This Week's Citation Classic®

Zukin S R & Zukin R S. [^{3}H]Phencyclidine binding in rat central nervous system. *Proc. Nat. Acad. Sci. USA* 76:5372-6, 1979; **Zukin R S & Zukin S R.** Demonstration of [^{3}H]cyclazocine binding to multiple opiate receptor sites. *Mol. Pharmacol.* 20:246-54, 1981; and **Zukin R S & Zukin S R.** Multiple opiate receptors: emerging concepts. *Life Sci.* 29:2681-90, 1981.

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In the first of these papers, the existence of a specific binding site for radiolabeled phencyclidine (PCP) was demonstrated in rat brain. These sites were shown to be selective for compounds capable of exerting PCP-like behavioral effects; moreover, drug potencies in the receptor assay correlated highly with their potencies in assays of PCP-specific behavioral effects. A unique regional distribution of the sites was also described. Taken together, the data suggested that the unique anesthetic and psychotomimetic properties of PCP-like drugs are mediated at specific PCP receptors. The observation that a benzomorphan σ opiate, *N*-allyl normetazocine (SKF-10047) bound to the PCP receptor, together with behavioral evidence that this opiate had PCP-like behavioral effects, led to the hypothesis that the PCP receptor might represent a common binding site for PCP derivatives and σ opiates. This was confirmed in the second paper, in which it was shown that a radiolabeled σ opiate could label PCP as well as μ and possibly K opioid receptors. This hypothesis was fully elaborated in the third paper. [The *SCI*® indicates that these papers have been cited in more than 370, 165, and 195 publications, respectively.]

PCP and Multiple Opiate Receptors

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The collaboration developed with one of us (SRZ) primarily interested in the biochemical mechanisms of the psychotomimetic actions of PCP and the other (RSZ) primarily interested in the molecular pharmacology of opiates. In 1979, PCP was a leading drug of abuse in the US. Although diverse neurochemical actions of PCP upon multiple systems had been described, none of those systems could account for the rank orders of potency of PCP derivatives in eliciting specific PCP-like animal behaviors.

The first study employed the scientific approach which SRZ had learned as a medical student at Johns Hopkins University, working under the preceptorship of Solomon Snyder, and which RSZ was independently applying to studies of opiate receptors.

One reason for the frequent citation of the first paper is undoubtedly that it was one of two independent, virtually simultaneous descriptions of the unique PCP receptor.[1] Another reason is that the PCP receptor turned out to be the σ opiate receptor which W.R. Martin had postulated to exist.[2]

The first paper cites the pioneering behavioral work of Harlan Shannon, who had just demonstrated that the prototypical opiate SKF-10047 elicited PCP-specific effects in a specific drug discrimination paradigm in rats.[3] We were able to show that the potencies (relative to that of PCP) of SKF-10047 trained animals correlated with their affinities for the PCP receptor.

Subsequent scientific developments are also likely to account for a continuing high frequency of citation of these papers. The PCP receptor is now known to represent a site within the *N*-methyl-D-aspartate (NMDA)-receptor gated cation channel, and PCP actions are used as probes of NMDA receptor functioning in physiological as well as biochemical paradigms[4] in the explosively developing area of NMDA receptor research. In retrospect we can consider that the demonstration of the PCP receptor was in fact the biochemical demonstration of the NMDA receptor complex.

1. **Vincent J P, Kartalovski B, Geneste P, Kamenka J M & Lazdunski M.** Interaction of phencyclidine ("angel dust") with a specific receptor in rat brain membranes. *Proc. Nat. Acad. Sci. USA* 76:4678-82, 1979. (Cited 240 times.)
2. **Martin W R, Eades C G, Thompson J A, Huppler R E & Gilbert P E.** The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J. Pharmacol. Exp. Ther.* 197:517-32, 1976. (Cited 1,530 times.)
3. **Shannon H E.** Pharmacological evaluation of N-allylnormetazocine (SKF 10047) on the basis of its discriminative stimulus properties in the rat. *J. Pharmacol. Exp. Ther.* 225:144-52, 1983.
4. **Javitt D C, Frusciante M J & Zukin S R.** Rat brain *N*-methyl-D-aspartate (NMDA) receptors require multiple molecules of agonist for activation. *Mol. Pharmacol.* 37:603-7, 1990.

Received November 28, 1990