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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

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when added *in vitro* to rat hippocampal slice preparations. However, these are only three of the many neuroleptics that exist; to suggest that this is a proven action for "all commonly used neuroleptics . . . in concentrations similar to those achieved clinically" (as Dinan states in his summary) is to extrapolate wildly beyond the available experimental results. To test whether there was any correlation between this effect and neuroleptic activity, a much larger number of compounds would need to be tested, including pairs of compounds such as (+) and (−) butaclamol and (α) and (β)-flupenthixol, where in a pair of isomers it is known that only one compound possesses neuroleptic activity. The question of drug concentration is also relevant, since the actions described by Dinan *et al* are elicited only at micromolar concentrations, much higher than those found free in body fluids clinically (although larger amounts of neuroleptic may be present in plasma tightly bound to protein), and also 100–1000 times higher than the concentrations required for dopamine receptor blockade.

The author goes on to relate these new findings to Broadbent's hypothesis of a defect in perceptual filtering in schizophrenic illness. The neural mechanisms involved in such a phenomenon, however, are quite unknown, so it is impossible to relate this is in any way to changes in ionic mechanisms as suggested.

Overall, Dinan seems to fall into many of the familiar pitfalls that have lured others in this field, and his arguments failed to convince me. It is inherently difficult to explain the actions of psychopharmacologically active compounds in terms of a molecular mechanism, but the "dopamine hypothesis" for explaining the actions of neuroleptics comes close to this, and has been one of the major achievements of research in this area in recent years.

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The Dopamine Hypothesis Survives, but There Must Be A Way Ahead*

T. J. CROW

Karl Popper has taught us that no hypothesis can be regarded as proved – merely as having survived the most stringent tests which have so far been devised. Dinan makes a further attempt to overthrow the dopamine hypothesis of the mechanism of the antipsychotic effect, and provides an alternative suggestion. As one time critic and later advocate of the theory, I think he underestimates its explanatory power and capacity for survival. I doubt that his alternative yet poses a serious challenge. I propose below a second (and perhaps more idiosyncratic) alternative. I do not claim it yet has the explanatory power of the dopamine theory, but I think it generates some new approaches.

*Commentary arising from preceding paper by T. G. Dinan

The survival of the dopamine hypothesis

A forerunner of the dopamine hypothesis was the view of Deniker (1960) that the extrapyramidal effects of neuroleptic drugs are related to their

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