ABSTRACTS

MULTIPLE INTERACTIONS OF PHENCYCLIDINE AT CENTRAL AND PERIPHERAL SITES.

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We have examined the interaction of phencyclidine [1-(1-phenylcyclohexyl) piperidine, PCP] and some of its analogs with the nicotinic acetylcholine receptor channel complex on the glutaminergic synapse of the locust and in potassium channels of spinal neurons and skeletal muscle. The endplate current at the neuromuscular junction, and voltage-dependent ionic channels on the sarcolemma and neurons were examined using current-voltage and patch clamp methodology. We found that substitution of the phenyl moiety of PCP with a thienyl moiety (e.g., 1-[1-(2-thienyl) cyclohexyl] piperidine, TCP) enhanced the ACh channel blocking activity 3-fold. Substitution of the piperidine moiety in PCP with an amino group [e.g., 1-(phencyclohexylamine), PCA] significantly reduced the potency in depressing the endplate current (2-fold) but replacement with an ethylamino group [e.g., N-ethyl-1-(phencyclohexylamine), PCE] did not appreciably alter the compounds ability to depress the endplate current. The substitution of the piperidine ring of PCP or TCP with a morpholine group [i.e., 1-(1-phenylcyclohexyl) morpholine, PCM and 1-[1-(2-thienyl) cyclohexyl]-morpholine, TCM] substantially reduced the depressant action on the endplate current 5- and 12-fold, respectively. In glutamate synapses PCP apparently does not interact with the receptor recognition sites, as reflected by a concentration-dependent depression of both EPSC peak amplitude and τ_{EPSC}. The shortening of the decay time constant of EPSC (τ_{EPSC}) occurred without significant change in the voltage sensitivity observed under control conditions. Under all experimental conditions, the decay of the EPSCs remained a single exponential function of time. Fluctuation analysis indicated that 5 μM PCP shortens the lifetime of the glutamate-activated channels by 25.7±3%. PCP (10–80 μM) did not induce desensitization of the glutamate receptors. These results suggest that PCP interacts with the open conformation of ion channels activated by the glutamate receptor. In spinal neurons, as in skeletal muscle, PCP was more effective in blocking the transient (sodium) and delayed (potassium) currents than either tetraethylammonium (TEA) or 4-aminopyridine (4-AP). In skeletal muscle, the behaviorally active analogs blocked potassium-mediated currents and were more potent in blocking endplate currents in muscle while the behaviorally inactive compounds did not. These results suggest that PCP may exert its effects on behavior in two ways: (1) by affecting potassium conductance(s) in neurons and (2) by altering synaptic transmission. (Supported in part by USPHS grant DA-02804.)

STEREOSELECTIVE EFFECTS OF *SIGMA* LIGANDS AND DIOXOLANES ON PRESYNAPTIC ION CHANNELS.

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The mechanism(s) by which phencyclidine (PCP) and related drugs produce a toxic confusional psychosis in man is unknown. By measuring efflux of ^{86}Rb and ^{42}K from isolated presynaptic nerve terminals (synaptosomes) from rat brain, we have shown that PCP and behaviorally active analogues potently and selectively blocked a presynaptic voltage-gated, noninactivating potassium (K) channel (Bartschat and Blaustein, *Proc Natl Acad Sci USA* **83**: 189). The rank order of potency for block of these K channels closely paralleled the behavioral potency of these drugs and their relative ability to displace [^{3}H]PCP from high affinity binding sites on synaptic plasma membranes. These results suggest that blockade of presynaptic K channels may be involved in the genesis of PCP intoxication. In order to test this hypothesis further, we examined the ability of the *sigma* ligands, N-allyl-normetazocine (NANM) and cyclazocine (CYCL), and the dioxolane, dioxadrol, to block presynaptic K channels in synaptosomes. These compounds are particularly noteworthy in that they exist as stereoisomer pairs and are chemically unrelated to PCP, yet they produce PCP-like behavioral effects in animals and displace [^{3}H]PCP from its high affinity binding site on synaptic membranes. We found that NANM, CYCL, and dioxadrol selectively blocked the same voltage-gated, noninactivating K channel as PCP itself. Moreover, this effect was stereoselective: (+)NANM was 6-fold more potent than (−)NANM, (−)CYCL was 1–2-fold more potent than (+)CYCL, and (+)dioxadrol (dexoxadrol; DEX) was 1000-fold more potent than (−)dioxadrol (levoxadrol; LEV). These effects were insensitive to the classical narcotic antagonist, naloxone. However, the effects of some of the above compounds were complicated: LEV, (−)NANM, and (−)CYCL also produced a naloxone-antagonized *increase* in K permeability. This latter effect is consistent with *mu* opioid receptor interaction leading to activation of a separate K channel. This is supported by the observation that morphine also produced a naloxone-antagonized increased in K permeability, while exhibiting no K channel blocking properties. Thus, we conclude that presynaptic K channel blockade may contribute to the PCP-like behavioral effects of (+)NANM and DEX, while the analgesia and sedation produced by LEV is a result of interaction with opioid receptors that are linked to activation of a separate K channel. The effects of (−)CYCL as well as (−)NANM are more complex, since both of the above mechanisms may occur simultaneously. (Supported by NS21758 and NS16106 to M.P.B.)