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Dopamine receptor stimulation and striatal kainic acid neurotoxicity

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Kainic acid (KA) has been shown to have specific neurotoxic effects on neuronal perikarya in the striatum which show striking similarities to striatal pathology seen in Huntington's disease (Coyle et al 1978). This model system has been useful for investigating the pathogenesis and treatment of Huntington's disease (Sanberg & Johnston 1981), as well as increasing our knowledge of the functions of the striatum. Recently, it has been demonstrated that dopamine receptors localized on the glutamatergic cortico-striatal terminals (Schwarcz et al 1978) have an inhibitory role on the release of glutamate (Mitchell & Doggett 1980; Rowlands & Roberts 1980). The neurotoxic effects of KA on striatal neurons are dependent on the presence of this pathway. In order to determine if the effects of this neurotoxin are dependent on a release of glutamate itself, as has been suggested, we have studied the effects of large doses of bromocriptine, a dopamine agonist which should reduce glutamate release, on KA neurotoxicity in the striatum.

Male 150 g albino Wistar rats (Charles River) were injected with 20 mg kg^{-1} bromocriptine (gift of Sandoz) in 0·9% NaCl (saline) vehicle. Control animals received vehicle injections only. Two h later all rats were given unilateral intrastriatal injections of 3 or 6 nmol KA as described previously (Sanberg et al 1979), with the exception that halothane anaesthesia was employed. Two hours after surgery, another injection of bromocriptine (10 mg kg^{-1}) or vehicle was given to the appropriate animals. Three weeks later the animals were decapitated and the striatum was bilaterally dissected, weighed, frozen and stored at −20 °C. Subsequently the activities of the acetylcholine synthesizing enzyme choline acetyltransferase, which is considered as a functional marker of cholinergic neurons, was measured as previously described (McGeer & McGeer 1976).

The results are depicted in Table 1. All groups showed significant decreases in choline acetyltransferase activity in the KA-lesioned striatum compared to their matched controls. The 6 nmol groups showed larger decreases than the 3 nmol groups. The percent difference between KA-injected and control striatum did not differ between bromocriptine and control treated groups at either dose of KA. However, bromocriptine did produce significant decreases in control striatal activities of choline acetyltransferase.

The surprisingly long term inhibition of choline acetyltransferase activity by bromocriptine may be consistent with the inhibitory action of dopamine on cholinergic neurons in the striatum (Stoof et al 1979), and with recent findings that bromocriptine is an irreversible dopamine agonist (Bannon et al 1980). This inhibition could be produced by a direct postsynaptic agonist action of bromocriptine on dopamine receptors localized on intrinsic cholinergic neurons. Alternatively, bromocriptine may be having a pre-synaptic agonist action on dopamine receptors localized on glutamatergic cortico-striatal terminals (Schwarcz et al 1978). Recently it was shown that activation of these pre-synaptic dopamine receptors inhibits glutamate release from the cortico-striatal pathway (Mitchell & Doggett 1980; Rowlands & Roberts 1980). Thus, a reduced release of this excitatory neurotransmitter in synapses localized on striatal cholinergic neurons could result in reduced cholinergic activity. The lack of effect of bromocriptine on KA striatal neurotoxicity suggests that the former explanation may be correct. The ability of KA to lesion striatal neurons is dependent on the glutamatergic cortico-striatal fibres in vitro (Mitchell & Doggett 1980; a lack of effect of bromocriptine on KA neurotoxicity may mean that a significant reduction in glutamatergic neurontransmission in bromocriptine-treated rats was not obtained. However, the fact that lower doses of dopamine agonists can markedly reduce glutamate release from cortico-striatal fibers in vitro (Mitchell & Doggett 1980; Rowlands & Roberts 1980), suggests that inhibition of glutamate was achieved in the present animals. Providing this is the case in vivo, the present results support the view (McGeer et al 1978b) that glutamatergic neurotransmission itself is not involved in KA neurotoxicity and that only the presence of the glutamate pre-synapse is required in some way for KA to exert its effects.

Table 1. The effect of bromocriptine on choline acetyltransferase activity in control and kainic acid lesioned striata†.

