AMPHETAMINE AND NORADRENERGIC REWARD PATHWAYS

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IN HIGHER animals, brain mechanisms have evolved for the selective facilitation or reinforcement of successful responses (i.e., behaviour that leads to reward or to the avoidance of punishment). Analysis of these central reward mechanisms has been accelerated by studies of amphetamine. At low doses, this agent causes a remarkable facilitation of all reinforced responses (STEIN, 1964a). The facilitation does not depend on the nature of the goal that motivates the behaviour: amphetamine facilitates both positively-reinforced behaviours maintained by reward and negatively-reinforced behaviours maintained by the avoidance of punishment. Furthermore, if small doses of amphetamine are given regularly after a response, as in self-administration experiments in animals, the response that delivers the drug is strongly reinforced (PICKENS and HARRIS, 1968); a similar demonstration of the powerful rewarding action of amphetamine in man is regularly provided by the amphetamine addict. These behavioural observations suggest that amphetamine acts on, or in intimate relation to, the reward system in the brain. Understanding of the biochemical nature of the facilitatory amphetamine response could therefore be expected to increase understanding of the biochemical nature of the reward system.

AMPHETAMINE AND BRAIN NOREPINEPHRINE

In early studies, it was found that the facilitating action of amphetamine on behaviour was indirect and probably dependent on the release of a catecholamine (STEIN, 1964b). In these experiments, the self-stimulation method of OLDS and MILNER (1954) was used to measure the behaviour enhancing effect of amphetamine. Depletion of catecholamine stores by reserpine decreased the facilitating action of amphetamine and preservation of catecholamines by monoamine oxidase inhibitors increased the facilitating action of amphetamine. Furthermore, in rats pretreated with monoamine oxidase inhibitors, a powerful enhancement of self-stimulation was obtained with phenethylamine, the chemical structure common to both amphetamine and the catecholamines. Subsequently, by the use of different behavioural methods and more specific inhibitors of catecholamine synthesis, other workers confirmed the conclusion that facilitatory action of amphetamine is mediated by a catecholamine (WEISSMAN, KOE and TENEN, 1966; HANSON, 1967; RECH and STOLK, 1970).

More recent work suggests that the relevant catecholamine is norepinephrine (WISE and STEIN, 1970). Selective blockade of norepinephrine biosynthesis by inhibition of dopamine-β-hydroxylase (E.C. 1.14.2.1), the enzyme responsible for the conversion of dopamine to norepinephrine, eliminated the facilitating action of amphetamine. Intraventricular infusion of norepinephrine after dopamine-β-hydroxylase inhibition reinstated the action of amphetamine. The noradrenergic receptor involved in behavioural reinforcement appears to be of the α-type (WISE, BERGER and STEIN, 1973). Intraventricular administration of the α-noradrenergic antagonist phentolamine, but not the β-antagonist propranolol, reduced the rate of self-stimulation and blocked the

facilitatory effect of amphetamine. In other experiments, rewarding brain stimulation or moderate doses of amphetamine administered to freely-moving rats with permanently-indwelling cannulas released norepinephrine and its metabolites into brain perfusates (STEIN and WISE, 1969). Both treatments caused shifts in the pattern of metabolites towards *O*-methylated products (see also, GLOWINSKI and AXELROD, 1965).

These pharmacological observations fit nicely with the results of self-stimulation mapping studies on the one hand (OLDS, 1962) and histochemical maps of norepinephrine pathways on the other (FUXE, 1965; FUXE, HÖKFELT and UNGERSTEDT, 1968). Self stimulation sites and noradrenergic areas overlap to a surprising degree: the most intensely rewarding points in the brain fall precisely along noradrenergic fibre bundles and in rich noradrenergic terminal areas (STEIN, 1968). Although most noradrenergic cell groups have not yet been systematically studied, high rates of self-stimulation are obtained in the almost exclusively noradrenergic cell concentrations of the locus coeruleus (CROW, SPEAR and ARBUTHNOTT, 1972; RITTER and STEIN, 1972). Self-stimulation of this region is quite sensitive to facilitation by amphetamine and suppression by chlorpromazine, but it is largely unaffected by the dopamine-antagonist pimozide (RITTER and STEIN, in press). These pharmacological observations support the inference from two independent mapping studies that self-stimulation can be localised in a relatively homogeneous noradrenergic site (the locus coeruleus). Contrary to the view that noradrenergic neurons merely activate behaviour by a nonspecific increase in arousal (ROLL, 1970; ANTELMAN, LIPPA and FISHER, 1972), this demonstration of 'pure' noradrenergic self-stimulation is presumptive evidence that at least some noradrenergic neurons specifically mediate rewarding effects.

