The role of brain catecholamines in morphine analgesic action in morphine tolerant rats

Recently, evidence for an adrenergic mechanism for the analgesic action of morphine in intact rats was presented (Vedernikov & Afrikanov, 1969). I now describe experiments in tolerant rats which support the role of noradrenaline in morphine analgesia.

The experiments were made on white female rats, 180–230 g, made tolerant to a test dose of morphine (5 mg/kg, s.c.) after 20 days of successive subcutaneous injections of 10 mg/kg of morphine. The analgesic activity was estimated using the change in pain threshold to mechanical pressure of the tail (Sangailo, 1962). By this test, before tolerance to the test dose developed, the pain threshold after morphine was 100 mm Hg (top limit); after tolerance, it was not changed significantly from base value.

Cocaine hydrochloride (50 mg/kg, s.c.), pyrogallol (50 mg/kg, s.c.) given 1 h, or (±)-tryptophan (400 mg/kg, i.p.) given 4 h before the morphine test dose increased the analgesic's action on the pain threshold. This increase was about 20 mm Hg. Iproniazid (100 mg/kg, i.p.) given 4 h before the morphine test dose had a similar effect; its administration for three successive days (50, 50, 100 mg/kg) increased the effect of the morphine test dose further, though not significantly. The most pronounced action on the restoration of the ability of the morphine test dose to elevate the pain threshold in groups of 10 rats was possessed by amphetamine (2 mg/kg, s.c.) injected 1 h before morphine. There was an increase of 80 mm Hg in the pain threshold 30 min after injection of morphine, which dropped to 18 mm Hg at 180 min, in animals previously treated for 26 days with morphine (10 mg/kg), but after a further 9 days morphine treatment, the test dose produced a rise in threshold that did not go above 20 mm Hg and that disappeared at 150 min. After 40 days of treatment with 10 mg/kg of morphine, the same dose (10 mg/kg) given as a test dose increasd the threshold to 65 mm Hg at 90 min; this was potentiated by amphetamine to 96 mm Hg at 90 min. On the other hand, disulfiram (50 mg/kg, i.p.) 2 h before 10 mg/kg of morphine significantly decreased the analgesic's action on pain threshold, while reserpine (1 mg/kg i.p.) or iproniazid (100 mg/kg, i.p.) 4 h before a dose of 15 mg/kg of morphine did not influence the activity of the analgesic significantly.

It seems that the inhibition of any mechanism by which noradrenaline is normally inactivated (monoamine oxidase inhibition by iproniazid, catechol-*O*-methyltransferase inhibition by pyrogallol, re-uptake inhibition by cocaine) is accompanied by the reappearance of analgesia to the test dose of morphine in tolerant rats. The marked potentiation by amphetamine of the analgesia induced by the morphine test dose can be explained by its action in releasing brain catecholamines; the decrease of this action after the development of tolerance is to be attributed to the loss of ability by morphine to release noradrenaline completely (Maynert, 1967). This concept seems likely since increasing the dose of morphine restored the ability of amphetamine to increase the analgesic action of morphine. Decrease of noradrenaline formation by the inhibition of dopamine-β-hydroxylase, produced by disulfiram, also weakened morphine's analgesic action. Iproniazid, in non-tolerant rats decreased the effect of low (2·5 mg/kg) and high (5·0 mg/kg) doses of morphine (Vedernikov & Afrikanov, 1969), while in tolerant rats it intensified the action of the test dose, but produced no effect on the activity of the high morphine dose. In non-tolerant rats (±)-tryptophan did not influence morphine analgesic action significantly, while in tolerant rats it promoted the reappearance of the effect of the morphine test dose on the pain threshold. Reserpine weakened morphine analgesia, in normal rats, but not in rats made tolerant to morphine.

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Central nervous system stimulant action of fenfluramine in rabbits

Fenfluramine is an anorexic drug which, although structurally related to amphetamine, has been described as having no central stimulant activity in animals or man (Le Douarec & Schmitt, 1964; Hill & Turner, 1967; Santer, 1968). Recently, Jespersen, Bonaccorsi & Garattini (1969) have shown that, like amphetamine, fenfluramine causes hyperthermia and clear signs of central nervous system excitation in mice treated with a combination of dopa and the monoamine oxidase inhibitor, pheniprazine. Although these experimental conditions are not comparable with those of the normal therapeutic use of fenfluramine, the findings are consistent with recent clinical reports of overdosage indicating that the drug can cause stimulation of the central nervous system in man (Riley, Corson & others, 1969; Gold, Gordon & others, 1969; Fleischer & Campbell, 1969; Campbell & Moore, 1969). Moreover, work in this laboratory has provided direct evidence of a cortical stimulant action of fenfluramine in rabbits.

Male adult rabbits, 3·5–5 kg, were prepared with indwelling stainless steel electrodes, placed superficially on the dura over the motor and occipital areas of the cerebral cortex. After complete recovery from the operation, the animals were trained to sit quietly in stocks for recording of electrocorticograms (ECoG). The normal ECoG showed an alert pattern, but after the intravenous administration of equi-anorectic doses of dexamphetamine sulphate (2 mg/kg) or fenfluramine hydrochloride (8 mg/kg) further arousal occurred although the effect was slight and barely distinguishable from the response to intravenous saline. In other experiments, to facilitate more quantitative evaluation of this effect, an ECoG pattern resembling deep sleep was first produced by the administration of pentobarbitone: under these circumstances, both anorectic drugs showed a clear-cut alerting action.

A comparison of the effects of dexamphetamine sulphate (2 mg/kg), fenfluramine hydrochloride (8 mg/kg) and normal saline (1 ml/kg) injected intravenously 30 min after an intravenous dose of pentobarbitone (20 mg/kg) was made in six rabbits using a cross-over design with an interval of at least two days between drug treatments. Recordings of ECoG were taken for 90 min after the administration of dexamphetamine or fenfluramine and their effects during this time were scored on a scale of 0 to 6, ranging from maximal arousal with persistent body movement artefact (score 0), to stage 4 sleep with low frequency, high amplitude records (score 6). Fig. 1 shows the abrupt change from an alert ECoG pattern to deep sleep after the administration of pentobarbitone; in contrast to the subsequent gradual lightening of sleep after intravenous saline administration, both dexamphetamine and fenfluramine caused a rapid and complete ECoG arousal accompanied by body movement artefacts, widely dilated pupils and intermittent masticatory movements.