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

implanted in the brains of male Sprague-Dawley rats (275–300 g) using standard stereotaxic techniques (Costall & Naylor, 1976). Locomotor activity was measured by placing rats in individual perspex cages, each fitted with one photocell unit, and measuring the number of interruptions of the light beam occurring every 10 min for a total of 4 h.

The injection of dopamine (3.13–50 μg) into the ACB of nialamide (100 mg/kg i.p. 2h) pretreated rats induced dose related hyperactivity. An established response to dopamine (50 μg) was antagonized by intra-ACB eserine (1.25–5.0 μg) and carbachol (>2.5 μg). Intra-ACB atropine (6.25–25 μg) caused a transient reduction in hyperactivity during the first hour with no subsequent enhancement. A 30 min pretreatment with atropine (5.0 mg/kg i.p.) antagonized the eserine (5.0 μg) induced reduction of dopamine hyperactivity, although peripherally administered atropine (1.0–10 mg/kg i.p.) failed to modify the dopamine hyperactivity *per se*. Intra-ACB mecamylamine (25 μg) failed to consistently modify dopamine hyperactivity or the response to eserine (5.0 μg). Haloperidol (0.1–0.8 mg/kg i.p.) antagonized an established dopamine (50 μg) hyperactivity: the antagonistic effect of 0.8 mg/kg i.p. haloperidol was not modified by a 30 min pretreatment with atropine (5.0 mg/kg i.p.).

It is concluded that whilst the hyperactivity induced by intra-ACB dopamine can be antagonized by an enhanced cholinergic muscarinic effect, the neuroleptic antagonism is not dependent on an enhanced cholinergic activity. The failure of atropine to enhance mesolimbic dopamine hyperactivity or to antagonise the neuroleptic inhibitory effects on a mesolimbic dopamine system differentiates the nature of the neuroleptic-cholinergic interaction from that in the extrapyramidal dopamine systems. This data may have implications for the understanding of the clinical effects of combined neuroleptic and anticholinergic therapy with respect to the antipsychotic (mesolimbic?) and extrapyramidal side effects associated with neuroleptic action.

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Neurotensin: electrophysiological studies of its action on the guinea-pig taenia coli

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Recently we reported that the tridecapeptide neurotensin (NT) contracted the guinea-pig taenia coli by directly interacting with this smooth muscle (Kitabgi & Freychet, 1978). This led us to study the effects of NT on the membrane potential and conductance of the guinea-pig taenia coli, using the sucrose gap method (Bülbring & Tomita, 1969). Single and double sucrose gap experiments were done at 37°C and 20°C, respectively. In double sucrose gap experiments, hyperpolarizing and depolarizing currents of constant intensity were alternately applied to the muscle preparations. Membrane potential and isometric change in tension were simultaneously recorded.

At 37°C, the guinea-pig taenia coli often exhibited spontaneous activity. Spikes (about 20mV) were accompanied by phasic contractions. NT at low concentration (0.5 nM) induced a slow depolarization (about 5 mv). The peptide reduced the size of the spikes but increased their frequency. This resulted in an increase in the frequency of phasic contractions. With NT (10 nM), the membrane depolarization (about 20 mv) was rapid. Spike frequency was initially increased and their size reduced until they were blocked by the depolarization. Initial phasic contractions were followed by a tonic contraction associated with the depolarization.

At 20°C, the guinea-pig taenia coli showed little or no spontaneous activity. Spikes were induced by depolarizing currents and accompanied by phasic contractions. NT (50 nM) rapidly depolarized the muscle. Spikes were blocked at maximal depolarization (20–25 mv). The depolarization was accompanied by a tonic contraction. Membrane conductance was increased as indicated by the reduction of electrotonic potentials induced by hyperpolarizing currents. Dose-response curves of NT-induced depolarization and contraction gave ED_{50} of 1.7 nM and 4.5 nM respectively. The maximally effective dose of peptide was the same (about 50 nM) for both dose-response curves.

When Na^+ in normal physiological solution was replaced by Li^+ or Mg^{++}, there was a marked inhibition of NT-induced depolarization (60–70%) and contraction (>50%). This was accompanied by a reduction in the NT-induced increase in membrane conductance. In Ca^{++}-free solution, the NT-induced depolarization was inhibited by 25% and in a solution containing Mn^{++} (5mM), the inhibition was 50%.