This Week's Citation Classic®

Koe B K & Weissman A. p-Chlorophenylalanine: a specific depletor of brain serotonin. *J. Pharmacol. Exp. Ther.* 154:499-516, 1966.
[Pfizer Inc., Groton, CT]

p-Chlorophenylalanine (PCPA) was reported in this paper to markedly deplete brain and peripheral stores of serotonin and 5-hydroxyindoleacetic acid in animals. Catecholamine concentrations were reported to be only slightly affected. Mechanistic studies indicated that PCPA effects serotonin depletion by inhibiting the biosynthesis of the monoamine at the tryptophan hydroxylase step. [The *SCI*® indicates that this paper has been cited in over 1,605 publications.]

PCPA: An Example of Serendipity

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The year 1991 will mark the twenty-fifth anniversary of our often-cited report that p-chlorophenylalanine (PCPA) depletes serotonin in mice, rats, and dogs by inhibiting tryptophan hydroxylase. Here is how the discovery was made: when p-chloroamphetamine was reported to moderately decrease serotonin concentrations in rat brain (e.g., reference 1), we quickly confirmed the finding and tried to extend it by testing likely metabolic precursors to p-chlorophenethylamines, among them PCPA. Fortuitously, serotonin concentrations were examined in rats at both 1 and 24 hours after treatment. Later we found that marked serotonin depletion in rat brain after PCPA could *only* have been detected after approximately 24 hours and that had we used mice the effect would have been less remarkable. In probing for the mechanism of the *in vivo* effect, we found that PCPA much more effectively than p-chloroamphetamine blocks the hydroxylation of tryptophan and phenylalanine.

Since our disclosure, PCPA has served as a research tool for inhibiting serotonin biosynthesis and for other purposes. The scope of experiments conducted with PCPA, usually based on information and samples provided by our company, and the scientific impact of PCPA have been extraordinary. PCPA perfectly illustrates the vast, mostly unsung contributions industrial pharmacological research has made to basic science.[2]

PCPA was not our only basic discovery during the mid-1960s. In 1965, after α-methyltyrosine (AMT) and its m-iodo derivative were reported to inhibit tyrosine hydroxylase,[3] we learned that Pfizer chemists had coincidentally synthesized a one-step precursor to AMT for a different purpose, enabling our rapid conduct of *in vivo* experiments. In planning one of these, we predicted that AMT would *increase* a rat's sensitivity to amphetamine by what was then termed denervation supersensitivity. The behavioral experiments yielded exactly opposite effects to those expected, and we were the first to report that AMT *blocks* amphetamine-elicited stimulation,[4,5] a finding that teaches much about how amphetamine exerts its stimulant action.

These forays into the pharmacology of ring-halogenated aromatic amino acids also led us to a neglected literature that low doses of m-fluorophenylalanine (m-FP) and m-fluorotyrosine (m-FT) are convulsant and lethal in rodents. While wondering how this toxicity could result from changes in brain amines, one of us, just then beginning a banal self-education project, found himself reading a review of fluoroacetate toxicity in volume 1 of *Pharmacological Reviews*.[6] Could lethal synthesis to fluoroacetate be the mechanism of m-FP and m-FT toxicity? Yes, and also of 5-fluorotryptophan toxicity, and analyzing the metabolic pathways had surprising benefits.[7-9]

Our main reason for reviewing these events is to emphasize that they were not predicted or sought in advance. We can provide many other anecdotes describing fortuitous drug discoveries. We are concerned that similarly important serendipitous discoveries seem to be less often made these days. For understandable reasons, the pharmaceutical industry now attempts to rationalize discovery research— to focus limited resources on proprietary goals, to foster teamwork, to minimize animal use, and to satisfy a widespread belief that modern drugs should be discovered and analyzed by using deductive logic. Analogous beliefs underlie the philosophies of most public and academic institutions that support research. But relying upon deductive reasoning as the *sole* basis for funding research, in our judgment, can undermine the possibility of just such serendipity as that we were lucky enough to encounter a quarter-century ago.

1. **Pletcher A, Burkard W P, Bruderer H & Gey K F.** Decrease of cerebral 5-hydroxytryptamine and 5-hydroxyindoleacetic acid by an arylalkylamine. *Life Sci.* 2:828-33, 1963. (Cited 45 times.)
2. **Weissman A & Koe B K.** Contributions of industrial research to basic neuropsychopharmacology: pre-clinical screening and discovery. (Meltzer H I, ed.) *Psychopharmacology, the third generation of progress.* New York: Raven Press, 1987. p. 1649-57.
3. **Udenfriend S, Zaltzman-Nirenberg P & Nagatsu T.** Inhibitors of purified beef adrenal tyrosine hydroxylase. *Biochem. Pharmacol.* 14:837-45, 1965. (Cited 315 times.)
4. **Weissman A & Koe B K.** Behavioral effects of L-alpha-methyl-tyrosine, an inhibitor of tyrosine hydroxylase. *Life Sci.* 4:1037-48, 1965. (Cited 140 times.)
5. **Weissman A, Koe B K & Tenen S S.** Antiamphetamine effects following inhibition of tyrosine hydroxylase. *J. Pharmacol. Exp. Ther.* 151:339-52, 1966. (Cited 465 times.)
6. **Chenoweth M B.** Monofluoroacetic acid and related compounds. *Pharmacol. Rev.* 1:383-424, 1949. (Cited 85 times.)
7. **Koe B K & Weissman A.** Convulsions and elevation of tissue citric acid levels induced by 5-fluorotryptophan. *Biochem. Pharmacol.* 15:2134-6, 1966. (Cited 5 times.)
8. **Weissman A & Koe B K.** m-Fluorotyrosine convulsions and mortality: relationship to catecholamine and citrate metabolism. *J. Pharmacol. Exp. Ther.* 155:135-44, 1967. (Cited 15 times.)
9. **Koe B K & Weissman A.** Dependence of m-fluorophenylalanine toxicity on phenylalanine hydroxylase activity. *J. Pharmacol. Exp. Ther.* 157:565-73, 1967. (Cited 10 times.)

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