AN ANXIOLYTIC-LIKE ACTION OF CLONIDINE AND MORPHINE WHICH IS NALOXONE-REVERSIBLE

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In animals, both the antihypertensive agent clonidine and the narcotic analgesic morphine have been shown to be capable of decreasing responsiveness to stimuli which normally elicit fear (Davis et al 1979). Since the antihypertensive action of clonidine in the rat has recently been shown to be prevented by the narcotic antagonist naloxone (Farsang & Kunos 1979) the effects of these and other drugs have been examined using a simple test designed to show both anxiolytic and anxiety-producing effects.

Male albino (T,O) mice were kept in their home cages in an experimental room for at least one week prior to test. After drug treatment they were placed individually in a wooden box (22 x 22 x 15 cm), the floor of which consisted of four metal plates raised 5mm from the base and separated from the sides and from each other by a 5mm gap. Initial exploratory activity was assessed by noting the number of times each mouse crossed from one plate to another during the first 90 seconds after introduction to the box. Mice were always introduced in the same position and each mouse was tested once only. Groups of 5-10 animals were used and significance from vehicle-injected controls assessed by the Mann-Whitney 'U' test.

Initial experiments showed that the anxiolytic agent diazepam produced the predicted effect: low doses (0.5 - 1.0 mg/kg sc) significantly increased the number of crossings while higher doses produced a decrease accompanied by ataxia and sedation.

Clonidine (0.05 mg/kg sc) and morphine (1.0 mg/kg sc) significantly increased the number of crossings. Naloxone (1.0 mg/kg sc) was without effect alone but prevented the effect of both clonidine and morphine. Since clonidine shows strong selectivity as an agonist at α_2-adrenoceptors (Drew 1976), the effects of yohimbine, a rather selective antagonist of this receptor (ibid) were examined. Yohimbine (5.0 mg/kg sc) alone significantly inhibited plate crossing without inducing either ataxia or sedation and also prevented the increase caused by both clonidine and morphine. The inhibition by yohimbine of plate-crossing was attenuated by clonidine, morphine and diazepam.

These preliminary results suggest that the anxiolytic-like effects of clonidine and morphine are closely interrelated, perhaps by an action on a common pathway such as the locus-coeruleus noradrenergic system. Both clonidine and morphine inhibit spontaneous firing of this system and it has also been implicated in anxiety (Davis et al 1979). The nature of the interaction however appears to be complex. We have also observed naloxone to prevent the inhibitory effect of clonidine in the co-axially stimulated guinea-pig ileum (Handley, Brown & Mithani, in preparation) and clonidine attenuates the narcotic withdrawal syndrome in man (Gold et al 1978). Since clonidine and naloxone do not appear to compete for either opiate receptors or adrenoceptors, Farsang and Kunos (1979) have suggested that the antagonism by naloxone of the antihypertensive effect of clonidine may indicate that clonidine releases endogenous opiates. This possibility would only partially account for the present findings. It will be necessary to establish whether the observed antagonism of morphine by yohimbine is indeed due to a selective action of the latter at α_2-adrenoceptors before the precise nature of the interactions described here can be further elucidated.

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