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Calcium-Activated Potassium Conductance

An Alternative to the Dopamine Hypothesis of Neuroleptic Action?

TIMOTHY G. DINAN

Neuroleptics are structurally a heterogenous group of compounds which possess antipsychotic activity. They increase dopamine metabolites by blocking dopamine receptors and enhancing presynaptic turnover. This forms the cornerstone of the dopamine hypothesis of neuroleptic action, which is supported by wide-ranging behavioural, physiological and biochemical studies. It is, however, clear that neuroleptics are far less specific for the dopamine receptor than was previously considered. They influence a range of neuronal activities, including calcium-activated potassium conductance, which governs the rate of action potential generation by many neurones. Recent physiological studies indicate that all commonly used neuroleptics alter calcium-activated potassium conductance in central neurones, in concentrations similar to those achieved clinically. An adaptive increase in calcium-activated potassium conductance mechanisms in key sensory processing neurones would render the psychotic patient less susceptible to bombardment by environmental stimuli. This action may explain in part the therapeutic effect of neuroleptics.

Neuroleptics are structurally a heterogeneous group of compounds which possess antipsychotic activity (Snyder *et al*, 1974). More than 20 years have passed since their capacity to increase dopamine (DA) metabolites, by enhancing the presynaptic turnover of DA, was demonstrated. Carlsson & Lindqvist (1963) observed that both chlorpromazine and haloperidol stimulate the accumulation of o-methylated metabolites of DA and also noradrenaline (NA). The authors postulated that these antipsychotic drugs act by blocking DA and NA receptors. A feedback activation was suggested as the mechanism underlying the acceleration of agonist synthesis. The work had a major intellectual impact and since then a vast literature has developed examining further the DA hypothesis of neuroleptic action.

Amphetamine is known to produce a paranoid psychosis in many respects indistinguishable from schizophrenia (Connell, 1958), and the stereotypic behaviour induced in rats by amphetamine has been advocated as an animal model of schizophrenia (Randrup & Munkvad, 1974). This latter behaviour pattern is claimed by Iversen (1978) to be due to overactivity of DA neurones and to be abolished when such neurones are selectively destroyed by the neurotoxin 6-hydroxydopamine or when postsynaptic receptors are blocked with neuroleptics. The potency of this response correlates highly with the rank order of neuroleptics in terms of clinical efficacy.

A high correlation ($r = 0.95$) has been found between the stimulating action of neuroleptics on striatal DA synthesis and their apomorphine antagonist action (Carlsson, 1978). Apomorphine is a powerful DA agonist and the fact that the ED_{50} values (amount of drug required to produce a 50% maximal response) in both cases are approximately equal, suggests similar affinities for receptors. Together with this, X-ray crystallographic studies indicate that chlorpromazine in its preferred conformation can be superimposed on DA and NA, while those phenothiazines lacking antipsychotic action are less liable to assume the conformation. This finding by Snyder *et al* (1974) provides a molecular mechanism by which phenothiazines can block DA receptors.

Further biochemical support

When DA receptors are labelled with ^{3}H-DA, the relative potency of phenothiazines against this receptor parallels their antipsychotic potency (Seeman *et al*, 1976). However, this high correlation is not maintained when the butyrophenones are tested. Snyder *et al* (1974) investigated the affinities of a wide range of phenothiazines and butyrophenones in competing for ^{3}H-haloperidol binding to the DA receptor. Spiroperidol, which is the most potent antagonist of DA-mediated behaviour in animals, was found to be the most potent inhibitor of ^{3}H-haloperidol binding.

It has five times greater affinity for this receptor than fluphenazine and a 40-fold greater affinity than chlorpromazine. Overall, a high correlation can be established between the molar pharmacological potencies of various neuroleptics and their affinities for the ^{3}H-haloperidol binding sites. The Johns Hopkins' group postulate that the DA receptors exist in two states, an agonist and an antagonist (Creese *et al*, 1975). This helps explain why DA agonists are over 50 times more potent in competing with ^{3}H-DA than ^{3}H-haloperidol for binding, while the reverse is true for antagonists.

