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This Week's Citation Classic

Koella W P, Feldstein A & Czicman I S. The effect of para-chlorophenylalanine on the sleep of cats. *Electroencephalogr. Clin. Neuro.* **25**:481-90, 1968. [Worcester Foundation for Experimental Biology, Shrewsbury, MA]

In cats chronically prepared for EEC, EMG, and EOG recordings, p-chlorophenylalanine (PCPA) reduces in a dose-dependent manner sleep (SWS and PS about equally) and brain 5-HT. Sleep and 5-HT return toward control only slowly but not in a parallel fashion, suggesting the involvement of a negative feedback link. [The *SCI*® indicates that this paper has been cited over 125 times since 1968.]

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"Early in my career I worked with W.R. Hess, in Zurich. I learned from him that sleep is not a passive 'falling into Morpheus's arms' but rather an actively induced state. So a good part of my research activities was directed toward finding the central nervous structures that control sleep. After some early 'dry' attempts to pinpoint these structures, I became interested, in the late-1950s (at the Worcester Foundation), in serotonin which Brodie and Shore[1] assumed to be *the* central controlling instrument of trophotropic-endophylactic activities. In 1960, I demonstrated that intracarotid 5-HT exerts a modulatory influence on evoked potentials.[2] With Czicman,[3] I showed that cats react to 5-HT (intracarotid) with a transient arousal response (with mydriasis) followed by long-lasting slowing of the EEC (with miosis) and that injection of small amounts of 5-HT into the fourth ventricle induces EEC slowing and miosis.

"What I aimed at then was the reversal experiment, namely, evidence that sleep would be reduced if 5-HT was taken away from the brain; reserpine was not specific enough to do this job. So it came as a godsend when Koe and Weissman[4] discovered p-chlorophenyl-alanine (PCPA) that allowed (almost) specific depletion of brain 5-HT. Late in 1966, we began a new, rather broad study on a dose-response basis, with long (up to four weeks) single experiments, on a large number of cats, including parallel biochemical probes (done by Aaron Feldstein). In that study we could show indeed that one shot of PCPA in a dose-dependent manner reduces sleep for several weeks *and* brain 5-HT levels. Because of the 'puristic' way in which we performed the experiments we were —unfortunately or fortunately- late with the publication of our results. But it was worthwhile waiting. We had results allowing good and reliable analysis of the quantitative and temporal relations between brain 5-HT levels and sleep (this paper). At that time we were convinced that 5-HT is important for sleep although it is also involved in other jobs such as pain and temperature regulation, drug habituation, and, peripherally, gut activity, blood clotting, and pupillary adjustment.

"Why would a paper like this one be cited so often? Perhaps because it is a manifestation of the 'endpoint' of a sequential and logical flow of ideas and experimental results; or, because it added by that time to our understanding of the organization and regulation of sleep; or, because by its very results it offered new possibilities for the development of new (and so badly needed) hypnotics. I have recently published in this field "5

1. **Brodie B B & Shore P A**. A concept for a role of serotonin and norepinephrine as chemical mediators in the brain**.** *Ann. NY Acad. Sci.* **66**:631-42, 1957.
2. **Koella W P, Smythies J R, Bull D M & Levy C K.** Physiological fractionation of the effect of serotonin on evoked potentials**.** ***Amer. 1. Physiol.* 198**:205-12. 1960**.**
3. **Koella W P & Czicman J**. Mechanism of the EEG-synchronizing action of serotonin**.** ***Amer. J. Physiol.* 211**:926-34, 1966.
4. **Koe B K & Weissman A.** p-Chlorophenylalanine: a specific depletor of brain serotonin. *J. Pharmacol. Exp. Ther.* **154**:499-516, 1966.
5. **Koella W P.** Neurotransmitters and sleep. (Wheatley D. ed.) *Psychopharmaeology of sleep.* New York: Raven Press. 1981. p. 19-52.