PHARMACOLOGICAL MODELS IN THE DEVELOPMENT OF ANTIPSYCHOTIC DRUGS - NEW STRATEGIES

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SUMMARY: In order to advance new therapeutic approaches to the treatment of psychosis it has been necessary to develop new animal models which diverge considerably from the traditional tests for neuroleptic activity. The latter generally reflected drug action on all cerebral dopamine receptors, but were not discrete or persistent in nature. In developing new tests it has been considered that the disturbances of schizophrenia are discrete to the mesolimbic system, and are persistent. The discrete disturbances have been mimicked by intracerebral locations using stereotaxic surgery and persistency of dopamine disturbance by intracerebral infusions from osmotic minipumps. Examples are given of the behavioural consequences of dopamine disturbance in mesolimbic terminal areas, the nucleus accumbens and amygdala, and of disturbance in the ventral tegmental area to initiate the release of endogenous dopamine. Examples of the ways in which the new test strategies have been used have focused around the new class of potential antipsychotic agents, the 5-HT\textsubscript{3} receptor antagonists, and have thus allowed the investigation of serotonin involvement in limbic dopamine dysfunction. In the presence of a raised limbic dopamine activity caused by the injection or infusion of dopamine agonists into the nucleus accumbens or amygdala, or direct stimulation of dopamine cells in the ventral tegmental area, rats and marmosets demonstrate an increased locomotor activity. 5-HT\textsubscript{3} receptor antagonists such as ondansetron, zacopride or ICS205-930 administered locally into the limbic nuclei or peripherally antagonised the behavioural hyperactivity. Neuroleptic agents caused a similar inhibition but, unlike the 5-HT\textsubscript{3} receptor antagonists, depressed activity to below normal values. The behavioural models reveal that 5-HT\textsubscript{3} receptor antagonists can inhibit a raised mesolimbic dopamine function in the total absence of an effect on normal levels of behavioural responding. The profile of action of the 5-HT\textsubscript{3} receptor antagonists is indicative of a novel antipsychotic potential. These compounds will therefore serve to test the validity of the new test procedures, and data from their trials in the clinic is eagerly awaited.

Major initiatives in the development of novel antipsychotic agents have been hindered by a lack of suitable animal models, and a lack of novel 'tools' to challenge those models. Thus, for many years the behavioural backing to the development of
neuroleptic agents was designed about the activities of these agents in their own right -
their ability to induce catalepsy, to inhibit stereotypies, to induce circling behaviour, to
inhibit climbing, and so forth (see review by Costall and Naylor, 1980). The key
element of all of these tests is now evident - they require a striatal dopamine blockade,
possibly combined with an inhibition of psychomotor initiative in the limbic system.
There now appears a limited rationale for such tests, although they did serve a most
valuable role in the detection of new chemical classes of neuroleptic drugs. The basis
for development was dopamine blockade with a lack of selectivity to any particular
brain region. Indeed, the classic tests measured ability to modulate striatal dopamine
function - but the importance of this action relative to the dopamine disturbance of
schizophrenia, which is believed to influence the limbic and cortical circuitry, remained
uncertain. Indeed, that neuroleptic agents antagonise at striatal dopamine receptors
reflects their undoubted ability to induce extrapyramidal side effects - dystonias,
parkinsonism, tardive dyskinesias (see review by Marsden et al., 1986). Our approaches
to the development of neuroleptic agents was necessarily pragmatic: we searched for
dopamine antagonist action in the brain per se, that would in turn help to reveal the
prime therapeutic target sites.

The dopamine hypothesis of schizophrenia: The dopamine hypothesis of
schizophrenia has remained a keystone in the search for novel antipsychotic therapy
(see review by Costall and Naylor, 1986). The differences in thinking are now in terms
of how this hypothesis can be refined. Firstly, as commented on above, it is now
considered essential to locate the disturbance of dopamine in schizophrenia to a discrete
brain circuitry. To administer a dopamine agonist peripherally to influence all cerebral
dopamine receptors is an unlikely reflection of the disease state - it is believed that any
'model' of psychosis should concentrate on local disturbance of the mesolimbic/cortical
circuitry. To this end, a battery of tests has been developed via which a target site in
this circuitry is located by stereotaxic techniques, whether this be an area of cell bodies
supplying the so-called mesolimbic/ cortical areas (the ventral tegmental area) or a
terminal region such as the nucleus accumbens or amygdala.

A second major consideration, in addition to the discrete enhancement of
mesolimbic dopamine function, is the persistency of the dopamine disturbance. Whilst
the treatment of schizophrenia tends to be directed to an acute or chronic presentation,
in no situation is it an event of a few minutes or hours. Thus, to disturb a discrete
mesolimbic nucleus persistently to cause a dopamine excess in the area would appear to
be the most ideal 'model' for assessment of antipsychotic drug activity. This has been