Kebabian *et al* (1972) found that when various phenothiazines are compared, their potency as inhibitors of DA-stimulated cAMP formation is similar to their *in vivo* potencies as antipsychotics. The authors postulated that the postsynaptic actions of DA were mediated by a DA-sensitive adenyl cyclase, and that this enzyme activity correlates with the post-synaptic effects of DA. However, butyrophenones and diphenylbutylpiperidines have been shown to be less potent than chlorpromazine as inhibitors of adenyl cyclase (Iversen, 1975). The most potent butyrophenone spiroperidol is weaker than haloperidol or chlorpromazine in inhibiting DA-sensitive adenyl cyclase, while sulpiride, a benzamide derivative, is devoid of such activity. It now seems clear that there are at least two types of DA receptor: the D-1 type, which enhance adenyl cyclase activity, and the D-2 type, which either decrease or have little effect on cAMP (Cross & Owen, 1980). High affinity binding sites for ^{3}H-haloperidol correspond to the D-2 receptor, while high affinity binding sites for ^{3}H-flupenthixol identify the D-1 adenyl cyclase linked receptor. The DA hypothesis can easily adapt to the fact that there is more than one type of DA receptor and that neuroleptics vary in their potency at a single subtype of receptor. Thus Iversen's (1975) finding that butyrophenones are less potent than chlorpromazine as inhibitors of adenyl cyclase is accommodated.

Physiological support

Direct physiological evidence to support the DA hypothesis was provided by Bunney *et al* (1973). They found that iontophoresed DA on dopaminergic zona compacta neurones of substantia nigra produces a powerful inhibition which is abolished by neuroleptics administered either systemically or iontophoretically. When neuroleptics are given alone they significantly increase the rate of neuronal firing by blockade of the DA autoreceptor. Similar results have been reported for postsynaptic DA receptors. Recordings from septal neurones, for instance, have demonstrated that neuroleptics block DA-induced but not NA-induced inhibition (Bunney & Aghajanian, 1978). Further physiological evidence is provided by the fact that intravenous amphetamine decreases the firing of substantia nigra neurones but firing is returned to normal by chlorpromazine (Graham & Aghajanian, 1971).

Arguments against the DA hypothesis

It is now clear that neuroleptics are far less pharmacologically specific for the DA receptor than was previously thought. There is abundant evidence to indicate that they alter a wide spectrum of neurochemical activities. Chronic haloperidol, for instance, increases ligand binding not only to DA receptors but also serotonin and to a lesser degree alpha-noradrenergic receptors in the cerebral cortex (Mueller & Seeman, 1977). These latter changes in noradrenergic receptor binding are associated with profound alterations in the physiology of the noradrenergic nucleus locus coeruleus (Dinan & Aston-Jones, 1984, 1985). In fact, the affinities of many neuroleptics in competing for WB-4101 binding are similar to those of the classic alpha-antagonists phenotolamine and phenoxybenzamine (Peroutka *et al*, 1977). Not only can neuroleptics alter monoaminergic systems other than those which use DA as a transmitter, but there is also evidence to demonstrate their effects on cholinergic (Sherman *et al*, 1978), peptidergic (Somoze, 1978) and amino-acidergic (Perry *et al*, 1979) transmission.

Further arguments against the DA hypothesis have also been put forward. It must be remembered, for instance, that the number of dopaminergic neurones in the mammalian brain is relatively small and largely confined to the brainstem (Ungerstedt, 1974). Although these neurones clearly influence those at a cortical level, it has been argued that a disease of higher cognitive functioning such as schizophrenia must involve neurones at the highest level and not simply reflect a dysfunction of brainstem neurones, irrespective of how highly arborised they might be (Dinan, 1984). If such is the case, it seems unlikely that the modification of dopaminergic function would significantly influence the psychic processes involved in schizophrenia and thus adequately account for the antipsychotic action of neuroleptics. The fact that amphetamine psychosis closely resembles paranoid schizophrenia is regarded as strong evidence for implicating DA with the psychopathology of schizophrenia (Iversen, 1978); however, there has been little in-depth investigation of amphetamine action on extra-monoaminergic systems, which might also conceivably mediate the psychic

effects of amphetamine. The bluderbuss lesioning of DA neurones abolishes the stereotypic behaviour produced by amphetamine in rats (Iversen, 1978), clearly implicating DA in stereotypic behaviour, but obviously not negating possible non-dopamine actions of amphetamine.

