

#### Augmentation of Response to Typical Neuroleptic Treatment Using Idazoxan, an Alpha-2 Antagonist, in Patients with Schizophrenia.

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Clozapine, an atypical neuroleptic which is more efficacious than typical neuroleptics, elevates plasma and urinary noradrenergic indices in schizophrenia patients (Pickar et al, 1992). Since one mechanism for clozapine's noradrenergic effects may be antagonism of  $\alpha_2$  receptors, we added idazoxan, a highly selective antagonist of  $\alpha_2$  receptors, to stable neuroleptic treatment in double-blind, placebo controlled fashion in 17 treatment-refractory patients with schizophrenia. Symptoms significantly decreased with the addition of idazoxan to stable fluphenazine treatment, and returned back to baseline levels following discontinuation of idazoxan. Idazoxan treatment resulted in reductions ( $p < 0.01$ ) in global psychosis and in the Brief Psychiatric Rating Scale (BPRS) score compared to treatment with fluphenazine alone. Idazoxan reduced positive and negative symptoms ( $p < .05$ ) and paranoia-suspiciousness ( $p > 0.01$ ) on the BPRS; changes in BPRS symptoms were correlated with idazoxan-induced changes in plasma norepinephrine (NE) in 9 patients. No effects of idazoxan on extrapyramidal symptoms, dyskinetic movements, or plasma fluphenazine levels were found. In a subgroup of 12 patients, idazoxan plus fluphenazine was as effective as clozapine in reducing symptoms of schizophrenia. These data suggest that the addition of idazoxan to stable neuroleptic treatment improves symptoms in neuroleptic-resistant schizophrenia patients. Correlations with idazoxan-induced changes in plasma NE support the hypothesis that the mechanism underlying idazoxan's therapeutic effects involves increased alpha-2 blockade. Moreover, these data suggest that potent alpha-2 blockade may be relevant to clozapine's mechanisms of action.

#### THE ADRENAL MEDULLAE AUTOTRANSPLANTED INTO THE THALAMI STILL PRODUCE ENKEPHALINS

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Enkephalin, an endogenous opioids, plays an important role in pain modulation. As enkephalin is produced by the adrenal medulla, a possible treatment for reduction of refractory pain is by adrenal medullary transplantation. One possible target for this transplantation is within the thalamus, a major site for processing ascending and descending nociceptive information. In the present study, quantitative estimates of L-enkephalin and M-enkephalin contents were determined in homogeneous adrenal medullae transplants. Male guinea pigs and Wistar rats (8 weeks old) were used. Right adrenal medullae were used as control. Following a two month survival time, animals were perfused with Zamboni's fixative. Thirty micron section were cut through the thalamic grafts and the left adrenal medulla and the tissue processed immunocytochemically for L-enkephalin and M-enkephalin. A micro-imaging analytic system was used to semi-quantitate the amount of L-enkephalin and M-enkephalin through the grey degrees of the immunostains. A students t-test was used to determine if the differences between the experimental and control groups were statistically significant. The results indicated that, following a two month survival time, there was a significant increase in the contents of L-enkephalin and M-enkephalin in the grafts of the thalami of both the guinea pigs and rats in comparison to control. This result suggests that L-enkephalin and M-enkephalin were produced by the grafts transplanted into the thalamus.

#### TRANSIENT CALCIUM CURRENT AND TRANSMITTER RELEASE INDUCED BY GABA IN CULTURED EMBRYONIC RAT THALAMIC NEURONS

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Although  $\gamma$ -aminobutyric acid (GABA) functions as an inhibitory neurotransmitter activating  $\text{Cl}^-$  and  $\text{K}^+$  channels throughout the adult vertebrate central nervous system (CNS), recent evidence indicates that during embryonic and early post-natal development GABA excites CNS cells at spinal and supraspinal levels. Here we report that GABA promptly activates a transient  $\text{Ca}^{2+}$  conductance in cultured embryonic rat thalamic neurons that is mimicked by the GABA<sub>B</sub> receptor agonist (-) baclofen (BAC), but not the GABA<sub>A</sub> receptor agonist muscimol, and is blocked by the GABA<sub>B</sub> receptor antagonist saclofen, but not the GABA<sub>A</sub> receptor antagonists picrotoxin or bicuculline, which antagonize  $\text{Cl}^-$  conductance. After 5-7 days in culture when functional networks have formed, GABA and BAC, but not muscimol trigger a flurry of synaptic-like transients, which reverse at the  $\text{Cl}^-$  equilibrium potential, are blocked by bicuculline and decay with kinetics similar to those of GABAergic synaptic currents. This stimulatory effect desensitizes and is  $\text{Ca}^{2+}$ -dependent. Taken together, the results indicate that exogenous GABA can trigger pulsatile transmission of endogenous GABA at GABA<sub>A</sub> receptors via activation of a presynaptic GABA<sub>B</sub> receptor-coupled, rapidly-decaying  $\text{Ca}^{2+}$  conductance. Since GABA emerges in cells and fibers during thalamic development, it may mediate developmentally important signals at both  $\text{Cl}^-$  and  $\text{Ca}^{2+}$  channels.

#### Magnetic Resonance and Positron Emission Tomography Imaging of the cerebellum in Schizophrenia

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Magnetic resonance imaging and positron emission tomography with fluorodeoxyglucose (FDG) were used to study the size and metabolic rate of eighteen schizophrenics, primarily never medicated, and eighteen normal controls. All subjects performed a CPT (Continuous Performance Task) during the FDG uptake period. The cerebellar region of interest was determined using a semi-automated computer algorithm on the MRI images. These outlines were superimposed on the matching PET scan images. The posterior and anterior cerebellar regions in the schizophrenic group were larger compared to the control group. In addition, the patients had lower relative glucose metabolic rates. Cerebellar area and glucose metabolism negatively correlated with the total brief psychiatric rating scale (BPRS) scores and the emotional withdrawal, conceptual disorganization and mannerism subscales. These results are suggestive of cerebellar dysfunction in schizophrenia.