not obviously common in the Galaxy. Their contribution to the lithium abundance is likely to remain small. It is more likely that the lithium abundance is a helpful clue towards an understanding of this specific object, rather than this object being a helpful clue towards an understanding of the evolution of lithium.

We are left with a picture of the formation and evolution of lithium in which the present abundance in warm stars with low heavy-element abundances may be a true record of primordial production, perhaps slightly modified by stellar depletion. Alternatively, much higher primordial production may have been compensated by greater depletion. Both these schemes may have to include significant production during the earliest stages of Galactic evolution. During the early stages of evolution of the galactic disk, the lithium abundance rose by an order of magnitude. Or was perhaps depleted less. All this time, convection destroyed, hot-bottom convective burning created, cosmic rays created and modified, close binaries produced, and perhaps even black holes spalled — a remarkable cross-section of astrophysics, whose full understanding remains as an exercise for the reader. □

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DOPAMINE RECEPTORS

Which D4 do *you* have?

Leslie Iversen

THE catecholamine dopamine continues to attract research interest because of its presumed pivotal role in brain pathways involved in mediating the actions of psychostimulant drugs and in maintaining 'drug seeking' behaviour for a variety of drugs of addiction. Dopaminergic mechanisms in the brain are also a key target for blockade by drugs used in the treatment of schizophrenic illness. On page 149 of this issue[1], Van Tol *et al.* show that one of the dopamine receptors in brain, the D4, exists in genetically determined polymorphic forms in the human population — this finding points to a possible basis for genetic differences in susceptibility to schizophrenia as well as for individual differences in response to drug treatment.

The history of biochemical studies of dopamine receptors extends over the past 20 years, following the discovery of Kebabian, Petzold and Greengard that some dopamine receptors in brain are positively coupled to adenylyl cyclase[2]. Subsequent studies revealed that some of the dopamine antagonist neuroleptic drugs used to treat schizophrenic illness do indeed potently inhibit the dopamine-stimulated cyclase response, but that not all categories of clinically active neuroleptics are effective[3]. It became apparent that at least two subtypes of dopamine receptor existed: D1 sites, positively coupled to adenylyl cyclase, and the D2, which are not coupled or are negatively coupled[4]. Drug affinities to the D2 sites reflected most accurately their behavioural effects and their clinical potencies in treating psychosis. More recently, both D1 and D2 receptors have been cloned[5,6] and have been shown to belong to the G-protein-coupled family of receptor proteins. Within the past two years molecular genetic studies have revealed the existence of three further members of the dopamine receptor family — the D3 and D4 subtypes[7,8], which resemble D2, and the D5 subtype, which resembles more closely the D1 subtype[9].

The D3 and D4 receptors resemble the D2 in their sensitivity to neuroleptic drugs, with some important differences. In particular, the D4 receptor is of considerable pharmacological interest as it binds the neuroleptic drug clozapine with an affinity some ten times higher than that of the D2 sites. This is intriguing because clozapine stands out clinically as one of the 'atypical' neuroleptics which retain antipsychotic efficacy but are much less likely to cause unwanted extrapyramidal motor side effects. This would probably have made clozapine the favoured drug for treating schizophrenic illness, were it not for the occurrence of rare haematological side effects. Could it be that the D4 receptor represents a site of especial importance in mediating the antipsychotic effects of such atypical neuroleptic drugs? Both D3 and D4 sites also have unusual anatomical distributions in brain; the messenger RNAs for these receptors are expressed in highest densities in limbic forebrain areas, thought to be key targets for antipsychotic drug actions, rather than in the basal ganglia which mediate extrapyramidal side effects.

Van Tol *et al.*[1] now add a new dimension to the complexity of dopamine pharmacology with their discovery that there are different polymorphic forms of the D4 receptor in the population. Screening human genomic libraries revealed three different forms, containing, respectively, two-, four- or sevenfold repeats of a 48-base-pair sequence in the putative third cytoplasmic loop region. A further two forms may exist containing one or five repeats of this sequence. These differences persist in the expressed receptors and, furthermore, the different forms of the D4 receptor display pharmacological differences when expressed in COS cells; the seven-repeat form, for example, is less sensitive to changes in agonist or antagonist (clozapine) affinity induced by addition of sodium chloride.

Whether the pharmacological differences observed *in vitro* translate into meaningful differences in drug sensitivity in the intact brain remains to be seen. The identification of these unexpected human variants of the D4 receptor, however, opens up many new and attractive vistas for molecular genetic studies of psychiatric illnesses[10]. Is it possible that the genetic disposition to schizophrenic illness could be linked to the presence of particular subtypes of dopamine receptor in susceptible individuals? Might the same be the case in those more likely to become addicted to drugs, which act in part through central dopaminergic systems?

In this fast-moving field there are inevitably more questions than answers. What, for instance, are we to make of the recent report by O'Mally *et al.*[11], claiming that the rat equivalent of the dopamine D4 gene is preferentially expressed in cardiovascular tissues? Are there yet more dopamine receptor subtypes to be discovered? Why have so many evolved? And, perhaps of most general interest, will this new knowledge help in the design of improved drug treatments for psychotic illness or drug addiction? □

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