Neuroleptics and calmodulin

The potent action of butyrophenones and phenothiazines as calmodulin antagonists has been described (Weiss & Levin, 1978). Calmodulin plays a pivotal role in mediating the second messenger actions of calcium within the neurone, including the activation of a variety of enzyme systems (Stoclet, 1981). The piperazine phenothiazine, trifluoperazine, has been shown not only to be a potent calmodulin antagonist but also to reduce inward calcium currents in neurones (Chapman & Neher, 1984). Together with other neuroleptics, it depresses platelet aggregation induced with platelet-activating factor, which Levy (1983) indicates is mediated by a calcium/calmodulin mechanism. Studies on the diphenylbutylpiperidines such as pimozide indicate their capacity to inhibit nitrendipine binding to the verapamil/prenylamine class of calcium channel (Gould *et al*, 1983). They also inhibit potassium-induced calcium-dependent contractions of rat vas deferens (Gould *et al*, 1983).

Calcium-activated potassium conductance

Many neurophysiologists are actively engaged in a study of Ca^{+2}-activated K^+ conductance mechanisms in a wide variety of neurones. This conductance is important in governing the rate of action potential generation by a neurone and thus the rate of transmitter release (for review see Meech, 1978). The process begins with the opening of voltage-gated Ca^{+2} channels, resulting in the movement of Ca^{+2} inward. This Ca^{+2} together with that mobilised within the cell brings about the opening of K^+ channels, probably acting via an intermediate calmodulin-like protein. The K^+ moves along its electrochemical gradient, causing a hyperpolarisation of the membrane, which can be sustained, in many cases, for several seconds. The mechanism thus plays an important role in determining the rate of information processing by an individual neurone and in modulating the signal transmitted by the neurone.

Recent work both on the noradrenergic nucleus locus coeruleus (Dinan & Aston-Jones, 1984, 1985; Dinan, 1986) and the hippocampal pyramidal CA1 neurones (Dinan *et al*, 1987) indicates that neuroleptics alter Ca^{2+}-activated K^+ conductance. When acutely administered, those neuroleptics effective as antipsychotics depress the slow afterhyperpolarisation seen in hippocampal CA1 neurones. This afterhyperpolarisation is mediated by a K^+ conductance which is Ca^{+2}-dependent. In the locus coeruleus, haloperidol depresses both orthodromic- and antidromic-induced poststimulus inhibition, which is again mediated by a similar conductance. Dinan & Aston-Jones (1985) have shown that chronic haloperidol treatment results in the inactivation of many locus coeruleus neurones, rendering them less sensitive to incoming stimuli. White & Wang (1983), working on zona compacta neurones of the substantia nigra, report similar findings.

Defective filtration in schizophrenia

Broadbent (1958, 1971, 1977) has postulated a defect in the perceptual filtration mechanism in schizophrenia, which results in the individual being bombarded by environmental stimuli, overloading his cognitive processing capacity. Several studies support this delineation of specific defects in the filtering phase of information processing. Broen & Nakamura (1972) found that chronic non-paranoid schizophrenics demonstrate a more restricted range of sensitivity toward peripheral sensory channels than do acute paranoid schizophrenics or normal subjects. They also found that schizophrenics perform significantly less well than controls on span-of-apprehension tests when irrelevant noise is present, but no differences are noted when there are no irrelevancies. Schizophrenics also perform poorly when tasks which involve switching attention between stimulus modalities are employed, or in tests of discrimination shifts (Kristofferson, 1967).

