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Leysen J E, Gommeren W & Laduron P M. Spiperone: a ligand of choice for neuroleptic receptors. 1. Kinetics and characteristics of *in vitro* binding. *Biochem. Pharmacol.* 27:307-16, 1978.
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Today, spiperone is one of the most popular ligands in binding studies. It binds remarkably on dopamine D_2 receptors in vitro as well as in vivo. But it has also allowed researchers to identify brain serotonin receptors. It is, therefore, a unique ligand because it recognized two receptors located in two different brain regions. One ligand for two receptors. [The *SCI*® indicates that this paper has been cited in more than 430 publications.]

Spiperone: From Dopamine to Serotonin Receptors

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Drugs have often provided a path through the extremely complex brain leading to the identification of receptors, in particular those of the "classical" neurotransmitters (dopamine, GABA, serotonin). Indeed, by 1975 neuroleptic drugs had already been used for more than 20 years in schizophrenia, and it was at this time that Seeman and Synder's group identified dopamine receptors in striatal membranes using ^{3}H-haloperidol as the ligand.

However, when another butyrophenone derivative, spiperone, became available in a radioactive form, Josée E. Leysen and I immediately realized its enormous potential as a ligand, mainly because of its ability to work in vivo.[1] In the first paper in a series of three, we reported on the in vitro binding properties of ^{3}H-spiperone with its three major characteristics: high affinity, low dissociation rate, and low nonspecific binding.

However, the reasons for frequent citing of this paper are that it provides a complete analysis of spiperone binding with more than 50 displacing compounds and that the in vitro binding affinity was correlated with the in vivo pharmacological potency. This latter point has always been an obsession with me because I strongly believe in Langley's principle that the physiological response defines the receptor.[2] Perhaps this concept came from my first meeting with Corneille Heymans in Ghent where I spent four years studying for my PhD. He said, "In vitro studies are more relevant with in vivo implications."

Yet another advantage of spiperone is that it enabled the solubilization of high affinity dopamine receptors,[3] something that was not possible with haloperidol. However, the binding sites obtained in the rat were not of a high affinity. It suddenly occurred to me one weekend to change the species from rat to dog, and within the next week the problem of solubilization of high affinity D_2 receptors, encountered for over a year, was solved.

One of the most striking properties of spiperone is its ability to label brain receptors in vivo.[1] This enables visualization of human brain receptors using the PET scanning technique. In addition to spiperone, we developed other ligands (dexetimide, lofentanil, ketanserin) that are also now used in PET scanning.

But spiperone was to yield yet another advantage. When studying ^{3}H-spiperone binding in vivo, I wondered why labeling declined more rapidly in the rat frontal cortex than in striatum. The simplest explanation appeared to be that these two brain regions contained different dopamine D_2 receptors. Beginning with this hypothesis, Leysen and I decided to examine ^{3}H-spiperone binding in rat frontal cortex homogenate. Fortunately, the hypothesis was wrong because unlike the striatum, in the frontal cortex serotonin agonists and antagonists were more effective displacers of ^{3}H-spiperone binding than dopamine antagonists. In fact, we had discovered serotonin receptors[4] in the brain that were subsequently named 5-HT_2 or S_2 receptors. This led yet again to the development of a better ligand, ^{3}H-ketanserin, which allowed us to further identify these sites in vitro and in vivo in animals and in man.[5] This finding opened up the way for the development of a new class of drugs, the 5-HT_2 antagonists, with anxiolytic and sleep quality improving properties. In 1980, we were extremely pleased to learn that two of our papers were among the most frequently cited in 1978-1979.[6]

Since my training period in Ghent, I have always had a great interest in subcellular fractionation studies initiated by Christian de Duve and his school. I have adapted his five fraction scheme to neurobiology to study the subcellular localization of receptors and the enzymes involved in catecholamine biosynthesis. This certainly gave me the idea of studying the more dynamic aspects as the axonal transport, and, in 1968, we demonstrated the axonal transport of dopamine β-hydroxylase. In 1980, I used the same model to provide the first evidence for the axonal transport of a neuroreceptor.[7] After having characterized such receptors, the question I am now faced with is what is the significance of their retrograde transport. Are they involved in the long-term effects of signal molecules?

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3. **Gorissen H & Laduron P M.** Solubilization of high-affinity dopamine receptors. *Nature* 279:72-4, 1979. (Cited 65 times.)
4. **Leysen J E, Niemegeers C J E, Tollenaere J P & Laduron P M.** Serotonergic component of neuroleptic receptors. *Nature* 272:168-71, 1978. (Cited 490 times.)
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6. **Garfield E.** The 1978 articles most cited in 1978 and 1979. 2. Life sciences. *Essays of an information scientist.* Philadelphia: ISI Press, 1981. Vol. 4. p. 686-95.
7. **Laduron P M.** Axoplasmic transport of muscarinic receptors. *Nature* 286:287-8, 1980. (Cited 75 times.)

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