POSTER COMMUNICATIONS

Use of the mouse circling model to demonstrate enhanced striatal actions for oxiperomide and tiapride following denervation

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The induction and antagonism of circling behaviour in rodents with unilateral disruption of the nigrostriatal dopamine system has been extensively used to investigate dopamine agonist-antagonist activity. Drug induced ipsilateral circling is considered to reflect drug action on 'normal' dopamine receptors within the intact striatum whilst contralateral circling is generally thought to be mediated via dopamine receptors of 'increased sensitivity' in the denervated striatum. Using the induction and antagonism of ipsilateral and contralateral circling in mice with electrolytic and combined electrolytic and 6-hydroxydopamine (6-OHDA) lesions of the striatum, the present studies assessed potential differences of agents to stimulate and block 'normal' (intact striatum) and 'denervated' (intrastriatal 6-OHDA) dopamine systems respectively.

Electrolesions were induced stereotaxically in the caudate-putamen of male albino mice (B.K.W., 35–40 g) anaesthetized with chloral hydrate (450 mg/kg i.p.). Lesions were induced using a stainless steel electrode, 0.65 mm diameter, and passing 1.5 mA for 15 s at coordinates 1.0 mm anterior to Bregma, 2.3 mm lateral and vertical 3.5 mm from the skull surface (incisor bar of Kopf instrument raised 2.0 mm). A group of mice prepared with unilateral electrolesions of the left striatum were subsequently subject to 6-OHDA lesions of the right striatum: mice were returned to the stereotaxic frame and 6-OHDA (4 mg/ml) was delivered at a rate of 1 μl/min for a total of 4 μl via a 0.3 mm stainless steel injection unit (coordinates for deposition as above). Immediately after drug treatment mice were placed in individual screened perspex boxes and the onset, intensity (number of complete revolutions in 2 min) and duration of circling recorded. Also, the presence or absence of asymmetry was noted. All animals received a test dose of apomorphine (1.0 mg/kg s.c.) and those failing to circle at least a revs/2 min were rejected from further studies.

Using apomorphine induced ipsilateral (in electrolesion animals) and contralateral (6-OHDA lesions) circling as indices of drug action on 'normal' and 'denervated' dopamine mechanisms respectively, typical neuroleptics such as haloperidol were found to be slightly more potent (×2) to inhibit circling in the denervated model whereas sulpiride, thioridazine, clozapine and metoclopramide were equieffective in the two models, although with these four agents the development of sedation and/or catalepsy prevented a definitive comparison. Oxiperomide and tiapride, neuroleptic agents with a particular efficacy to reduce dyskinetic phenomena, were *four* and *eight* fold, respectively, more active in the denervated model.

The demonstration that denervation can quantitatively change the receptivity of 'dopamine mechanisms' (pre- or postsynaptic components) to neuroleptic inhibition is important since neuroleptics are frequently used in neurological disease states associated with neuronal degeneration. The greater potency of oxiperomide and tiapride in the 'denervated model' is of particular interest in view of their unusual efficacy to reduce dyskinesias in the clinic (Marsden, personal communication) which are frequently purported to involve excessive dopamine activity in denervated systems.

The relationship between cholinergic and dopaminergic mechanisms in the nucleus accumbens for the control of locomotor activity

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The interaction between cerebral dopaminergic and cholinergic systems in motor control is established, and many studies have focussed on the extrapyramidal system. However, although the mesolimbic system is known to influence locomotor activity via dopamine, little is known of a cholinergic relationship to the function of dopamine. In the present studies, the nucleus accumbens (ACB) was selected as a mesolimbic area shown to exert marked locomotor control via dopamine, and the importance of acetylcholine for the modulation of this dopamine response and the action of neuroleptic agents was investigated.

Guide cannulae for intra-ACB injections (Ant. 9.4, Vert. 0.0, Lat. ±1.6, De Groot, 1959) were chronically