The acute antipsychotic actions of neuroleptics, together with their long-term prophylactic effects, may partly be explained in terms of rectification of a defective perceptual filter. As Ca^{+2}-activated K^+ conductance is an important processing mechanism for many sensory input neurones, it provides a key neuronal site for altering the filtration of environmental and internal sensory information. For example, some visual system neurones rely heavily on such a conductance for processing information (Llinas & Lopez-Barneo, 1983). An adaptive increase in Ca^{+2}-activated K^+ conductance in such neurones, in the weeks following commencement of neuroleptic treatment, would render the individual less susceptible to bombardment by environmental stimuli. We know for instance that neuroleptics enable schizophrenics to withstand greater levels of expressed emotion from the environment without breakdown (Brown & Birley, 1968; Leff & Wing, 1971).

Crow *et al* (1976) have provided a concise summary of the DA hypothesis:

Since many behavioural effects of the amphetamines are due to increased central DA release and since most neuroleptic compounds are blockers of central DA receptors, the symptoms of schizophrenia may be due to abnormal increase in central DA release, and the effects of this increase are diminished by partial blockade of the receptor site.

The hypothesis so stated is clearly heavily influenced by our present understanding of the aetiology of Parkinson's disease and does not adequately explain how an increase in DA might produce the intriguing psychopathology of schizophrenia. The present hypothesis is not implying that schizophrenia is due to underactivity of Ca^{+2}-activated K^+ conductance mechanisms in central neurones. It simply states that schizophrenics process information from their environments inappropriately and one site at which pharmacological manipulation might alter such aberrant processing is at the level of Ca^{+2}-activated K^+ conductance mechanisms in sensory input neurones. The theory takes the focus from the receptor site and directs it on the neurone as an information processing unit.

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Timothy G. Dinan, MA, MD, MRCPsych, *Lecturer/Senior Registrar, Department of Psychological Medicine, St Batholomew's Hospital Medical College, West Smithfield, London EC1A 7BE*

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Commentary on Dinan's Hypothesis*

LESLIE L. IVERSEN

Dinan's paper seeks to question the validity of the now widely accepted hypothesis that neuroleptic drugs of various different chemical categories all act by a common mechanism, namely by blockade of dopamine receptors of the D2 type in brain (for review see Creese *et al*, 1978, 1983; Iversen, 1985). While it is always refreshing to re-examine existing scientific dogma, his criticisms did not appear to me to be very substantial. Having quite fairly reviewed the evidence in favour of the "dopamine hypothesis" for neuroleptic drug action, Dinan summarises his reasons for questioning it. He points out that many neuroleptic drugs have potent actions on a number of other targets, apart from the dopamine receptors in brain. This is indeed so, and the archetypal compound, chlorpromazine, has a particularly rich spectrum of pharmacological activity, being a potent antagonist of serotonin (5-HT_2) receptors, α-adrenoceptors, and histamine (H1) receptors in brain and other tissues. Other neuroleptics also have potent actions on a number of other systems. Indeed, if one were to have studied only chlorpromazine, it is doubtful whether the "dopamine hypothesis" could ever have been developed. The strength of this hypothesis lies in the fact that of all the diverse pharmacological actions which different neuroleptic drugs exhibit, this is the only action that is common to *all* neuroleptic compounds. Furthermore, in a large group of neuroleptics, which differ widely in potency (doses in man ranging from 1 mg/day to almost 1000 mg/day), the potencies of these drugs as dopamine (D2) antagonists correlate significantly with their clinical potencies. Attempts to make such correlations with any other known pharmacological properties of these drugs fail to show significance (Creese *et al*, 1978, 1983).

To suggest, as Dinan does, that "a disease of higher cognitive functioning such as schizophrenia must involve neurones at the highest level and not simply reflect a dysfunction of brainstem neurones . . . " is simple prejudice, not based on any scientific facts. In any case, dopamine neurones do exist in the limbic forebrain, and they send important projections to certain areas of frontal cortex.

Dinan's alternative proposal to explain how neuroleptic drugs act is that they block a particular ionic channel in neuronal membranes, a calcium-activated potassium conductance. This may be related to the known property of some neuroleptics to act as antagonists of the calcium–calmodulin system. The new findings reported by Dinan *et al* are original and of interest, showing that haloperidol, chlorpromazine and trifluoperazine have this effect

*Commentary on preceding paper by T. G. Dinan.