CC/NUMBER 18
APRIL 30, 1984

This Week's Citation Classic™

Clement-Cormier Y C, Kebabian J W, Petzold G L & Greengard P.
Dopamine-sensitive adenylate cyclase in mammalian brain: a possible site of action of antipsychotic drugs. *Proc. Nat. Acad. Sci. US* **71**:1113-17, 1974.
[Dept. Pharmacology, Yale Univ. Sch. Med.. New Haven, CT]

Dopamine produced a twofold increase in striatal adenylate cyclase activity (half-maximal increase in activity with 5 µM dopamine) Selected phenothiazines were potent and competitive inhibitors of enzyme activity with low inhibition constants (nanomolar range). The butyrophenones were competitive but weak antagonists; nonpsychoactive phenothiazines were without effect [The *SCI*® indicates that this paper has been cited in over 475 publications since 1974.]

Yvonne C. Clement-Cormier
Department of Pharmacology
Medical School
University of Texas
Health Science Center
Houston, TX 77225

March 14, 1984

"By the early 1970s, substantial evidence had accumulated for a functional role for cyclic nucleotides in the nervous system. When I joined Paul Greengard's laboratory as a graduate student, the presence of a dopamine-sensitive adenylate cyclase in the caudate nucleus of rat brain had just been reported.[1,2] This observation was significant because it focused attention on dopamine-sensitive cyclase as a possible biochemical marker for the dopamine receptor.

"As part of the research for my PhD thesis, I chose a pharmacological approach to investigate the potential usefulness of the dopamine-sensitive adenylate cyclase assay as a marker for the dopamine receptor. First, several studies were performed which documented the presence of the enzyme exclusively in dopaminergic brain areas and in a variety of mammals including humans. In addition, the enzyme activity was found to be enriched in subcellular fractions of the caudate associated with postsynaptic structures. These studies also demonstrated that the action of dopamine was directly on a receptor and not via metabolites of the neurotransmitter. Thus, on the basis of the results of these experiments, we theorized that the 'dopamine receptor' of the caudate nucleus, as described physiologically, was closely associated with dopamine-sensitive adenylate cyclase activity.

"At the time I was performing these studies, it was known that drugs of the phenothiazine and butyrophenone classes could assume a conformation similar to that of dopamine.[3] Thus, the dopamine-sensitive adenylate cyclase assay provided a readily accessible tool to evaluate the hypothesis that part of the mechanism of action of the antipsychotic drugs involved a direct interaction with the dopamine receptor.

"Over 15 different antipsychotic drugs (representing the phenothiazines, butyrophenones, and dibenzodiazepines), as well as nonpsychoactive drugs, were tested to determine if they blocked the effect of dopamine on brain adenylate cyclase. The results demonstrated that the antipsychotic drugs were competitive inhibitors with extremely high affinities (in the nanomolar range) for the enzyme. More importantly, drugs which had little or no antipsychotic or extrapyramidal actions clinically had relatively high inhibitory constants. Similar studies which confirmed our observations were reported by Leslie Iversen's group.[4]

"Not surprisingly, there were some discrepancies between the results of various test substances observed in this enzyme system with the results of clinical trials and laboratory studies *in vivo.* Whereas the data fit well for the phenothiazine class of antipsychotic drugs, the butyrophenones, which were known to be potent antipsychotics, were weak antagonists of dopamine-sensitive adenylate cyclase activity. At about this time, studies using radioligand binding as a tool for tagging dopamine receptors also showed differences between dopaminergic sites which were identified by labeled butyrophenones and those coupled to adenylate cyclase.[5,6] These observations were at the forefront of describing what is now the widely accepted view of the heterogeneity of the dopamine receptor.[7,8]

"There are several reasons why this paper has been highly cited. First, it provided strong support for the conclusion that some physiological effects of dopamine may be initiated by increases in intracellular cyclic AMP. Recent studies have substantiated this point of view.[9] Second, for the first time a rapid, accurate, and inexpensive pharmacological tool for identifying a drug as a direct agonist or antagonist at dopamine receptors coupled to adenylate cyclase was established, as well as a useful procedure for calculating the affinity of the drugs for the receptor. Third, the identification of additional categories of dopamine receptors arose, in part, as a consequence of the comparison of the efficacy of antagonists upon the dopamine-sensitive adenylate cyclase and other biochemical models of dopamine receptor sites."

1. **Kebabian J W, Petzold *G* L & Greengard P.** Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain. and its similarity to the "dopamine receptor." *Proc. Nat. Acad. Sci. US* **69**:2145-9. 1972.
2. **Kebabian J W.** Citation Classic. Commentary on *Proc. Nat. Acad Sci. US* **69**:2145-9. 1972. *Current Contents Life Sciences* **26**(11):18. 14 March 1983.
3. **Snyder S H.** Catecholamines in the brain as mediators of amphetamine psychoses. *Arch. Gen. Psychiat.* **27**:169-79, 1972. (Cited 215 times.)
4. **Iversen L K, Horn A S & Miller R J.** Actions of dopaminergic agonists on cyclic AMP in rat brain homogenates. *Advan. Neurol.* **9**:197-212. 1975. (Cited .55 times.)
5. **Snyder S H. Creese I & Buri D R.** The brain's dopamine receptor: labeling with [^{3} H] dopamine and [^{3}H] haloperidol. *Psychopharmacol Commun.* **1**:663-73, 1975. (Cited 55 times)
6. **Seeman P & Lee T.** Antipsychotic drugs: direct correlation between clinical potency and presynaptic action of dopaminergic neurons. *Science* **188:**1217-19. 1975. (Cited 230 times.)
7. **Clement-Cormier Y C & George R J.** Multiple dopamine binding sites: subcellular localization and biochemical characterization. *J Seurochemistry* **32**:1061-9. 1979. (Cited 25 times)
8. **Kebabian J W & Calne B.** Multiple receptors for dopamine. *Suture* 277:93-6 1979. (Cited 775 times.)
9. **Walaas S I. Aswad D W & Greengard P.** A dopamine- and cyclic AMP-regulated phosphoprotein in dopamine-innervated brain regions. N*ature **301***:69-71. 1983.