on food intake. *Q. Jl. exp. Psychol.*, **22**, 406–419.

PICKENS, R. & THOMPSON, T. (1971). Characteristics of stimulant drug reinforcement. In *Stimulus properties of drugs*, Thompson, T. & Pickens, R., eds., pp. 177–192. New York: Appleton-Century-Crofts.

STOLERMAN, I.P., KUMAR, R. & STEINBERG, H. (1971). Development of morphine dependence in rats; lack of effect of previous ingestion of other drugs. *Psychopharmacologia*, **20**, 321–336.

Actions and interactions of morphine and dopamine on single neurones in the rat caudate nucleus

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Acetylcholine, 5-hydroxytryptamine, noradrenaline and dopamine have all been implicated in both the acute and chronic effects of morphine, but it is not at all certain which, if any, of these neurotransmitters in brain is involved in the central actions of the drug. However, dopamine is of special interest as binding studies have shown that some areas with high opiate-binding capacity (Pert & Snyder, 1973, 1975) also contain a high proportion of dopamine-sensitive neurones, e.g. the striatum, and this structure also contains relatively high levels of the endogenous morphine-like substance, enkephalin (Hughes, 1975). We have therefore used the microiontophoretic technique to study the effects of morphine on single neurones in the caudate nucleus of the rat and to