ELECTROPHYSIOLOGICAL STUDIES OF THE INTERACTION BETWEEN PHENCYCLIDINE/*SIGMA* RECEPTOR AGONISTS AND EXCITATORY AMINO ACID NEUROTRANSMISSION ON CENTRAL MAMMALIAN NEURONES.

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Since the original observations that low doses of ketamine, phencyclidine (PCP), etoxadrol and cyclazocine were selective antagonists of N-methyl-D-aspartate (NMA) on spinal neurones were reported at the 1st of these French-U.S. seminars in Montpellier 1982, much work has gone into attempting to ascribe some of the biochemical and behavioural properties of PCP-like drugs to reduced excitatory transmission. In the spinal cord, cerebral cortex and other parts of the CNS, synaptic excitations which on other grounds are thought to be mediated by NMA receptors but not those mediated by other receptors are also reduced by *sigma* opiates and dissociative anaesthetics. Using hemisected frog spinal cords and wedges of cerebral cortex, we have estimated the IC_{50}s of a series of such drugs to reduce neuronal depolarisation by NMA. Their potency as NMA antagonists appears to correlate with their ability to displace PCP binding, to mimic PCP in drug discrimination studies, to prevent epileptiform activity, to reduce glutamate-induced calcium uptake into brain slices and to limit the neuronal damage that follows hypoxia *in vitro* and ischaemia *in vivo*. Synaptosomal release of rubidium, a measure of potassium conductance, is inhibited by these and related drugs in a manner that does not correspond to PCP receptor activity. Furthermore, the fact that PCP-like drugs do not increase central synaptic transmission argues against them causing an enhanced presynaptic release of neurotransmitter. NMA antagonism by PCP-like compounds is not competitive. The observation of a dependency on exposure of *in vitro* preparations to NMA agonists in order to fully develop the block of their action by some of the PCP-like compounds as well as the voltage-dependency of this antagonism reported elsewhere suggest that the PCP/*sigma* receptor may be located in the channel opened by activation of the NMA receptor. If this concept of a channel plugging action of PCP proves correct, then it seems unlikely that a PCP receptor antagonist will be found. If on the other hand PCP proves to modulate the activation of the NMA receptor channel in a manner akin to that of the benzodiazepine-GABA interaction then PCP antagonists should be found. If our hypothesis that NMA antagonism explains some of the behavioural properties of PCP, it should be possible to mimic or ameliorate the action of PCP by pharmacological modulation, reduction or facilitation respectively, of synaptic excitation mediated by NMA receptors. (Supported by the MRC and the Wellcome Trust.)

DIFFERENT PATTERNS OF CEREBRAL GLUCOSE UTILIZATION PRODUCED BY PHENCYCLIDINE AND (+)N-ALLYLNORMETAZOCINE.

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Phencyclidine (PCP) and N-allylnormetazocine (NANM) share several properties, including the abilities to produce psychotomimetic effects, to be self-administered and to bind at specific cerebral sites. Because of interest in the mechanisms which mediate the behavioral effects of PCP and *sigma* agonists, we studied the effects of PCP (0.5, 1, 5, 10 mg/kg) and (+)NANM HCl (5 mg/kg) on rates of local cerebral glucose utilization (LCGU) in awake rats, by the autoradiographic 2-deoxy-D-[1-^{14}C]glucose method (L. Sokoloff *et al.*, *J Neurochem* **28:** 897, 1977). This method has been used to demonstrate a close relation between cerebral function and glucose utilization, and has been helpful in identifying brain areas affected by various drugs *in vivo* (J. McCulloch, in: *Handbook of Psychopharmacology*, vol 15, edited by L. L. Iversen *et al.*, New York: Plenum, p. 321, 1982). Rats received an IV injection of PCP, NANM, 2 or 15 min before the radiotracer, respectively, or 0.9% NaCl at corresponding times, and LCGU was determined as described by Sokoloff *et al.* (1977). PCP produced stereotypies, ataxia, and various effects on LCGU, which varied with dose. LCGU increased throughout the limbic system, except the habenula. LCGU increased in most sensory structures, but decreased in specific layers of the somatosensory and auditory cortices and the inferior colliculus. Responses of specific thalamic relay areas appeared to be dissociated from activity in their terminal fields in the cortex. LCGU increased throughout the motor system, showing a striking pattern of columnar activity in the motor cortex. However, LCGU was reduced in the frontal cortical pole. Rats given injections of NANM also showed ataxia and stereotypies, but the quality and distribution of the effects of (+)NANM on LCGU differed widely from those of PCP. LCGU was generally reduced, with statistically significant effects in the cerebellum, superficial layers of the visual and auditory cortices, the superior colliculus and its thalamic projection, the lateral posterior thalamic nucleus. NANM also decreased LCGU in the superficial layers and layer 4 of the motor cortex and in the superficial layers of the frontal pole. The dorsal hippocampus showed a reduction of LCGU in CA1. Significant decreases also were seen in the habenula. Differences between the anatomical distribution of PCP- and (+)NANM-induced effects on LCGU are consistent with the differential localizations of haloperidol-sensitive *sigma* (σ) and PCP receptors in the rat brain (B. L. Largent *et al.*, *J Pharmacol Exp Ther* **238:** 739, 1986). Further studies with specific agonists and antagonists may help clarify a neuroanatomical basis for specific behaviors produced by interactions at PCP and σ receptors.

1-(1-ALKYNYLCYCLOHEXYL) PIPERIDINES (ACETYLENIC ANALOGS OF PHENCYCLIDINE).

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Phencyclidine analogs bearing an alkynyl or alkyl substituent instead of phenyl, were prepared and their physiological and pharmacological activity tested with the following results: (a) the hydrophobic properties of the substituent contribute to the antiacetylcholine activity of the drug at least as much as the electron density of unsaturated bonds, (b) the degree of central activity in intact animals is considerably reduced when the phenyl group is replaced by an alkyl (saturated or unsaturated) with a maximum activity for a three-carbon chain, (c) the general effects elicited in higher mammals resemble those produced by phencyclidine al-