The Effects of Serotonergic and Antiserotonergic Drugs on the Flexor Reflex of Spinal Rat: a Proposed Model to Evaluate the Action on the Central Serotonin Receptor

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With 10 Figures

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Summary

The effects of serotonergic and antiserotonergic drugs on the hind limb flexor reflex (measured as a contraction of musculus tibialis anterior or as a flexion of the paw) in the spinal rat was studied. All serotonergic drugs used (L-5-hydroxytryptophan, L-tryptophan, LSD, fenfluramine, p-chloroamphetamine) stimulate the flexor reflex. Serotonin receptor blockers (cyproheptadine, WA-335, methergoline), which given alone are inactive, inhibit the stimulation induced by serotonergic drugs but do not influence that one caused by noradrenergic agents (amphetamine, clonidine). Both types of stimulation (serotonergic and noradrenergic) are antagonized by noradrenaline receptor blockers (phenoxybenzamine, clozapine). The anti-serotonergic action of serotonin antagonists used was confirmed on the basis of the antagonism to the head twitches induced by L-5-hydroxytryptophan.

The flexor reflex in the spinal rat may be a good model to evaluate the effect on the central (spinal cord) serotonin receptor and to differentiate this effect from that on the noradrenaline system.

Introduction

The flexor reflex of the hind limb of the spinal rat is controlled by noradrenaline (NA) neurons. The agents stimulating those neurons, e.g. amphetamine or clonidine, potentiate this reflex, while the drugs blocking noradrenergic transmission, as phenoxybenzamine or haloperidol, abolish it. Owing to that the flexor reflex is regarded as a good model for studying the action of drugs on central NA neurons (Andén, 1970).
We have noticed that LSD (Palider, Przewlocka, 1975) and L-5-hydroxytryptophan (5-HTP) (unpublished data) also potentiate the flexor reflex of the spinal rat. Therefore the purpose of the present paper was to examine the effect of serotonergic and antiserotonergic agents in this preparation.

As serotonergic agents we used two 5-hydroxytryptamine (5-HT) precursors — 5-HTP and L-tryptophan (TP), an agent regarded as mimicking the central 5-HT action, LSD (Andén et al., 1968; Aghajanian, Haigler, 1974), and fenfluramine (FF) and p-chloroamphetamine (PCA). The two latter compounds release 5-HT from neurons shortly after the administration, and inhibit the uptake of the amine, thus increasing the availability of 5-HT at the receptor (Bartholini et al., 1964; Dubault et al., 1967; Opitz, 1967; Carlsson et al., 1970; Costa et al., 1971; Tagliamonte et al., 1971; Southgate et al., 1971; Wrong et al., 1973). PCA also inhibits the 5-HT synthesis, but this effect appears much later, several hours after the injection (Pletscher et al., 1964; Fuller et al., 1965; Miller et al., 1971).

The antiserotonergic agents used were cyproheptadine (CH), WA-335 (9,10-dihydro-10-/1-methyl-4-piperidilidene/-9-anthrol) and methergoline (ME). CH was reported to block 5-HT receptors (Stone et al., 1961; Frey, Magnussen, 1968; Vargaftig et al., 1971; Van Riezen, 1972). WA-335 displays similar properties (Engelhardt, 1975; Käbling et al., 1975; Maj et al., 1975), and ME was also shown to be a potent 5-HT antagonist (Beretta et al., 1965; Ferrini, Glässer, 1965). The antiserotonin action of those compounds was found on peripheral tissues, and the data concerning their central antiserotonin effect are scanty or lacking (see Discussion).

The effect of the compounds affecting 5-HT neurons on the flexor reflex was studied using the method described by Andén (1967, 1972), which was modified by us by employing electrical stimulation of the hind limb instead of pinching, and recording the muscular contraction instead of assigning semiquantitative score to express the intensity of the reaction (Maj et al., 1974; Palider, Przewlocka, 1975). To assess the central antiserotonin effect of the compounds tested as 5-HT antagonists we investigated also their effect on the 5-HTP syndrome, which consists predominantly of characteristic head twitches (Corne et al., 1963).

**Materials and Methods**

The experiments were carried out on male Wistar rats, weighing 180 to 270 g.

The flexor reflex of hind limb of the spinal rat.