Clonidine-Induced Sedation in Rats: Evidence for Mediation by Postsynaptic $\alpha_2$-Adrenoreceptors

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Summary

The effect of low doses of clonidine on exploration and motility was investigated in rats after destruction of central noradrenergic systems by 6-hydroxydopamine (6-OHDA) or DSP-4. In accordance with previous results, clonidine decreased exploration and motility in control animals. This sedative effect of clonidine was potentiated in animals that suffered selective and extensive depletions of brain NA as a result of neonatal treatment with 6-OHDA. Depletion of NA by administration of DSP-4 to adult animals did not influence clonidine's sedative effects. Yohimbine, but not phentolamine, antagonized clonidine-induced hypomotility both in control and in neonatal 6-OHDA treated groups. The results suggest that clonidine-induced sedation is mediated by postsynaptic $\alpha_2$-adrenoreceptors.

Key words: Clonidine, phentolamine, yohimbine, $\alpha_2$-receptors, locomotor activity, sedation, 6-hydroxydopamine.

Introduction

Clonidine is a drug with a wide spectrum of activity. Its hypotensive and bradycardic properties have stimulated much research and have been the subject of several recent reviews (Kobinger, 1978; Schmitt, 1977; Van Zwieten, 1975). In man a common side-effect of clonidine administration is sedation (Van Zwieten, 1975). Both hypotension and sedation appear to result from the stimulation of central...
\( \alpha \)-adrenoreceptors (Bruner and Klein, 1968; Van Zwieten, 1975) and the available evidence suggests that these receptors possess the general characteristics of the peripheral \( \alpha_2 \)-adrenoreceptors (Kobinger, 1978; Drew et al., 1979) that are located presynaptically on or near the noradrenergic nerve terminals (Langer, 1977, 1981; Starke, 1977; Westfall, 1977). Stimulation of these receptors can inhibit the release of noradrenaline (NA) and it has been thought that this might be the basis of clonidine’s hypotensive effects. However, more recent evidence has indicated that clonidine induces hypotension through stimulation of postsynaptic \( \alpha_2 \)-adrenoreceptors (Langer, 1981). This postulation is supported by the finding that the majority of specific \( ^3H \)-clonidine binding sites in the forebrain are not located on NA axons or terminals (U’Pricbard et al., 1979, 1980) and may explain why clonidine induced-hypotension and bradycardia persist after depletion of endogenous stores of NA (Haeusler, 1974).

A number of investigators have suggested that the hypomotility that is induced by low doses of clonidine in experimental animals (Strombom, 1975, 1976) is mediated through activation of presynaptic \( \alpha_2 \)-adrenoreceptors (Delini-Stula et al., 1979; Drew et al., 1979; Zebrowska-Lupina et al., 1977; Strombom and Svensson, 1980). The present study was undertaken in an attempt to provide further information on the type and location of \( \alpha \)-adrenoreceptors that interact with clonidine to induce decreased exploration and hypomotility in rats. To this end, the effects of clonidine and \( \alpha \)-antagonists on motor activity were investigated in control and in NA depleted animals.

**Materials and Methods**

**Subjects:** Male Wistar rats were used in all experiments. They were housed in groups of five with free access to water and standard laboratory rat chow (Purina). The colony room had a temperature of 22–25 °C, humidity of 44–55 %, and a 12 hours light-dark cycle. Independent groups of animals were used in each experimental condition. That is, animals were used only once and then analyzed biochemically or discarded.

**Behavioural Testing**

**Exploration:** Exploratory activity was measured by placing the animal in a Hebb-William apparatus (Whishaw, 1970) with squares, parallel alleyways, start and goal boxes. Each animal was placed in the start box of the maze and 3 sec later the door leading to the maze was raised. The number of squares and alleyways entered in successive 3-min periods for a total of 21 min was measured.