

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Psychotomimetic Effects of Drugs — A Common Pathway to Schizophrenia?

David J. Gerber, Ph.D., and Susumu Tonegawa, Ph.D.

Researchers have long been interested in identifying a final, common pathway for psychosis. The existence of such a pathway is implied by the fact that various drug intoxications, schizophrenia and bipolar disorders, psychotic depression, severe sensory deprivation, and Alzheimer's disease can all cause similar psychotic phenomena. Fueling the interest in finding a common pathway is the possibility that the side effects of antidopaminergic neuroleptic agents — principally movement disorders, such as tardive dyskinesia — might be averted by precise targeting of molecules downstream of the dopamine receptor. Svenningsson and colleagues¹ recently described a candidate pathway in a mouse model.

Focusing on the psychotomimetic effects of three drugs linked to symptoms of schizophrenia — amphetamine, lysergic acid diethylamide (LSD), and phencyclidine hydrochloride (PCP), which target the dopaminergic, serotonergic, and glutamatergic neurotransmitter pathways, respectively — the authors report that an endogenous 32-kD dopamine and cyclic adenosine monophosphate–regulated phosphoprotein termed DARPP-32 represents a point of convergence. Normally, these drugs impair prepulse inhibition of the acoustic startle response and increase repetitive movements, but mice lacking DARPP-32 are resistant to the drugs' behavioral effects. Moreover, the drugs have similar effects on the phosphorylation status of DARPP-32 and two downstream molecules in the striatum and frontal cortex. Mice in which specific phosphorylation sites of DARPP-32 are mutated have consistent perturbations in their response to these compounds and in the phosphorylation of molecules downstream of DARPP-32.

These findings suggest the need for additional experiments, in several ways. First, although prepulse inhibition and repetitive movements are important measures of schizophrenia in mouse models, it would be useful to examine other relevant behavioral factors, such as working memory, social

interaction, and latent inhibition in mice treated with amphetamines, LSD, and PCP, and thereby to obtain a more comprehensive view of the role of DARPP-32 in the psychotropic effects of these agents. Second, a careful dissection of relevant dopamine receptors is warranted, given that amphetamine has been shown to disrupt prepulse inhibition in mice lacking the dopamine D1 receptor but not in those lacking the dopamine D2 receptor.² Thus, the D1 receptor may not mediate such effects of amphetamine, in contrast to the D2 receptor and possibly other receptors upstream of DARPP-32. (Perhaps not uncoincidentally, common antipsychotic agents such as haloperidol antagonize D2 receptors.)

Third, studies are needed to determine whether it is the lack of DARPP-32 in the striatum, in the cortex, or in both regions that underlies resistance to the psychotomimetic effects of the drugs. DARPP-32 is highly expressed in the striatum and less so in the cortex, where the homologous protein, inhibitor 1, may have a similar function. Such studies could examine mice deficient in DARPP-32 or inhibitor 1 in a region-specific manner — for example, in the cortex or striatum. And finally, a potential association should be investigated between schizophrenia and variations in the gene for DARPP-32.

The provocative study by Svenningsson and colleagues raises the possibility that DARPP-32 and its downstream effectors have a causative role in schizophrenia. This is consistent with recent work^{3,4} showing that altered calcineurin function contributes to schizophrenia, since DARPP-32 is a major substrate of calcineurin. It is the general hope in the field that a combination of pharmacology and the study of human and mouse molecular genetics will ultimately be used to pinpoint the molecular alterations that contribute to the pathogenesis of schizophrenia and thereby identify a set of specific and relevant targets for therapy. The use of therapies directed at precisely defined targets may help to prevent the side effects that are characteristic of

currently available antipsychotic medications and provide a more comprehensive treatment of the various symptoms.

From the Picower Center, Massachusetts Institute of Technology, Boston.

1. Svenningsson P, Tzavara ET, Carruthers R, et al. Diverse psychotomimetics act through a common signaling pathway. *Science* 2003; 302:1412-5.
2. Ralph-Williams RJ, Lehmann-Masten V, Otero-Corchon V, Low

MJ, Geyer MA. Differential effects of direct and indirect dopamine agonists on prepulse inhibition: a study in D1 and D2 receptor knock-out mice. *J Neurosci* 2002;22:9604-11.

3. Miyakawa T, Leiter LM, Gerber DJ, et al. Conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia. *Proc Natl Acad Sci U S A* 2003;100:8987-92.

4. Gerber DJ, Hall D, Miyakawa T, et al. Evidence for association of schizophrenia with genetic variation in the 8p21.3 gene, PPP3CC, encoding the calcineurin gamma subunit. *Proc Natl Acad Sci U S A* 2003;100:8993-8.

Copyright © 2004 Massachusetts Medical Society.

ELECTRONIC ACCESS TO THE JOURNAL'S CUMULATIVE INDEX

At the *Journal's* site on the World Wide Web (www.nejm.org), you can search an index of all articles published since January 1975 (abstracts 1975–1992, full text 1993–present). You can search by author, key word, title, type of article, and date. The results will include the citations for the articles plus links to the abstracts of articles published since 1993. For nonsubscribers, time-limited access to single articles and 24-hour site access can also be ordered for a fee through the Internet (www.nejm.org).