Dose (n)	Control Striata	KA-lesioned Striata	% Control
3 nmol KA			
Vehicle (4)	2·21 ± 0·17	1·15 ± 0·36*	52·2 ± 16·2
Bromocriptine (4)	1·36 ± 0·12**	0·75 ± 0·27*	55·3 ± 19·6
6 nmol KA			
Vehicle (4)	1·55 ± 0·22	0·30 ± 0·13*	19·5 ± 8·3
Bromocriptine (4)	0·97 ± 0·08**	0·30 ± 0·16*	31·0 ± 16·1

† Values are expressed as means ± s.e.m. in nmoles mg^{-1} wet wt/15min
* Significantly different from control striatum, $P < 0·05$ (Student's t-test).
** Significantly different from vehicle-treated group, $P < 0·05$.

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Antidiarrhoeal effects of quipazine and 1-(*m*-trifluoromethylphenyl)piperazine in mice

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Quipazine (1-[2-quinolyl]piperazine) and 1-(*m*-trifluoromethylphenyl)-piperazine (TFMPP) are thought to be agonists at 5-hydroxytryptamine (5-HT) receptors. Quipazine stimulates contraction of the rat uterus and other peripheral smooth muscles, and these effects are antagonized by 5-HT antagonists (Hong & Pardo 1966; Hong et al 1969). In addition, various in vivo effects suggest that quipazine stimulates 5-HT receptors in brain. These effects include antagonism of reserpine-induced sedation and hypothermia in mice and rats (Rodriguez & Pardo 1971), antagonism of muricidal activity in rats (Rodriguez & Pardo 1971), sham-rage reactions and other behavioural changes in cats (Rodriguez et al 1973), inhibition of sexual activity in male rats (Grabowska 1975), decreased brain 5-HT turnover in rats (Grabowska et al 1974), a behavioural syndrome associated with 5-HT stimulation in rats (Green et al 1976), elevation of serum corticosterone (Fuller et al 1978a) and prolactin (Meltzer et al 1976) in rats, antinociception in rats (Samanin et al 1976), head twitch in mice (Malick et al 1977), potentiation of the flexor reflex of the hind limb in spinal rats (Palider & Rawlow 1977), and decreased food intake in rats (Samanin et al 1977).

Quipazine competes for the binding of tritiated 5-HT to rat brain membrane receptors in vitro (Whitaker & Seeman 1978). Another substituted piperazine, TFMPP, also competes for the binding of tritiated 5-HT to rat brain membrane receptors in vitro (Fuller et al 1978b) and causes many of the same in vivo effects as quipazine (Fuller et al 1978b; Fuller & Clemens 1979). Since the 5-HT precursor 5-hydroxytryptophan (5-HTP) causes diarrhoea in mice that is antagonized by 5-HT antagonists (Woolley 1958), and since quipazine has been reported to cause increased gastrointestinal motility and diarrhoea in humans (Parati et al 1980), it might be expected that quipazine and TFMPP would cause diarrhoea in mice but they proved to be potent antagonists of the diarrhoea induced by 5-HTP.

Cox standard mice (Laboratory Supply, Indianapolis, Indiana), 20–25 g, were given i.p. injections of drugs dissolved in distilled water. Each mouse was placed in a glass beaker and observed continuously for the character of its faecal excretion during the first 30 min after injection and again at 1 h. Quipazine maleate (Miles Laboratories) was injected at doses equivalent to 10, 15, 20, 25, 32 and 10 mg kg^{-1} of the free base. TFMPP (Aldrich Chemical) was injected at doses of 10, 15, 20, 25, 32 and 40 mg kg^{-1}. 5-HTP was injected at 25 mg kg^{-1}. Control mice received injections of distilled water. Each treatment group contained 5 mice.

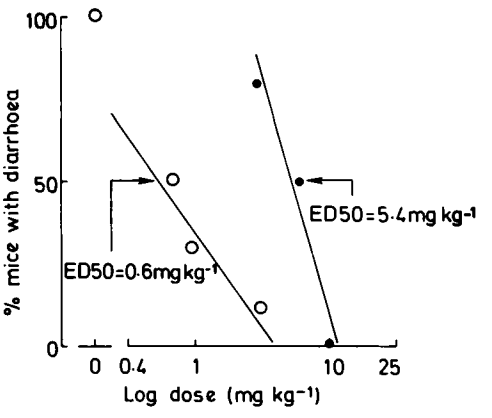

FIG. 1. Antagonism of 5HTP-induced in mice by TFMPP (○) and quipazine (●) in mice.

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