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Drug-induced changes of striatal cholinergic and dopaminergic functions in rats with spreading depression

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In rats with reversible, functional inactivation of one striatum by spreading depression (SD), dopaminergic stimulation of the intact striatum by Ro 4-4602 plus L-dopa, pargyline plus Ro 4-1284 as well as apomorphine or methamphetamine caused body torsion and rotational movements towards the side of SD. Neuroleptic drugs lead to contralateral body torsion. The apomorphine-induced functional changes were antagonized by the acetylcholine-like drugs arecoline and oxotremorine, but not by nicotine. Atropine, but not methylatropine, blocked the action of arecoline. It is concluded that in the regulation of muscle tone and locomotor activity, a cholinergic system (probably with muscarinic cholinoceptive sites) and a dopaminergic system in the striatum, antagonistic to each other, are involved.

Changes of motor activity and muscle tone can be produced in various animal models by alterations of extrapyramidal function. In rats with one striatum removed (Andén, Dahlström & others, 1966) or deafferentiated from dopamine neurons by a unilateral lesion in the nigro-striatal pathway (Ungerstedt, 1971), treatment with drugs interacting with the dopaminergic transmission induced marked asymmetries of body posture and/or rotational movements. Similar behavioural changes were obtained by injection of drugs into the striatum (Costall, Naylor & Olley, 1972).

Recently, animals with unilateral spreading depression (SD) have been proposed as a new model for investigating the function of the basal ganglia (Keller, Bartholini & others, 1972). SD is induced by unilateral epidural application of a hypertonic KCl solution. The resulting depolarization wave invades the whole ipsilateral cortex and, through the amygdala and claustrum, reaches subcortical structures, e.g. the striatum (Fifková & Syka, 1964). As a consequence, a marked unilateral reversible diminution of cortical and striatal electrical activity occurs (Stille, 1971; Pieri, Bartholini & others, 1973).

In the present experiments the effect of various drugs affecting the cerebral cholinergic and dopaminergic systems was investigated in rats with unilateral SD.

METHODS

Male albino rats (Füllinsdorf), 180–220 g, were used. A cotton plug impregnated with hyperosmolar KCl solution (25%) was applied on the dura of the right parietal cortex through a plastic cannula implanted 24 h earlier over a skull opening of 2 mm in diameter (Keller & others, 1972). Equimolar NaCl solutions (20%) were used in control rats. The following drugs were injected intraperitoneally: (*a*)

Ro 4-4602* (50 mg kg^{-1}) and L-dopa (200 mg kg^{-1}) 90 and 60 min, respectively, before KCl; (*b*) pargyline (75 mg kg^{-1}) followed after 2 h by Ro 4-1284** (10 mg kg^{-1}) given immediately before KCl; (*c*) (+)-*N*-methylamphetamine HCl (5 mg kg^{-1}) immediately before, haloperidol (2 mg kg^{-1}) or chlorpromazine (5 mg kg^{-1}) 1 h before KCl application; (*d*) apomorphine (5 mg kg^{-1}) immediately before KCl, followed 15 min later by oxotremorine (1 mg kg^{-1}) or arecoline (5 mg kg^{-1}); (*e*) apomorphine (5 mg kg^{-1}) together with either atropine sulphate (10 mg kg^{-1}) or methylatropine (atropine methylnitrate; 10 mg kg^{-1}) immediately before KCl, followed in both cases after 15 min by arecoline; (*f*) apomorphine (5 mg kg^{-1}) together with hexamethonium (10 mg kg^{-1}) or hexamethonium alone (10 mg kg^{-1}), both immediately before KCl, followed 15 min later by nicotine hydrogen tartrate (1 mg kg^{-1}). The behaviour of the animals was observed for 2 h after KCl application, and the number of rotations per 5 min was counted.

