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Kebabian J W & Calne D B. Multiple receptors for dopamine. *Nature* 277:93-6, 1979.
[Experimental Therapeutics Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, MD]

A review summarizing pharmacological, physiological, and biochemical evidence for the existence of two categories of dopamine receptors. [The *SCI*® indicates that this paper has been cited in more than 2,020 publications.]

Multiple Receptors for Dopamine

J.W. Kebabian
Research Biochemicals, Inc.
1 Strathmore Road
Natick, MA 01760

This review paper was derived from earlier work that I had done with the enzyme dopamine-sensitive adenylate cyclase. In one paper, this receptor-enzyme complex provided a biochemical model of a dopamine receptor in the brain;[1] in another, the receptor recognized a number of antipsychotic drugs known to be dopamine receptor antagonists.[2] Two publications describing this work have been designated as *Citation Classics* by the Institute for Scientific Information®.

The genesis of this review was my realization that the above-mentioned enzyme could not account for all the known pharmacology of dopaminergic drugs. The first piece of evidence for this came from a study I performed with Donald B. Calne while I was a postdoctoral fellow with Julius Axelrod. We tested lergotrile, an experimental dopamine receptor agonist Calne was using to treat his parkinsonian patients at the clinical center; we found lergotrile to be an antagonist in the biochemical test system. At the time, we didn't know what to do with this observation, so it was quietly buried in a little known journal.[3] Through a convoluted series of happenings, I found myself not only working in the group headed by Calne but also working in a laboratory next door to his office in the clinical center at NIH. As I went about my work, I gathered enough evidence to make me look long and hard at the pharmacology of a number of dopamine receptors. Finally, Calne and I decided to summarize the evidence suggesting the existence of at least two dopamine receptors in a review that was sent to *Science*. The manuscript was rejected. Accompanying the manuscript were stinging comments from the referees. The first referee's first reason for rejection was that the work was "not of sufficient general interest." This referee then went on to state that the paper "should not be published in any journal." (I keep the letter of rejection from the editor of *Science* and the referee's comments framed on my office wall to remind me that good ideas are frequently not well received.) Having received the letter of rejection, I went on the lecture tour in Europe and presented the views expressed in the recently rejected review. The response from my peers was sufficiently encouraging that the review was redrafted and submitted to *Nature* where it appeared early the next year. At several of the meetings I attended that summer, P.E. Spano discussed the idea of two dopamine receptors that he designated as the D1 and D2 receptors.[4] We decided to adopt this nomenclature rather than the alpha and beta nomenclature proposed initially. The revised paper was well received, being the second most-cited paper in the following three years. The designation of the paper as a *Citation Classic* indicates that it has survived the test of time.

The manuscript has been cited frequently for several reasons. First, the paper gave a conceptual framework of dopamine receptor pharmacology that was more useful than the schemes based on binding assays that led different investigators to claim the existence of one, three, or four dopamine receptors. Second, the paper presented examples of simple peripheral tissues where one or the other of the dopamine receptors could be identified. Third, within a short period of time, my colleagues and I were able to identify several chemical compounds capable of discriminating between the two categories of dopamine receptor.[5,6] These molecules have become widely used research tools, and at least one, a D2 receptor antagonist, may soon be marketed as a therapeutic agent in Japan. Fourth, the work prompted my colleagues and me to initiate a series of studies of the dopamine receptor in the intermediate lobe of the pituitary gland. Using this system, we were able to experimentally verify many of the points that were inferred about the pituitary dopamine receptor. The investigation of dopamine receptors continues to attract the interest of many individuals; most recently both the D1 and the D2 dopamine receptors have been cloned. Using this technology, at least six structurally distinct dopamine receptors have been identified.

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2. **Clement-Cormier Y C, Kebabian J W, Petzoid G L & Greengard P.** Dopamine-sensitive adenylate cyclase in mammalian brain: a possible site of action of antipsychotic drugs. *Proc. Nat. Acad. Sci. USA* 71:1113-7, 1974. (Cited 530 times.) [See also: **Clement-Cormier Y** C. Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology.* Philadelphia: ISI Press. 1986. p. 300.]
3. **Kebabian J W, Calne D B & Kebabian P R.** Lergotrile mesylate: an *in vivo* dopamine agonist which blocks dopamine receptors *in vitro. Commun. Psychopharmacol.* 1:311-8. 1977.
4. **Garau L, Govoni S, Stefanini E, Trabucchi M & Spano P F.** Dopamine receptors: pharmacological and anatomical evidences indicate that two distinct dopamine receptor populations are present in rat striatum. *Life Sci.* 23:1745-50. 1978. (Cited 120 times.)
5. **Tsuruta K, Frey E A, Grewe C W, Cote T E, Eskay R L & Kebabian J W.** Evidence that LY 141865 specifically stimulates the D-2 dopamine receptor. *Nature* 292:463-5. 1981. (Cited 250 times.)
6. **Grewe C W, Frey E A, Cote T E & Kebabian J W.** YM-09151-2: a potent antagonist for a peripheral D-2 dopamine receptor. *Eur. J. Pharmacol.* 81:149-52, 1982.

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