ON THE POSSIBLE INTERRELATIONSHIP IN MECHANISM OF ACTION BETWEEN MORPHINE, AMPHETAMINE AND NEUROLEPTIC DRUGS

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MORPHINE interacts with the brain catecholamines, dopamine and noradrenaline (CLOUET and RATNER, 1970; GUNNE *et al.*, 1969; LOH *et al.*, 1973; SMITH *et al.*, 1972), but neither the biochemical nor the pharmacological mechanism of action of morphine is presently understood.

In our laboratory the interest on morphine arose from reported studies in mice and rats which on one side indicate that morphine produces central stimulant effects which apparently may be related to amphetamine and on the other side points to similarities between morphine and neuroleptic drugs. These findings seem apparently paradoxical since it is well-established that amphetamine and neuroleptic drugs show mutual antagonism and that this effect is a highly characteristic property of neuroleptica (FOG, 1972; JANSSEN *et al.*, 1960; VAN ROSSUM, 1966). However, our comparative studies in rats between amphetamine sulphate (0·25–10 mg/kg) and small acute doses of morphine chloride (0·5–2 mg/kg) revealed significant differences in mechanism of action: The morphine hyperactivity induced by 1–2 mg/kg appeared as a general stimulation of locomotion, rearing, grooming, eating and drinking in the rats. The morphine induced locomotion and rearing was very characteristic and seen in phases as bursts of activity followed by phases of sedation. Morphine in doses above 5 mg/kg induced sedation and catalepsy. For further details see FOG, 1970; AYHAN and RANDRUP, 1973a,b.

In contrast amphetamine induced a more selective and continuous stimulation of locomotion and rearing which at increasing doses became more and more stereotyped. At no dose levels stimulation of grooming, eating and drinking have been observed. High doses of amphetamine (5–10 mg/kg) led, after a prephase of locomotion and rearing, to an extremely stereotyped stimulation consisting only of sniffing, licking or gnawing of the cage wires (SCHEEL-KRÜGER, 1971).

As further differences should be underlined that amphetamine very strongly abolish social activity in rats (and monkeys) (SCHIØRRING and RANDRUP, 1971) whereas morphine did not abolish any social activity (SCHIØRRING and HECHT, in preparation).

Recently α-methyltyrosine, an inhibitor of the catecholamine biosynthesis, has been shown to antagonise the locomotion of small acute doses of morphine in rats (DAVIS *et al.*, 1972) and mice (CARROL *et al.*, 1972; STRUBELT *et al.*, 1970). This finding was confirmed in the rat and furthermore that inhibition of noradrenaline biosynthesis with FLA-63 or blockade of noradrenaline or dopamine receptors in the

brain also antagonised the morphine-induced locomotion, rearing and grooming. (AYHAN and RANDRUP, 1973a).

These findings thus strongly indicate a significance of the catecholamines in the morphine stimulation. A similar relationship in the amphetamine stimulation is already well-established (SCHEEL-KRÜGER, 1971), but the biochemical and pharmacological mechanisms of actions must be different since it was found that these two drugs showed mutual antagonism. (FOG, 1970; AYHAN and RANDRUP, 1973b).

The simultaneous injection of morphine (2 mg/kg) and amphetamine led to the inhibition of morphine type excitation: bursts of locomotion and rearing, increased grooming. 0·25 mg/kg of amphetamine produced a significant inhibition and a further increase of amphetamine dose (0·5 and 1·0 mg/kg) caused almost complete inhibition. The mutal antagonism was evident since morphine (2 mg/kg) antagonised the stimulation of locomotion and rearing after higher doses of amphetamine (AYHAN and RANDRUP, 1973b). Stimulation of central dopamine mechanism with apomorphine (0·5 mg/kg) or L-dopa (100 mg/kg) given after a peripheral decarboxylase inhibitor (Ro-4-4602) produced also a significant inhibition of the morphine-type excitation.

The mechanism of the morphine stimulation must thus be different from that of amphetamine since apomorphine or L-dopa in the above mentioned doses potentiated the amphetamine stimulation (AYHAN and RANDRUP, 1973b).

It is well-known that the behavioural sedation and catalepsy after a single high dose of morphine to rats changes to behavioural excitation (EIDELBERG and SCHWARTZ, 1970) and typical amphetamine-like stereotyped, licking gnawing activity (FOG, 1970; AYHAN and RANDRUP, 1972) during chronically injection of morphine. Pretreatment with drugs which deplete the catecholamines, reserpine, α-methyltyrosine, FLA-63, diethyldithiocarbamate or antagonised dopamine or noradrenaline receptors antagonise the excitation after chronic morphine. (EIDELBERG and SCHWARTZ, 1970; AYHAN and RANDRUP, 1972). Comparison between morphine and amphetamine stereotypy indicated that brain noradrenaline plays a more important role than dopamine in morphine stereotypy (AYHAN and RANDRUP, 1972) in contrast to amphetamine stereotypy where dopamine is the most important amine (SCHEEL-KRÜGER, 1971).

The simultaneous injection of amphetamine (20 mg/kg) with the daily injection of morphine (100 mg/kg) to chronically morphinized rats antagonised the stereotyped licking/biting activity which otherwise would have been present. Mutual antagonism between amphetamine and morphine is thus even present at dose levels of these drugs which given separately induce stereotypy (FOG, 1970). Morphine in a single high dose shows antagonism of apomorphine (JANSSEN *et al.*, 1960) and amphetamine stereotypy (FOG, 1970). Other characteristic neuroleptic properties in rats are development of catalepsy which biochemically seems correlated with the increase of homovanillic acid a major dopamine metabolite (KUSCHINSKY and HORNYKIEWICS, 1972; STILLE, 1971; STILLE and LAUENER, 1971).

In conclusion of the present discussion it is hoped that the presented evidence has underlined the clear-cut key position between amphetamine and neuroleptic drugs which morphine occupy and that further investigation along these lines might provide a very fruitful understanding of the central mechanism underlying these types of drugs.

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