RESULTS

Dopamine-like drugs. In animals pretreated with Ro 4-4602 plus L-dopa, with pargyline plus Ro 4-1284 and with methamphetamine or apomorphine, unilateral epidural application of KCl, but not of NaCl, produced marked functional changes. At first a reduction in muscle tone, especially of the neck and the legs, was felt on the side contralateral to the SD. Consequently, a torsion of the whole body towards the side of KCl application occurred, followed a few minutes later by a vigorous rotation towards the same side which lasted for various periods of time depending on the drug regimen (Figs 1 and 2A). The rotation was due to the activity of extremities on the side of SD while the legs of the contralateral side passively dragged behind. Epidural application of KCl or NaCl in control rats did not produce an appreciable alteration of motility and muscle tone.

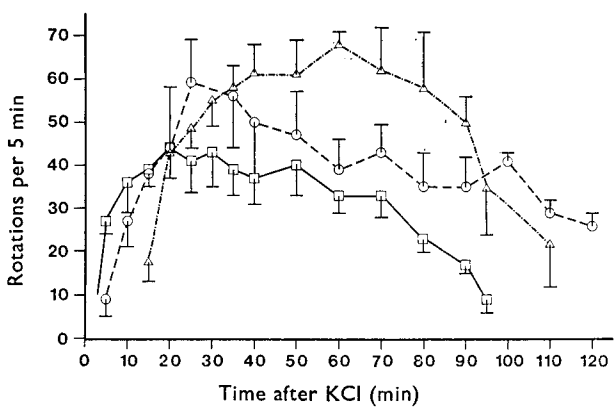

FIG. 1. Rotational activity induced by dopamine-like drugs in rats with unilateral spreading depression. KCl (25%) was applied to the dura of the right parietal cortex. The drugs were administered i.p. The values represent means with s.e. of 4–6 rats per group. △—·—△ methamphetamine (5 mg kg^{-1}) immediately before KCl. ○– – –○ pargyline (75 mg kg^{-1}) 120 min plus Ro 4-1284 (10 mg kg^{-1}) immediately before KCl. □——□ Ro 4-4602 (50 mg kg^{-1}) plus L-dopa (200 mg kg^{-1}) 90 and 60 min, respectively, before KCl.

* 1-DL-seryl-2-(2,3,4-trihydroxybenzyl)hydrazine-hydrochloride.

** 2-hydroxy-2-ethyl-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11 βH-benzo[a]quinolizine-hydrochloride.

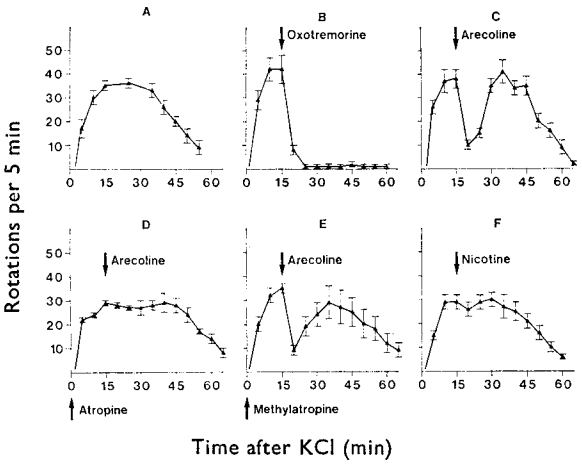

FIG. 2. Effect of acetylcholine- and anti-acetylcholine-like drugs on the apomorphine-induced rotation in rats with unilateral spreading depression. In all groups (A–F), KCl (25%) was applied to the dura of the right parietal cortex immediately after i.p. injection of apomorphine (5 mg kg^{-1}) (time 0). The values represent means with s.e. of 4–7 rats per group. Doses of the drugs (mg kg^{-1}, i.p. injection): oxotremorine 1, arecoline 5, atropine 10, methylatropine 10, nicotine 1. In group F, hexamethonium (10 mg kg^{-1}) was injected i.p. together with apomorphine.