AMPHETAMINE AND BRAIN DOPAMINE

While it is evident that norepinephrine is involved in the behavioural-facilitating action of amphetamine, the role of dopamine is still unclear. At high doses, amphetamine induces a stereotyped behaviour pattern that appears to be mediated by the release of dopamine (RANDRUP and MUNKVAD, 1967, 1970); however, at these high doses of amphetamine, goal-directed behaviour is usually suppressed rather than facilitated (Fig. 1). Similarly, activation of central dopamine receptors by apomorphine over

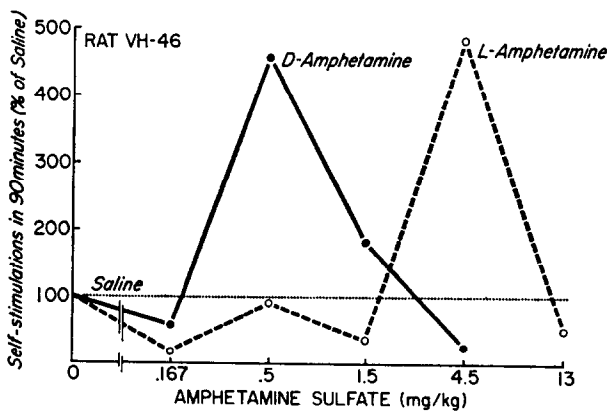

FIG. 1.—Facilitation and suppression of internal capsule self-stimulation by various doses of *d*- and *l*-amphetamine. Note 9-fold difference between the two isomers in potency for peak facilitation. Rat VH-46.

a wide dose range suppresses self-stimulation and other rewarded behaviours (DE OLIVEIRA and GRAEFF, 1972). It is conceivable that dopamine-mediated stereotyped behaviour can compete with and disrupt norepinephrine-mediated goal-directed behaviour. This idea implies that it might be possible to reverse the suppressive effects of dopaminergic agents on goal-directed behaviour by administration of noradrenergic agents. Such seems to be the case. The suppressive effects of apomorphine on self-stimulation are reversed by *d*-amphetamine, but only poorly by *l*-amphetamine (KOJIMA, RITTER, WISE and STEIN, in preparation) (Fig. 2). The different activities of the two isomers is consistent with the suggestion that *d*-amphetamine is many times more potent than *l*-amphetamine as a potentiator of central noradrenergic activity (TAYLOR and SNYDER, 1971).

The effects of norepinephrine and dopamine on self-stimulation were directly examined by injecting these agents in the lateral ventricle via permanently-indwelling cannulas. *l*-Norepinephrine facilitated medial forebrain bundle self-stimulation over a wide range of doses (WISE, BERGER and STEIN, 1973) (Fig. 3). Similar doses of dopamine are much less effective or may even suppress self-stimulation. The mild facilitating effects of dopamine are sometimes observed after a delay of several minutes, and thus may reflect conversion of the dopamine to norepinephrine. If this step is

