

Iversen L L. Dopamine receptors in the brain. *Science* 188:1084-9, 1975.

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This review summarised data on the dopamine-stimulated adenylyl cyclase in brain as a model for central dopamine receptors. The potent inhibitory effects of a number of antischizophrenic drugs provided support for the hypothesis that such drugs act by blocking dopamine actions in the central nervous system [The SC® indicates that this paper has been cited in over 505 publications since 1975]

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"By the early 1970s, the idea that the drugs used in treating schizophrenia (major tranquilisers or neuroleptics) acted by virtue of their ability to block dopamine receptors in brain had become increasingly attractive.<sup>1</sup> It had not been possible to test the hypothesis directly, however, as no simple means of testing drug actions on dopamine receptors in brain were available. The discovery, in 1972, by Brown and Makman<sup>2</sup> and Keblavian, Petzold, and Paul Greengard<sup>3,4</sup> that dopamine specifically stimulated cyclic AMP formation in homogenates of dopamine-rich areas of the central nervous system (retina and basal ganglia) was, therefore, immediately recognised as an important step forward, since it might offer a suitable model system.

"In the Neurochemical Pharmacology Unit in Cambridge, a PhD student, Richard Miller, Alan Horn, and I tested a number of antischizophrenic drugs as possible antagonists of dopamine responses. The results of

this and similar work carried out in Greengard's group<sup>5</sup> and by Brown and Makman were summarised in this short review article. The data at first sight seemed to support the hypothesis, as drugs in the phenothiazine and thioxanthene classes proved to be potent inhibitors of the dopamine-stimulated adenylyl cyclase in brain; furthermore, pharmacologically inactive drugs in these classes were also inactive in the *in vitro* model.

"An important group of antischizophrenic drugs, however, the butyrophenones, which are pharmacologically very potent, proved to be only very weak antagonists of dopamine in the test-tube system. It is now recognised that the adenylyl cyclase model represents only *one* class of dopamine receptors in brain, the so-called D1 type.<sup>6</sup> The D2 type of receptors which were subsequently characterised by their ability to bind radio-labeled butyrophenones<sup>7</sup> are not cyclase-linked, and are thought to represent the more likely target of antischizophrenic drugs, since compounds of all chemical classes interact potently at these sites.<sup>8</sup> The D1 receptors, nevertheless, may contribute to the actions of antischizophrenic drugs of the phenothiazine and thioxanthene classes. A highly specific antagonist of the D1 dopamine receptors was recently discovered,<sup>9</sup> SCH 23390, and this compound has a pharmacological profile very similar to that of classical neuroleptic drugs in animal tests.<sup>10</sup>

"The significance of being asked to write an invited review article for *Science* was not clear to me at the time, although the subsequent popularity of this review of an active and topical area of psychopharmacology research shows how widely read such articles are. I am indebted to my colleagues Horn and particularly Miller, whose experimental findings formed the basis of the review."

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