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Comment on "Diverse Psychotomimetics Act Through a Common Signaling Pathway"

Svenningsson *et al.* (1) claimed that amphetamine, D-lysergic acid diethylamide (LSD), and phencyclidine (PCP) are diverse psychotomimetics that act on dopamine, serotonin, and glutamate neurotransmission, respectively. However, it is essential to point out that these compounds may not specifically affect diverse systems. LSD and phencyclidine are also potent direct agonists at dopamine D2 receptors. The effects are as potent as amphetamine's indirect action through dopamine. In fact, all three compounds are equally potent agonists at D2, with dissociation constants of 1.5 to 1.8 nM for dopamine (2–4), 0.8 nM for LSD-25, and 1.3 nM for phencyclidine at the physiological and functional (5) high-affinity state of D2 (Fig. 1). The competition data between each of these psychotomimetics and [³H]raclopride, a D2-selective ligand, reveal a sharply demarcated

biphasic pattern with high- and low-affinity components, consistent with these compounds being D2 agonists. These three agonists recognize a high proportion of the high-affinity D2 sites: 40 to 50% for dopamine (2–4), 60% for phencyclidine, and 80% for LSD. This is especially evident when using 10 mM NaCl to reveal the high-affinity states of D2, all of which are converted to low-affinity states by guanine nucleotide (2–4). Thus, the psychotomimetic behaviors induced in wild-type mice by amphetamine, LSD, and phencyclidine, and altered in DARPP-32 (6) knockout mice [as reported by Svenningsson *et al.* (1)], are consistent with the dopamine hypothesis of psychosis or schizophrenia (7), because all three compounds are potent dopamine mimetics.

It is not surprising, therefore, that DARPP is involved in the action of these three drugs,

because DARPP is involved in the action of D2 agonists (8). LSD is not selective, having actions at multiple receptors, including serotonin receptors and dopamine D1 and D2 receptors (9). Moreover, LSD is a partial agonist, activating D2 receptors at 0.1 nM, while antagonizing D2 at 10 nM (10). Phencyclidine is also not selective, antagonizing the *N*-methyl-D-aspartate (NMDA)-type of glutamate receptors (11) while acting as an agonist at the D2 receptor (2). Thus, the multi-receptor actions of LSD and phencyclidine

do not clarify the neurochemical psychotic pathways, especially when tested on prepulse inhibition (PPI). PPI is influenced by multiple neurotransmitters, including serotonin, glutamate, dopamine and neurotensin (12–15). There are also mouse strain-specific effects of psychotomimetics (16) and compensatory changes in multiple receptors are known to occur in knockout mice (17). Most importantly, haloperidol or pimozide, which occupy D2 but not serotonin or glutamate receptors at clinical doses, remit all psychotic symptoms induced by PCP, amphetamine or LSD in patients [see references in (2)]. Because LSD, phencyclidine, and amphetamine affect multiple neurotransmitter pathways, more selective compounds must be used to test the contributions of the serotonin, glutamate and dopamine neurochemical pathways to psychotomimetic action (18).

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References and Notes

1. P. Svenningsson *et al.*, *Science* **302**, 1412 (2003).
2. S. Kapur, P. Seeman, *Mol. Psychiatry* **7**, 837 (2002).
3. P. Seeman, T. Tallerico, F. Ko, *Synapse* **49**, 209 (2003).
4. P. Seeman, S. Kapur, *Synapse* **50**, 35 (2003).
5. S. R. George *et al.*, *Endocrinology* **117**, 690 (1985).
6. DARPP-32 is an adenosine 3',5'-monophosphate (cAMP)-regulated phosphoprotein of 32 kD.
7. P. Seeman, *Synapse* **1**, 133 (1987).
8. P. Greengard, P. B. Allen, A. C. Nairn, *Neuron* **23**, 435 (1999).
9. V. J. Watts *et al.*, *Psychopharmacology* **118**, 401 (1995).
10. S. Giacomelli, M. Palmery, L. Romanelli, C. Y. Cheng, B. Silvestrini, *Life Sci.* **63**, 215 (1998).
11. B. Moghaddam, *Neuron* **40**, 881 (2003).
12. A. Ouagazzal, A. J. Grottick, J. Moreau, G. A. Higgins, *Neuropsychopharmacology* **25**, 565 (2001).
13. S. A. Brody, S. C. Dulawa, F. Conquet, M. A. Geyer, *Mol. Psychiatry* **9**, 35 (2004).
14. R. J. Ralph-Williams, V. Lehmann-Masten, M. A. Geyer, *Neuropsychopharmacology* **28**, 108 (2003).
15. P. D. Shilling, G. Melendez, K. Priebe, E. Richelson, D. Feifel, *Psychopharmacology (Berl.)* (Epub ahead of print) (2004).
16. R. J. Ralph, M. P. Paulus, M. A. Geyer, *J. Pharmacol. Exp. Ther.* **298**, 148 (2001).
17. P. Seeman, unpublished data.
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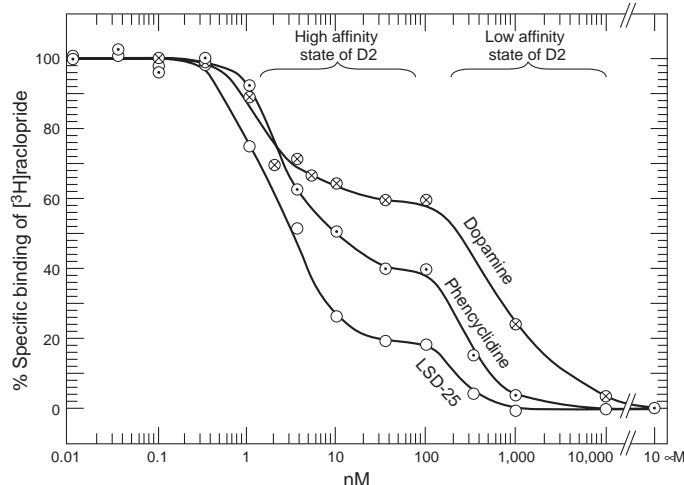


Fig. 1. Psychotomimetic affinity for dopamine D2 receptors. Using [³H]raclopride (2) to label human cloned dopamine D2 receptors in 10 mM NaCl, dopamine, phencyclidine, and LSD-25 all reveal agonist-type biphasic competition curves and have dissociation constants between 0.8 and 1.8 nM at the functional high-affinity state of D2. These three compounds act as dopamine agonists in this range of concentrations.