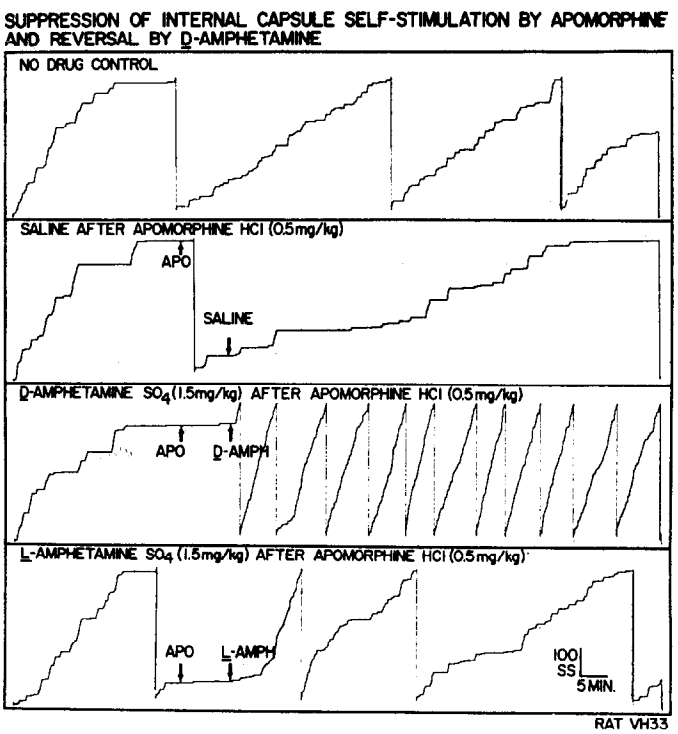

FIG. 2.—Suppression of self-stimulation by apomorphine (APO) and reversal by *d*-amphetamine. The same dose of *l*-amphetamine has only a small effect. Pen cumulates self-stimulation responses (SS) over time and resets automatically after 500 responses (see Key). Intraperitoneal injections marked by arrows. Rat VH-33: internal capsule.

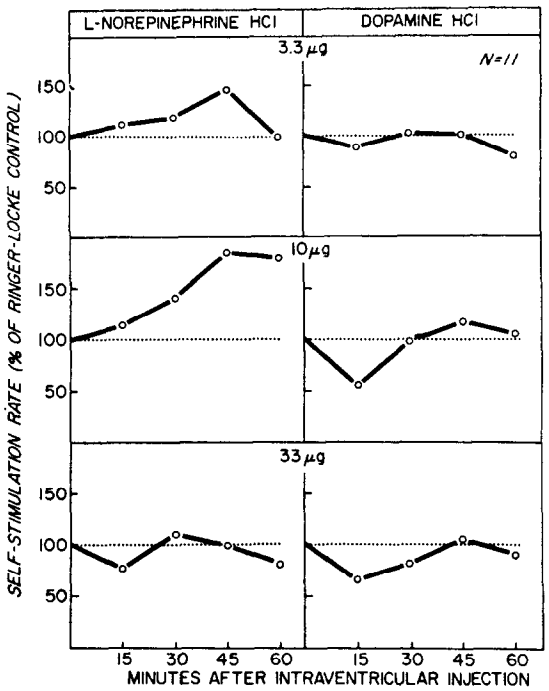

FIG. 3.—Facilitation of self-stimulation by norepinephrine and suppression by dopamine. The catecholamines were dissolved in 10 μl of Ringer–Locke solution and injected in the lateral ventricle one-half hour after the start of the 90-min test. Averaged data of 11 rats with electrodes in the medial forebrain bundle (level of posterior hypothalamus).

blocked by inhibitors of dopamine-β-hydroxylase, dopamine is ineffective (WISE and STEIN, 1969). In contrast, the facilitating action of exogenous norepinephrine is especially evident after inhibition of dopamine-β-hydroxylase, since depletion of the endogenous stores of norepinephrine causes suppression of the self-stimulation baseline.

