Involvement of 5-HT₂ Receptors in the LSD- and L-5-HTP-Induced Suppression of Lordotic Behavior in the Female Rat

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Summary

Copulatory behavior in the ovariectomized rat, the lordotic response (L.R.), was induced by estrogen followed by progesterone. L.R. is inhibited by lysergic acid diethylamide (LSD) (≥ 0.05 mg/kg) and by Levo-5-hydroxytryptophan (L-5-HTP) (≥ 2.5 mg/kg). The effects of the putative 5-HT antagonists lisuride, metergoline, methysergide, mianserin, cinanserin, cyproheptadine, pirenperone and altanserin on the LSD-induced inhibition of L.R. were tested. Lisuride, metergoline, methysergide and mianserin were found to have no LSD-blocking effect. In contrast, cinanserin, cyproheptadine and pirenperone acted antagonistically to LSD, within a critical dose range. The selective 5-hydroxytryptamine₂ (5-HT₂) receptor antagonist altanserin effectively prevented the LSD-induced inhibition of L.R., and the doses required (0.05-0.20 mg/kg) indicated a comparatively high antagonistic potency. In addition altanserin (0.2 mg/kg) effectively prevented the lordosis inhibitory effect induced by L-5-HTP (2.5 mg/kg), after pretreatment with pargyline and RO4-4602. It is suggested that the suppression of copulatory behavior caused by LSD and L-5-HTP is mediated by 5-HT₂ receptors.

Key words: Lordotic behavior, 5-HT antagonists, LSD, 5-HT₂ receptors.

Introduction

The possible existence of more than one population of central 5-hydroxytryptamine (5-HT) receptors has been discussed in several
reports. Aghajanian and colleagues have suggested the presence of at least two postsynaptic 5-HT receptors, on the basis of the differential effect of microiontophoretically applied 5-HT in specific regions of the rat brain (McCall and Aghajanian, 1979; Aghajanian, 1981). Binding studies have also indicated the possibility of multiple 5-HT receptors. Peroutka and Snyder (1979) have proposed that there are two classes of 5-HT receptors, one class labelled by (3H)5-HT (5-HT₁ receptors) and the other by (3H)spiroperidol (5-HT₂ receptors). The idea of the existence of subtypes of 5-HT receptors is supported by the results of other binding studies (Seeman et al., 1980; Blackshear et al., 1981; Pedigo et al., 1981; Peroutka et al., 1981).

Attempts have been made to correlate receptor-mediated functional changes with radioligand binding to 5-HT receptors (Peroutka et al., 1981; Leysen et al., 1982). That 5-HT₂ receptors are involved in 5-HT-mediated behaviors in the rat has recently been confirmed in a number of reports (Niemegeers et al., 1983; Yap and Taylor, 1983; Green et al., 1983; Colpaert and Janssen, 1983).

There is considerable pharmacological evidence suggesting that brain 5-HT has an influence on reproductive functions regulated by ovarian steroids, and in particular on copulatory behavior (lordotic response, L.R.) in the female rat (for review see Meyerson and Malmnäs, 1978). It has been proposed that L.R. is inhibited by increased 5-HT activity. Thus, the 5-HT agonist lysergic acid diethylamide (LSD, Andén et al., 1968; Aghajanian et al., 1972) inhibited the estrogen + progesterone-activated L.R. in the ovariectomized female rat in a dose-dependent manner ($\geq 0.05$ mg/kg) (Eliasson and Meyerson, 1976, 1977; Sietnieks and Meyerson, 1980). An endogenous increase in 5-HT produced by the precursor Levo-5-hydroxytryptophan (L-5-HTP) also induced dose-dependent ($\geq 2.5$ mg/kg) suppression of the copulatory behavior activated by estrogen + progesterone in the ovariectomized rat (Meyerson and Malmnäs, 1978).

The purpose of the present experiments was to investigate which sub-type of 5-HT receptors are involved in the sexual behavior of the female rat. The ability of eight putative antagonists in blocking LSD-induced inhibition of L.R. was examined. Six of the compounds tested were: lisuride, metergoline, methysergide, mianserin, cinanserin and cyproheptadine. These have all been demonstrated in binding studies to have affinity for both receptor types, although the latter three showed a higher affinity for the 5-HT₂ receptor population (Peroutka and Snyder, 1979; Leysen et al., 1981; Blackshear et al., 1981; Martin and Sanders-Bush, 1982). Lisuride will in the following be referred to as a 5-HT antagonist, although its central 5-HT antagonistic properties are equivocal (see for discussion Rogawski and Aghajanian,