

Snyder S H, Banerjee S P, Yamamura H I & Greenberg D. Drugs, neurotransmitters, and schizophrenia. *Science* 184:1243-53, 1974.

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Effects of antipsychotic, neuroleptic drugs and amphetamines on schizophrenic symptoms are reviewed. Interactions of these drugs with dopamine systems suggest a role for this neurotransmitter in modulating psychotic symptoms. [The *SCI*® and *SSCI*® indicate that this paper has been cited in over 685 publications.]

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The antischizophrenic neuroleptic drugs were introduced into general psychiatry in the mid- to late 1950s. Only by the mid-1960s did American psychiatrists accept that these agents exert uniquely antischizophrenic effects, distinct from generally sedating actions. Accordingly, psychopharmacologists began addressing how these extraordinary therapeutic effects might be mediated. Seminal work of Arvid Carlsson in 1962<sup>1</sup> suggested that neuroleptics might act by blocking dopamine receptors, though no direct evidence was available at that time. A role for dopamine was also favored by the remarkable psychotomimetic effects of amphetamines, in evidence as hippies in the late 1960s turned from LSD to intravenous amphetamines. At a high enough dose, almost every amphetamine user experienced an acute psychosis that often was clinically indistinguishable from acute paranoid schizophrenia.

I completed my psychiatry residency in 1968 and, with the assistance of Alan Green and Joseph Coyle, then medical students, and Ken Taylor, a postdoctoral fellow, began to examine catecholamine uptake and release and the effects of amphetamines. Our work, along with that of other groups, suggested that release of dopamine or inhibition of its uptake could

account for the psychotomimetic effects of amphetamines. To understand how neuroleptics could block dopamine receptors, Alan Horn, another postdoctoral fellow in the laboratory, developed a molecular model whereby phenothiazine neuroleptics occupied dopamine receptor sites.

By the early 1970s the concatenation of data from numerous sources clearly implied a link of dopamine and the modulation of schizophrenic symptoms. About that time receptor binding techniques, first employed in our laboratory in studies of opiate receptors, were applied to a number of receptors. Henry I. Yamamura and I found that the prominent extrapyramidal side effects of neuroleptic drugs could be predicted by the ability of drugs to block muscarinic cholinergic receptors.<sup>2</sup>

Because of increasing interest in drugs and schizophrenia, I was invited to prepare a review article for *Science*. Interestingly, techniques to measure dopamine receptors by ligand binding and direct evidence that the therapeutic potencies of neuroleptics parallel their affinity for dopamine receptors came about one to two years after publication of the review.<sup>3,4</sup>

Why is this article still cited? In the 14 years since its publication much effort has been devoted to studies of neurotransmitters and schizophrenia. It has become increasingly clear that dopamine does not explain all features of schizophrenic response to therapy. For instance, the positive symptoms of schizophrenia, such as florid hallucinations and delusions, respond well to the drugs, but the negative symptoms of apathy and general withdrawal are relatively resistant. More and more psychiatrists appreciate the gravity of neuroleptic side effects, such as the sometimes irreversible nature of tardive dyskinesia. Nonetheless, up to this day no other candidate molecular system has emerged that can explain as much about drug effects in schizophrenia as dopamine.

With our present ability to monitor many neurotransmitter receptors, numerous strategies have been implemented to design more effective and safer antipsychotic drugs. Target sites include the sigma and phencyclidine receptors.<sup>5,6</sup> However, so far no new agents have appeared that are clinically effective in wide-scale therapeutic trials. Thus, despite deficiencies associated with the dopamine "working hypothesis," it has led to abundant research that we hope will yield new therapeutic advances in treating schizophrenia, the most diabolic and disabling of mental illnesses.

1. Carlsson A & Lindqvist M. Effect of chlorpromazine and haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol. Toxicol.* 20:140-4, 1963. (Cited 130 times.)
2. Snyder S, Greenberg D & Yamamura H I. Antischizophrenic drugs and brain cholinergic receptors. *Arch. Gen. Psychiat.* 31:58-61, 1974. (Cited 320 times.)
3. Creese I, Burt D R & Snyder S H. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* 192:481-3, 1976. (Cited 635 times.)
4. Seeman P, Lee T, Chau-Wong M & Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* 261:717-9, 1976. (Cited 335 times.)
5. Largent B L, Gundlach A L & Snyder S H. Pharmacological and autoradiographic discrimination of sigma and phencyclidine receptor binding sites in brain with (+)-[<sup>3</sup>H]SKF 10,047, (+)-[<sup>3</sup>H]-3-[3-hydroxyphenyl]N-(1-propyl)piperidine and [<sup>3</sup>H]-1-[1-(2-thienyl)cyclohexyl]piperidine. *J. Pharmacol. Exp. Ther.* 238:739-48, 1986.
6. Zukin R S & Zukin S R. Phencyclidine, sigma and NMDA receptors: emerging concepts. (Domino E F & Kamenka J M, eds.) *Sigma and phencyclidine-like compounds as molecular probes in biology*. Ann Arbor, MI: NPP Books, 1988. p. 407-24.

13-4