The action of muscimol on neurones of the substantia nigra of the rat[1]

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Summary. Muscimol and GABA applied microiontophoretically onto nigral neurones reduce the discharge rate of most of these cells. Bicuculline reversibly antagonizes the action of muscimol. I.p. applied muscimol reduces the firing rate of about half of the nigral cells tested.

Muscimol, a isoxazole found in the mushroom *Amanita muscaria*, is a structural modification of GABA. It potentiates morphine analgesia[2] and the cataleptic and amphetamine-antagonistic action of haloperidol[3]. These latter effects are probably resulting from striatal dopamine receptor blockade. It is conceivable that the potentiating effect of muscimol is produced through its depressant action on nigral dopaminergic cells. To test this hypothesis, the effect of microiontophoretically and i.p. applied muscimol on nigral neurones was investigated.

Methods. The experiments were performed on 20 male Sprague-Dawley rats (250–350 g) anaesthetized with chloralhydrate (400 mg/kg i.p.). Body temperature was maintained at between 36 °C and 38 °C. Extracellular action potentials were recorded from spontaneously active nigral cells. Amplified spike discharge was routed through a level discriminator and ratemeter. The following substances were applied by means of 3-barrel micropipettes into the immediate environment of single spontaneously active neurones: GABA (0.5 M, pH 3.5), muscimol (0.5 M, pH 3.5), bicuculline methiodide (20 mM, pH 3.0 in 165 mM NaCl). In some experiements, 1 barrel was filled with 3 M NaCl in order to balance ejecting currents. The caudate putamen complex was stimulated by means of small bipolar electrodes (single pulses 0.3 msec, 3–5 V). Nigral cells were approached stereotactically using the atlas of De Groot. The site of the stimulation electrode was verified on cyrostat sections.

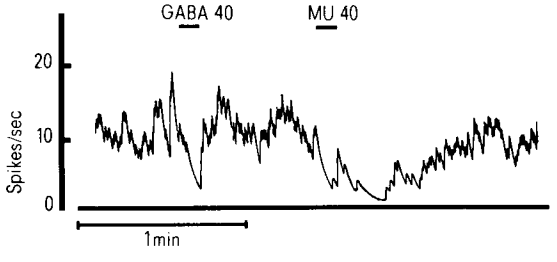

Fig. 1. Ratemeter record from a neuron of the substantia nigra which was inhibited in response to striatal stimulation. Depressant actions of muscimol (MU) and GABA. In this and the subsequent figure; the electrophoretic administration of agonists are indicated by horizontal lines and bars.

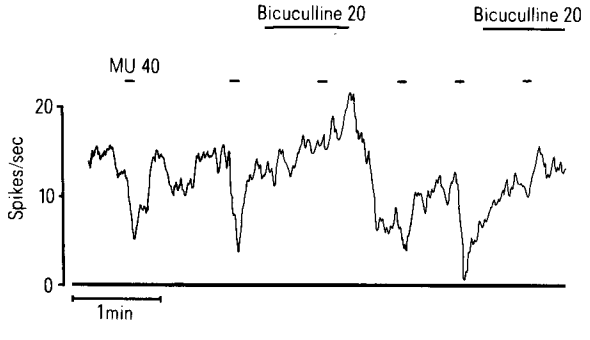

Fig. 2. The effect of bicuculline on the sensitivity of a spontaneously active nigral cell to muscimol.

Results and discussion. There is good evidence for an inhibitory descending gabaergic tract impinging on nigral cells deriving from the striatum[4,5]. In the present study, many nigral cells were found to be inhibited in response to striatal stimulation as revealed on peristimulus-time histograms. Drugs were applied to cells which were inhibited and to cells which were not inhibited in response to striatal stimulation. Both cell types were strongly depressed by muscimol (5–30 nA, 5–30 sec) and to somewhat lesser extent by GABA (5–30 nA, 5–30 sec). Most cells of the inhibited type (8 out of 13 cells), as well as of the noninhibited type (14 out of 22 cells), were more strongly depressed by muscimol than by GABA, as judged from the comparison of ejecting currents (figure 1). A similar fast onset of action was observed with both compounds but recovery from the depression of firing was often considerably slower after muscimol (figure 1). Biscuculline (20–30 nA, 1–2 min) very potently and reversibly antagonized the action of muscimol on 8 out of 10 cells tested (figure 2).

The effect of i.p. applied muscimol was tested on 13 nigral cells. 7 cells were of the inhibited and 6 of the noninhibited type. There was no significant difference in the way the 2 cell groups responded to various doses of i.p. applied muscimol. At a dose of 0.1 mg/kg i.p. the activity of only 1 cell was markedly reduced. With 0.5 mg/kg i.p., 6 out of 13 cells were depressed by 10–42%. When the dose was further increased to 1.0 mg/kg i.p., a total of 7 cells tested were depressed by 16–50%.

The present study confirms earlier reports demonstrating a GABA-like activity of muscimol on spinal neurones[6,7]. The results corroborate other investigations showing that muscimol is more potent than GABA[8,9]. In contrast to GABA, muscimol – as shown in the present study – is able to penetrate the blood brain barrier. Muscimol therefore could be an interesting compound for studying the biological function of GABA in brain, and to examine the potential therapeutic value of GABA agonists. A depressant action of muscimol on nigral dopaminergic cells may account for its potentiating effect on the cataleptic and amphetamine antagonistic action of haloperidol in rats.

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