Acetylcholine- and anti-acetylcholine-like drugs. The acetylcholine-like drugs, oxotremorine or arecoline, abolished or considerably diminished body torsion and rotational movements induced by apomorphine plus SD. Atropine, but not methylatropine, prevented the inhibitory action of arecoline. Nicotine (in hexamethonium-treated animals) or hexamethonium alone did not influence the action of apomorphine in SD (Fig. 2).

The unilateral muscular hypotonia produced by apomorphine during SD was accentuated by high doses of atropine (50–100 mg kg^{-1}) to such a degree that the animals showed an extreme twist of the body, the snout of the rat virtually touching its back. Under these conditions, rotational movements did not occur any more.

Dopamine receptor blocking agents. In animals with unilateral epidural application of KCl, but not of NaCl, pretreatment with chlorpromazine (5 mg kg^{-1} i.p.) and haloperidol (2 mg kg^{-1} i.p.) caused muscular rigidity on, and torsion of the body towards the side contralateral to SD.

DISCUSSION

The present results show that drugs which act by different mechanisms on the dopaminergic system induce in rats with unilateral SD similar functional changes, i.e. rotational movements and/or body torsion, as observed in rats with one striatum removed (Andén & others, 1966). The combination of the monoamine oxidase inhibitor pargyline with the monoamine-depleting benzoquinolizine Ro 4-1284 as well as methamphetamine alone probably cause an elevation of dopamine at the striatal dopamine receptors by displacement of the amine from intra- and extra-vesicular stores, respectively (Pletscher, Brossi & Gey, 1962; Carlsson, 1970). L-Dopa in combination with Ro 4-4602, an inhibitor of extracerebral decarboxylase, induces an increase of dopamine of exogenous origin, especially in the striatum (Bartholini, Bates & others, 1967; Bartholini & Pletscher, 1968; Bartholini, Pletscher & Kuruma, 1971).

Apomorphine directly stimulates and neuroleptics block dopamine receptors (Andén, Carlsson & Häggendal, 1969). The similarity of the drug-induced functional changes in unilateral SD to those observed in rats with one striatum removed (Andén & others, 1966) indicates that the striatum on the side of SD is inactivated. This is in line with the marked reduction of electrical activity in this structure following epidural KCl application (Stille, 1971; Pieri & others, 1973).

The absence of appreciable functional changes after unilateral SD alone may be due to a compensatory adjustment of the functional imbalance between the two striata. However, this adjustment seems to be overcome by drugs. Thus, dopamine-like agents probably caused such a predominance of the dopaminergic system in the intact striatum that the balance between both sides could not be maintained. This led to a decrease of muscle tone on the body side corresponding to the intact striatum. Since the muscle tone on the side of SD probably did not change, body torsion towards this side occurred. Furthermore, the enhanced locomotor activity resulted in rotation towards the side of SD. On the other hand, the interhemispheric balance was also disturbed by dopamine receptor blocking agents. These drugs induced muscular rigidity on and torsion towards the contralateral side, possibly due to a predominance in the intact striatum of a system antagonistic to the dopaminergic activity. This system has been suggested to be cholinergic (Andén & others, 1966). The present experiments with acetylcholine- and anti-acetylcholine-like drugs provide a direct evidence for this hypothesis. Thus, acetylcholine-like drugs (arecoline and oxotremorine) antagonized the functional changes due to apomorphine, whereas atropine enhanced the action of apomorphine on muscle tone, probably due to further accentuation of the imbalance between the dopaminergic and cholinergic system.

The effect of acetylcholine-like drugs in antagonizing apomorphine is probably of central origin, since it was blocked by atropine, but not by methylatropine which does not cross the blood/brain barrier to an appreciable extent. Moreover, the effect of arecoline and oxotremorine probably depends on stimulation of a muscarinic cholinoceptive site as nicotine did not block the rotation induced by apomorphine.

In conclusion, the present experiments in animals with SD provide further evidence for the existence in the striatum of a cholinergic and a dopaminergic system antagonistic to each other in the regulation of muscle tone and locomotor activity.

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