Evidence for Involvement of Central Noradrenergic Neurons in the Cardiovascular Depression Induced by Morphine in the Rat

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Summary

Morphine caused in the anaesthetized rat reduction in brain noradrenaline (NA) turnover, hypotension and bradycardia, similarly to the antihypertensive, α-adrenergic agonist, clonidine. All effects of morphine were antagonized by naloxone, as well as the α-receptor antagonist, yohimbine. In contrast, naloxone did not affect the circulatory depression and reduction in brain NA utilization by clonidine, which both previously have been found to be antagonized by yohimbine. In contrast to clonidine, morphine even in high doses did not facilitate the flexor reflex activity of acutely spinalized rats. Pretreatment with protriptylin largely attenuated the circulatory depressive effects of morphine, as it has previously been found to block the corresponding effects of clonidine. Thus, the morphine-induced cardiovascular depressive effects are primarily elicited by activation of opiate receptors. However, the inhibition of brain NA neurotransmission by morphine appears critically involved in the mediation of the circulatory depression.

Introduction

Previous studies indicate that the cardiovascular effects of morphine are of central origin (Mansour et al., 1970; Laubie et al., 1974; Marmo et al., 1975), and they resemble in several ways, those

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of the $\alpha$-adrenergic agonist clonidine, used clinically as an antihypertensive agent. Both morphine (Kayaalp and Kaymakçalan, 1966; Evans et al., 1952; Svensson and Trolin, 1975) and clonidine (see Trolin, 1975) cause in the anaesthetized animal, e.g. rat, hypotension and bradycardia, and both drugs also decelerate central noradrenaline (NA) turnover (or utilization) (Svensson and Trolin, 1975; Gomes et al., 1976a; Andén et al., 1970; Braestrup, 1974; Rochette et al., 1974; Andén et al., 1976). In agreement with these biochemical findings, both morphine (Korf et al., 1974) and clonidine (Svensson et al., 1975) have been found to inhibit the firing rate of brain NA neurons, and this effect is in all probability not secondary to the hypotensive action of the drugs (see Gomes et al., 1976a; Svensson et al., 1975). Morphine and clonidine also inhibit the electrically induced release of NA from cortical brain slices (Montel et al., 1975a, b; Starke and Montel, 1973). Consequently, the hypothesis has been advanced that the cardiovascular effects of morphine might be related to, or mediated by, its effect on central noradrenergic mechanisms (Svensson and Trolin, 1975; Gomes et al., 1976a).

Recently, the $\alpha$-adrenergic antagonist yohimbine was found to antagonize both the clonidine-induced cardiovascular effects (Schmitt et al., 1971, 1973; Bolme et al., 1974), and its above mentioned biochemical effects on brain NA turnover (Andén and Grabowska, 1975; Andén et al., 1976). Thus, in order to test our hypothesis we investigated, whether yohimbine might antagonize also the morphine-induced cardiovascular as well as biochemical effects on brain NA turnover in the anaesthetized rat. The opposite question, namely whether naloxone, which antagonizes the morphine-induced effects on both cardiovascular function and brain NA turnover (Svensson and Trolin, 1975; Gomes et al., 1976a), might antagonize the clonidine-induced effects on circulation and central NA turnover, was also analyzed.

Another drug, known to antagonize the clonidine-induced hypotension and bradycardia is protriptyline (van Spanning and van Zwieten, 1973), a drug which also interferes with brain noradrenergic mechanisms, e.g. inhibits the NA uptake mechanism at the cell membrane (see Carlsson et al., 1969). In the present study the ability of protriptyline (PTP) to block the morphine-induced circulatory depressant effects was also explored.

In a third set of experiments, the action of morphine, also in a high dose, on the flexor reflex activity in the rat hindlimb was studied, inter alia since this reflex is augmented by high doses of clonidine, in all probability due to its NA-receptor activating properties (Andén et al., 1970).