Glutamatergic Hypothesis in Schizophrenia

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The Authors in this paper intend to try, as their experience, through a research, functional data about plaquettes carriage of glutamine in schizophrenic inpatients with Huber's Model of Basic Symptoms. The emersed data propose interesting considerations not only in the schizophrenic Pathology but also in other psychopathological spheres as Bipolar Disorders.

THE ANTISPASTIC TRIAZOLE MDL 27531 SELECTIVELY ENHANCED GABA-ACTIVATED CHLORIDE CURRENT IN SPINAL CORD MOTORNEURONS.

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The triazole MDL 27531, 4-methyl-3-methylsulfonyl-5-phenyl-4*H*-1,2,4-triazole was identified as an antispastic agent selective for protection against strychnine-induced seizures and hyperreflexia. These compounds did not displace the binding of [^{3}H]muscimol, [^{3}H]flunitrazepam or [^{35}S]TBPS to the $GABA_A$ receptor. The present experiments were performed to better understand the mechanism of action of this compound.

Whole cell and single channel patch clamp recordings were obtained from $GABA_A$-receptor activated chloride channels using cultured murine spinal cord motorneurons or rat hippocampal pyramidal neurons. GABA (2-5 μM) or GABA plus MDL 27531 (100nM or 1μM) was applied from blunt micropipettes using positive pressure.

In spinal motorneurons, the application of GABA plus MDL 27531 (100nM) potentiated GABA-activated chloride currents relative to GABA alone. However, GABA plus MDL 27531 (1μM) did not change or slightly reduced GABA-activated chloride currents. No increase in chloride current was observed with GABA plus MDL 27531 on hippocampal pyramidal neurons.

These data indicate that MDL 27531 modulates GABA-activated chloride current selectively. This may be due to selective modulation of subunit configurations of the $GABA_A$ receptor. The effect observed with higher concentrations of MDL 27531 may reflect either the modulation of different subunit configurations of the $GABA_A$ receptor or interactive effects with additional binding sites. Preliminary studies indicate that MDL 27531 does not modulate glycine-activated chloride currents. Further studies are planned using cloned subunit configurations of the $GABA_A$ receptor complex.

NALTRINDOLE, A DELTA OPIOID ANTAGONIST, REDUCES ADDICTING PHENYLISOPROPYLAMINES' ENHANCEMENT OF PRESSING FOR REWARDING BRAIN STIMULATION

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MDMA and amphetamine (AMPH), as other addicting drugs, enhance rats' pressing for rewarding brain stimulation. A drug reducing such enhancement, without interfering with pressing itself, is apt to be useful in treating addiction to the drugs producing the enhancement. Rats were fixed with chronically indwelling bipolar electrodes for stimulation of the medial forebrain bundle of the hypothalamus. They were trained to press a lever in a standard operant box for stimulation near threshold for maintaining pressing and for higher intensities. Doses of MDMA and AMPH each unequivocally increased rates of pressing at each intensity. A 10 mg/kg dose of naltrindole, clearly blocked MDMA's enhancement of pressing and attenuated AMPH's enhancement. It is concluded that delta specific opioid antagonists will effectively block stimulants' effects that sustain their ability to produce an addiction.

COMBINED AGONIST-ANTAGONIST TREATMENT FOR NICOTINE AND OTHER DRUG DEPENDENCIES.

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Co-administration of an agonist with an antagonist may regulate receptor activation, resulting in relief of withdrawal symptoms and blockade of drug reward. In one study, 12 smokers rated the rewarding effects of cigarette smoke after separate and combined administration of nicotine and the nicotinic antagonist mecamylamine. While each drug offset potential side effects of the other, they acted in unison to attenuate smoking reward. In a second study, 48 subjects participated in a randomized, double-blind, placebo-controlled smoking cessation trial. Nicotine skin patch therapy (21 mg/day for 6-8 weeks) + oral mecamylamine (2.5-5 mg b.i.d. for 5 weeks) was compared to nicotine patch + placebo. Mecamylamine treatment began two weeks before smoking cessation. Combined agonist-antagonist treatment produced significantly higher continuous smoking abstinence than agonist-alone treatment: 50% *vs* 16.7% at seven weeks (p=.015), 37.5% *vs* 12.5% at six months (p=.046) and 37.5% *vs* 4.2% at twelve months (p=.004). Concurrent agonist-antagonist treatment may prove useful in treating other drug dependencies, and has potential advantages over treatment using agonists alone, antagonists alone or partial agonists.