Phencyclidine, Dizocilpine, and Cerebrocortical Neurons

Olney et al. (1) report that treatment with phencyclidine and the related compounds dizocilpine (MK-801), ketamine, and tiletamine leads to reversible vacuolization in some neurons in rat cerebral cortex. These changes were restricted to cingulate and retrosplenial areas of cortex, and subsided within 18 to 24 hours after drug administration.

We had noted earlier observations which demonstrated a profound elevation in glucose metabolism in these same areas of rat cerebral cortex after treatment with dizocilpine or phencyclidine (2) and carried out neurohistopathological studies to determine whether this elevation might be associated with long-term damage to neurons in the rat cerebral cortex.

Groups of five male adult rats were treated with single intraperitoneally administered doses of dizocilpine in the range from 0.625 to 5.0 mg/kg. Brains were examined histologically 48 hours after drug administration, with particular attention being paid to the cingulate cortex. There was no evidence of vacuolization in any cortical neurons, presumably because this transient effect would have subsided 48 hours after drug treatment. After doses of dizocilpine of 0.625, 1.25, or 2.5 mg/kg, respectively, were given, we found no evidence of necrotic changes in cingulate neurons. After the highest dose of 5.0 mg/kg, small numbers of necrotic neurons could be observed (mean 5 per tissue section out of a total of approximately 1500 cingulate neurons sampled).

The excitatory effects of dizocilpine (MK-801) in rodents are well known, but the significance of the morphologic changes induced in some cortical neurons is unclear. In our experience the rat is significantly more sensitive to the stimulant effects of MK-801 than is the rhesus monkey. Our results confirm the findings of Olney et al. that permanent cell damage is unlikely to occur after clinically relevant doses of dizocilpine, which are considerably lower than the doses found to cause necrotic cell changes.

H. L. Allen
Merk Sharp & Dohme Research Laboratories,
West Point, PA 19486
L. L. Iversen
Terlings Park, Harlow,
United Kingdom

REFERENCES
17 July 1989; accepted 27 October 1989

Response: An intriguing feature of our studies is the evidence of pathomorphological effects of phencyclidine (PCP) and related agents on cerebrocortical neurons in the cortex of rats. The effect was limited to multipolar and pyramidal shaped neurons in layers III and IV of the posterior cingulate and retrosplenial cortices. We are indebted to Allen and Iversen for pointing out evidence we had overlooked that these agents cause a striking elevation of glucose utilization localized to these same cerebrocortical regions. It is not clear whether the increased metabolic rate occurs in the same cells that manifest pathomorphological changes, or in some other neural elements in this region, but it seems likely that the two phenomena are mechanistically interrelated.

Of considerable interest is the evidence presented by Allen and Iversen that dizocilpine, at a high dose, causes necrosis of cerebrocortical neurons. The mechanism by which these compounds exert either reversible or irreversibly effects on cerebrocortical neurons remains obscure, but we have recently observed that the acute vacuolation response is produced by direct injection of the competitive N-methyl-D-aspartate (NMDA) receptor antagonist, d-2-amino-5-phosphonopentanoate (D-AP5), into the cingulate cortical region (1). It would appear, therefore, that antagonism of the NMDA receptor complex can cause this effect whether the blockade occurs at the NMDA receptor itself or at the PCP receptor within the NMDA receptor-gated ion channel. Thus, persistent inactivation of NMDA receptor function in the cerebrocortical zone apparently can cause certain neurons in this zone to undergo pathological changes which, depending on how persistent the inactivation process is, can be either reversible or irreversible.

While we agree that the apparent reversibility of the pathological changes following low doses is basis for optimism with relation to the possible use of these agents as neuroprotective drugs, one cannot but harbor concern over evidence that these changes become irreversible at higher doses. We do not know precisely what dose range is being projected as clinically relevant in humans, but most animal studies seeking to show a neuroprotective effect against ischemic brain damage have used dizocilpine doses in the range of 0.1 to 10 mg/kg, and the dose range causing reversible vacuolization in the rat is 0.1 to 2.5 mg/kg, with these changes becoming irreversible, according to the data of Allen and Iversen, at 5 mg/kg. However, if rescue from devastating brain damage is the nature of benefit to be derived from this class of drug, the risk of losing a relatively small subpopulation of cerebrocortical neurons as a side effect of treatment, although not desirable, may be acceptable.

Evidence for permanent loss of cingulate-retrosplenial neurons secondary to excessive activation of PCP receptors invites speculation that such a process might be operative in schizophrenia, that is, a pathological process permitting chronic excessive activation of PCP receptors; hence chronic suppression of NMDA receptor function might cause permanent loss of a select subpopulation of cingulate-retrosplenial neurons and chronic dysfunction (without degeneration) of many other NMDA-PCP receptor-bearing neurons throughout the brain. Since cingulate neurons normally mediate affective responses to pain (2), this would explain why schizophrenics are often hypersensitive to pain (3) and, since PCP receptor stimulation is known to produce psychotic symptoms in humans, this hypothesis provides a credible explanation for the symptomatology of schizophrenia. Perhaps the most interesting feature of this hypothesis, however, is that it does not even require PCP receptor dysfunction, rather, any pathological process that renders the NMDA receptor complex chronically hypofunctional might produce PCP-like psychotic effects and loss of cingulate-retrosplenial neurons.

J. W. Olney
J. Labuyere
M. T. Price
Department of Psychiatry,
Washington University School of Medicine,
St. Louis, MO 63110

REFERENCES
4 August 1989; accepted 31 October 1989
Phencyclidine, dizocilpine, and cerebrocortical neurons
HL Allen and LL Iversen

Science 247 (4939), 221.
DOI: 10.1126/science.2403696