Recent findings of self-stimulation in the dopamine cell concentrations of the substantia nigra have been taken as evidence of a dopaminergic reward system (CROW, 1972; PHILLIPS and FIBIGER, 1973). This interpretation is rendered hazardous, however, by the presence of noradrenergic fibres of passage in this region (UNGERSTEDT, 1971). To further evaluate the hypothesis that dopamine mediates rewarding effects, rostally-projecting dopamine pathways were mapped for self-stimulation at points in the brain where UNGERSTEDT (1971) describes a somewhat better separation of noradrenergic and dopaminergic systems than that in the substantia nigra. Self-stimulation was obtained from some electrodes in the dopamine tracts of the internal capsule, particularly from sites surrounding the tip of the crus cerebri, but maximal rates were only about 20 per cent of the maximal rates obtained from medial forebrain bundle electrodes (KOJIMA, RITTER, WISE and STEIN, in preparation). The most reinforcing internal capsule placements were located either in medial sites that border on the noradrenergic fibre system in the medial forebrain bundle, or in ventrolateral sites just dorsal to the noradrenergic projection into the amygdala.

Internal capsule self-stimulation was facilitated by *d*- and *l*-amphetamine, but *d*-amphetamine was about 9 times more potent (Fig. 1). As already noted, such a result has been taken to reflect a noradrenergically-mediated behavioural process (TAYLOR and SNYDER, 1971).

Although the above observations may be interpreted in a number of ways, the overall pattern of results does not support the idea that dopamine is an important transmitter in the reward system. Indeed, while we cannot at this point rule out the possibility that some dopamine pathways may facilitate behaviour, our evidence generally favours the idea that at least some dopamine systems can suppress goal-directed behaviour.

AMPHETAMINE AND BEHAVIOURAL PUNISHMENT: POSSIBLE ROLE OF BRAIN SEROTONIN

Like other higher functions, the regulation of goal-directed behaviour appears to be mediated by antagonistic mechanisms — the behaviourally-facilitatory reward system mentioned above, and a behaviourally-suppressant punishment system (MAGOUN, 1958). The reward and punishment mechanisms seem to be neurochemically distinct. As already suggested, the reward system may be mainly noradrenergic, whereas the punishment system appears to contain both cholinergic and serotonergic components (MARGULES and STEIN, 1967, 1969; WISE, BERGER and STEIN, 1970, 1973; STEIN, WISE and BERGER, 1973).

Amphetamine has long been known to intensify the suppressive effects of punishment on goal-directed behaviour (GELLER and SEIFTER, 1960; KELLEHER and MORSE, 1964). This effect seems paradoxical, since amphetamine generally facilitates goal-directed behaviour. Furthermore, because intraventricular administration of norepinephrine markedly reduces the suppressant effects of punishment (WISE, BERGER and STEIN, 1973), it might be expected that a strong potentiator of central noradrenergic activity like amphetamine would lessen rather than increase punishment effects. In attempts to resolve this paradox, the possible involvement of other monoamine transmitters should be considered. Recent evidence suggests that the suppressant effects of punishment may be mediated at least in part by serotonergic neurons (WISE, BERGER and STEIN, 1970, 1973). Since amphetamine releases serotonin as well as catecholamines from central neurons (FUXE and UNGERSTEDT, 1970; RUTLEDGE, AZZARO and ZIANCE, 1972), it is logical to speculate that the punishment-enhancing effects of amphetamine may be mediated via the release of serotonin (STEIN, WISE and BERGER, 1973). In the amphetamine addict, enhancement of the effects of punishment could lead to apprehension and suspiciousness, and eventually to paranoia.

Whether in any given case amphetamine predominantly facilitates the release of norepinephrine, or whether it mainly facilitates the release of serotonin, probably depends to a large extent on the nature of the test situation. Norepinephrine release may be predominantly facilitated in tests that depend on the activation of the reward system (e.g., self-stimulation), whereas serotonin release may be selectively facilitated in tests that depend on the activation of the punishment system (e.g., conflict test of GELLER and SEIFTER, 1960).

In summary, amphetamine enhances both the behaviourally-facilitatory effects of reward and the behaviourally-suppresant effects of punishment; at high doses, a species-typical pattern of stereotyped behaviour is observed. All of these effects of

amphetamine may be mediated via the release of different brain monoamines; reward (and addiction) by norepinephrine, punishment (and paranoia) by serotonin, and stereotyped behaviour by dopamine.

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