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Evidence for dopamine receptors on GABA-releasing nerve terminals in rat nucleus accumbens

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The rat nucleus accumbens is considered to be intimately involved in motor function (Kelly & Moore, 1976) and in the action of neuroleptic drugs (Bartholini, 1976), and is densely innervated by ascending axons of the mesolimbic dopamine (DA) pathway (Lindvall & Björklund, 1974). Turnover studies have suggested that neurones utilizing DA and γ-aminobutyric acid (GABA) may be closely interrelated within the nucleus accumbens (Marco, Mao, Cheney, Reveulta & Costa, 1976). The present study investigates the DA-GABA interrelationship in rat nucleus accumbens.

The nucleus accumbens was dissected from male Sprague–Dawley rats (150–200 g) and was found to contain a high GABA concentration: 6.3 ± 0.5 μmole/g (s.e. mean, $n = 6$). Slices of nucleus accumbens (0.2 × 0.2 mm) were incubated with [^{3}H]-GABA (9 nM) for 10 min at 37°C and accumulated [^{3}H]-GABA to a tissue: medium ratio of 65 ± 4 ($n = 7$). Nipecotic acid (25 μM), an inhibitor of the neuronal high affinity uptake of [^{3}H]-GABA (Johnston, Krogsgaard-Larsen, Stephanson & Twitchin, 1976), caused $63 \pm 6\%$ ($n = 4$) inhibition of control uptake ($P < 0.001$). The release of newly accumulated [^{3}H]-GABA was examined by superfusion of slices of nucleus accumbens with Krebs bicarbonate and collection of serial fractions. The resting release of [^{3}H]-GABA rapidly reached a steady baseline and protoveratrine A (100 μM), one of a group of veratrine alkaloids acting on neuronal release processes, increased the rate of efflux of [^{3}H]-GABA.

DA (500 μM) alone had no effect on the resting efflux of [^{3}H]-GABA, but during the exposure of slices of nucleus accumbens to protoveratrine A inhibited the release of [^{3}H]-GABA. This effect could also be mimicked by a range of dopamine agonists. The rank order of potency determined in these experiments was apomorphine > N-n-propylnorapomorphine > 1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine (SKF 38393A) > 2-amino-5,6-dihydroxy-1,2,3,4-tetrahydronapthalene (isoADTN) > 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronapthalene (ADTN) > epinine > dopamine. Clozapine, sulpiride and thioridazine, a group of neuroleptic drugs considered to act in limbic regions (Bartholini, 1976), attenuated the inhibitory action of apomorphine, while fluphenazine and *cis*-flupenthixol were ineffective.

The results provide evidence for a transmitter role for GABA in the rat nucleus accumbens and indicate that a population of DA receptors may modulate the activity of GABA-releasing nerve terminals.

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Neurotoxicity of kainate and the inactivation of L-glutamate *in vivo*

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Destruction of neurones by kainic acid and related 'excitotoxic' amino acids (Olney, 1978) is partly dependent on intact excitatory pathways in which glutamate is likely to be the transmitter (McGeer, McGeer & Singh, 1978). The neurotoxicity of kainate may thus depend on excessive membrane depolarization by a combination of a direct action of this potent excitant and an increased effectiveness of synaptically released L-glutamate. Since kainate and the derivative dihydrokainate, which is only a weak excitant of neurones, inhibit the high affinity uptake of L-glutamate to a similar extent (IC_{50} 302 ± 30 and 176 ± 10 μM respectively) (Johnston, Kennedy & Twitchin, 1979), and kainate is known to potentiate the action of L-glutamate on cortical neurones (Shinozaki & Shibuya, 1976), interference with L-glutamate transport may contribute to the neurotoxic effects of kainate.

Using microelectrophoretic techniques, experiments were performed on 7 cats anaesthetized with pentobarbitone to study the specificity of the effects of kainate and dihydrokainate on the excitation of spinal neurones by a variety of excitant amino acids and acetylcholine.

Dihydrokainate enhanced the action of L-glutamate, L-aspartate, D-glutamate and L-homocysteate but had little or no effect on the actions of D-homocysteate, kainate, N-methyl-D-aspartate and acetylcholine. Since only the substances in the 'enhanced' group are likely to be actively transported into neuronal tissue, these results suggest the importance *in vivo* of dihydrokainate-sensitive uptake systems for the neurotransmitters L-glutamate and L-aspartate.

Attempts to demonstrate a differential effect of kainate on the firing of neurones by L-glutamate, NMDA and acetylcholine were not successful largely because in concentrations likely to influence the uptake of L-glutamate, kainate produced excessive excitation followed by inactivation. At lower doses the effects of L-glutamate, NMDA and acetylcholine were all enhanced to a similar extent. Nevertheless, it seems likely, from *in vitro* observations and the *in vivo* action of dihydrokainate described here, that following injection into the brain (usually 1–2 μl of 1–10 mM soln.) kainate would enhance the effects of L-glutamate and L-aspartate and that this action would contribute to its neurotoxicity.

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