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Involvement of K-opioid receptors in the direct and indirect presynaptic control of dopamine release by ACH in striosomal and matrix compartments of the cat caudate nucleus

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Using a new *in vitro* technique, attempts were made to investigate the cholinergic presynaptic regulation of ^{3}H-dopamine (DA) release in the striosome and matrix compartments (areas defined as poor and rich in acetylcholinesterase activity respectively) of the cat caudate nucleus (CN).

Experiments were made on frontal brain slices (1 mm thick) placed in an open perfusion chamber. Microsuperfusion devices were applied on selected striosomal and matrix areas, exhibiting a constant localization from one animal to another. In each case the tissue was continuously superfused with an artificial CSF enriched in ^{3}H-tyrosine (60 μCi/ml) and ^{3}H-DA release was estimated in successive 5 min. superfusate fractions.

In previous experiments we have shown that, both in the striosomal area and the matrix zone, acetylcholine (ACh) exerts a facilitatory control of ^{3}H-DA release mediated by muscarinic receptors located on DA nerve terminals. Nevertheless, in the matrix, the cholinergic regulation was found to be much more complex. In fact additional data indicated that ACh exerts 1) an indirect stimulatory action on ^{3}H-DA release through nicotinic receptors, 2) an indirect muscarinic inhibitory effect since in the presence of TTX or atropine, a prolonged stimulation of H-DA release was detected while a short lasting action was found in the absence of the neurotoxine or the antagonist.

In the present study, attempts were made to identify the local neuronal loop involved in the TTX-sensitive inhibitory effect of ACh. In the presence of naloxone (10^{-6} M), the initial stimulatory effect of ACh was more pronounced and a sustained facilitation of ^{3}H-DA release occurred. Moreover the effect of naloxone was reversed when dynorphin (DYN, 10^{-6} M, an agonist of K opioid receptors) was simultaneously applied with ACh suggesting that DYN containing neurons are involved in the inhibitory component of the effect of ACh on ^{3}-DA release. Furthermore the K receptors which mediate the inhibitory effect of ACh in the matrix are directly located on DA nerve terminals since both DYN (10^{-6} M) or U50488 (a selective K agonist, 10^{-6} M), completely abolished the prolonged stimulatory effect of ACh on ^{3}H-DA release obtained in the presence of TTX. Moreover, the latter effect of U50488 was reversed when naloxone (10^{-6} M) was added into the superfusion medium.

Identical results were found in the striosomal area under DYN or U50488 application, suggesting that, in this compartment as well, DYN released from DYN containing neurons is able to reduce the ACh-evoked release of 3H-DA through K opioid receptors located on DA nerve terminals.

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Novel approach in the experimental treatment of MPTP-induced hemiparkinsonism in monkeys

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Several drugs of abuse, including cocaine, d-amphetamine, and phencyclidine, either block uptake or release dopamine from dopaminergic neurons in the brain. Some of these are possible prototypic compounds whose derivatives may be useful in the treatment of mild to moderate parkinsonism in which not all dopamine neurons are destroyed. Although drugs of abuse obviously will never be useful in the treatment of human parkinsonism, some of their derivatives might be if they had unique neurochemical and behavioral effects. Phencyclidine, an arylcyclohe-

xylamine, has a wide spectrum of neurochemical effects. The actions of phencyclidine as a non-competitive antagonist of glutamic acid acting on the ion channel of the NMDA receptor, as well as a blocker of neuronal uptake of amines, are well known. Kamenka and his colleagues have been successful in synthesizing arylcyclohexylamines in which the two major pharmacologic properties of phencyclidine are quantitatively separated (Chaudieu *et al.*, 1989; Vignon *et al.*, 1988).

The purpose of the present study was to determine the effects of phencyclidine, ketamine, and N-[1-(2-benzo(b)thiophenyl)cyclohexyl]piperidine (GK-13, BTCP, a chemical derivative of phencyclidine), d-amphetamine and cocaine in an animal model of Parkinson's disease. The model used involved MPTP induced hemiparkinsonism in monkeys, as described by Bankiewicz *et al.* (i986). Four adult female Macaca nemestrina monkeys were infused over a 15 minute period with 3 mg of MPTP into the right internal carotid artery while the animals were under pentobarbital anesthesia. Usually within a week, the animals exhibited a marked decrease in the use of the left arm, which was opposite to the side of the lesion. The monkeys preferred to use the right arm for most purposes, while the left arm was neglected, showed rigidity and, on occasions, tremor. The tremor was not always present and could not be induced reproducibly. On the other hand, the left hemineglect syndrome was very prominent. Video recordings made of the unrestrained monkeys indicated a tendency to turn to the right (ipsiversive). The animals were able to groom and feed themselves and required no nursing care once they recovered from surgery. The drugs listed above were administered in logarithmic doses, varying usually from 0.1, 0.32, 1.0, 3.2, and 10.0 mg/kg given i.m. The effects of these agents were then videotaped on different days. Marked differences in circling and other behaviors were observed with the various drug treatments, consistent with previous literature in rats with unilateral dopaminergic lesions, although some important differences were noted. It is concluded that only some of the compounds studied showed potential therapeutic merit, confirming the validity of this approach.

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Pharmacological effects of GYKI 52 895, a new selective dopamine uptake inhibitor

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The activity spectrum of 1-(aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (GYKI 52 895) seems to be unique and differs profoundly from that of other 2,3-benzodiazepine derivatives showing minor or major tranquilizing activity (Andrási et al., 1987, Horváth et al., 1989). GYKI 52 895 exerts antidepressant and antiparkinson efficacy by influencing the dopaminergic system.

The compound is active in a 10 mg/kg oral dose in the Porsolt's behavioral despair test in rats. It antagonizes tetrabenazine-induced ptosis (ED_{50} = 10.2 mg/kg p.o.) and reserpine-induced hypothermia in mice (ED_{50} = 25 mg/kg p.o.). The compound potentiates the stereotypy evoked by amphetamine in rats in doses of 2.5-10 mg/kg i.p., and inhibits the hypothermia produced by clonidine in mice (ED_{50} = 19.5 mg/kg i.p.).

On the other hand, it does not induce turning behavior in unilaterally substantia nigra lesioned rats and provoks no vomiting in dogs.

The antagonism of oxotremorine-induced tremor in mice (ED_{50} = 13.6 mg/kg p.o.) together with the attenuation or prevention of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine)-toxicity in mice indicate a potential antiparkinson efficacy.

In electrophysiological experiments in rats, GYKI 52 895 inhibits dose-dependently the firing of the dopaminergic cells of substantia nigra pars compacta (ED_{50} = 8.9 mg/kg i.v.). This effect may be reversed by haloperidol. On the