CLOZAPINE RESPONSE IN CHRONIC SCHIZOPHRENIA AND BRAIN MORPHOLOGY ON MRI: A PRELIMINARY REPORT

Jeffrey Aronowitz, Houwei Wu, Simcha Pollack, Robert Bilder, John Kane, Allan Safferman, Jeffrey Lieberman.
Department of Psychiatry Research, Hillside Hospital, P.O. Box 38, Glen Oaks, NY 11004

Clozapine is a dibenzodiazepine atypical antipsychotic agent with demonstrated efficacy in treatment resistant and treatment intolerant schizophrenic populations (Kane 1988;Pickar 1992). Previous reports suggest clozapine's efficacy in schizophrenia may be related to morphologic abnormalities in lateral frontal and prefrontal cortices as measured on CT (Friedman 1991;Honer 1993) and MRI (Breier 1993). To examine this issue further, 18 chronic schizophrenic (DSM-III-R) patients (mean age 27 years,89% male) who received standardized treatment with clozapine (mean duration of treatment=30 months ± 19.43), underwent assessments for psychopathology (BPRS, CGI, SANS) and brain morphology with magnetic resonance imaging. MRIs were acquired using a gradient echo pulse sequence (3D flash) on a Siemens-Magneton (1.0 tesla) system. Images were analyzed under blind conditions by trained personnel using quantitative (total brain volume, interhemispheric fissure volume) and qualitative (evaluation of sulcal prominence, cerebral cortex, lateral ventricles, third ventricle, medial temporal lobe structures) measures. Data analyses examined the relationship between brain morphologic variables and measures of psychopathology at baseline and during clozapine treatment. Preliminary analyses to date have found no significant associations between the specific morphologic variables described above and treatment outcome. Mean severity of psychopathology at baseline was associated with increased interhemispheric fissure volume ($r=0.54, p=0.02$), due to positive symptom factors on the BPRS. These results mainly reflecting replicate previous findings of abnormal brain morphology being associated with poorer response to clozapine. Reasons may include differences in patient samples and the limited number of patients studied. This issue will be reexamined in the context of a larger patient sample as data become available.

[3H]Paroxetine and [3H]Citalopram as Markers of the Human Brain 5-HT Uptake Site

Belén Arranz[1,2], Jan Marcusson[1]
[1]Department of Geriatric Medicine, Linköping, Sweden.
[2]Department of Clinical Chemistry (Hormone Unit), Hospital Princeps d'Espanya, Barcelona, Spain

The binding of [3H]paroxetine and [3H]citalopram to the brain serotonin (5-HT) uptake site was characterized and compared in human hypothalamus, frontal cortex and caudate nucleus. Our results showed that the binding exclusively related to the 5-HT uptake site (specific or 5-HT displaceable binding) was identical for both [3H]ligands. The selective 5-HT uptake inhibitor citalopram displayed the highest potency (Ki) in inhibiting the [3H]paroxetine and [3H]citalopram binding, as compared with the values obtained for desipramine and norzimelidine. This fact is in accordance with the reported blockage of these compounds of the 5-HT uptake. Furthermore, similar Bmax values were obtained for both radioligands in the brain regions under study, indicating their binding to the same presynaptic membrane protein. These findings give evidence of the suitability of both [3H]paroxetine and [3H]citalopram as markers of the 5-HT transporter. However, the higher affinity of [3H] paroxetine (10 to 30-fold with respect to [3H]citalopram) confirms that the radiolabelled form of this compound is the best tool for the study of the 5-HT uptake site available today.

Neuropeptidergic and Monoaminergic Function in Suicide Victims

Belén Arranz[1,2], Kaj Blennow[2], Rolf Ekman[2], Jan-Eric. Månsson[2], Jan.Marcusson[1]
[1] Department of Geriatric Medicine, Linköping, Sweden;
[2] Department of Psychiatry and Neurochemistry, University of Göteborg, Mölndal Hospital, Sweden.

Neuropeptide Y (NPY), somatostatin (SOM) and corticotropin releasing factor (CRF), together with the monoamines noradrenaline (NA), dopamine (DA), serotonin (5-HT) and their metabolites DOPAC, HVA and 5-HIAA were determined in hypothalamus, gyrus cinguli and frontal cortex of 19 suicides and 23 age-matched controls. The suicide victims were subclassified according to their method of death (violent, drug overdose, carbon monoxide poisoning) and to the existence of depressive symptoms prior to death. Overall suicides did not show statistical differences with respect to the control group in any of the measured compounds (Student's t test). Significant increases in NA ($p=0.01$) and DA ($p=0.008$) concentrations were noted in the hypothalamus of those suicides dying from carbon monoxide poisoning, while significant higher NPY concentrations ($p=0.05$) were found in the frontal cortex of the same suicide subgroup (Kruskal-Wallis ANOVA). These findings suggest that the suicidal behaviour does not contribute to any modification in the measured compounds. However, the reported increases could be secondary to the action of carbon monoxide in some metabolic pathways.

ALPHA-TOCOPHEROL SUCCINATE, BUT NOT ALPHA-TOCOPHEROL OR OTHER VITAMIN E ANALOGS STIMULATES PROLACTIN AND GROWTH HORMONE RELEASE FROM RAT ANTERIOR PITUITARY CELLS in vitro.

M. Badamchian[+], B. Spangelo[*], Y. Hagiwara[**], H. Hagiwara[**], H. Veyama[**] and A.L. Goldstein[+].
[+]Department of Biochemistry The George Washington University School of Medicine, Washington, D.C. 20037 [*]Department of Physiology, Medical University of South Carolina, SC 29425, [**]The Hagiwara Institute of Health, Hyogo, Japan

Green barley leaf extract, a dried extract of young green barley leaves, is widely used in Japan and other countries as a nutritional supplement. We have recently reported (Badamchian, et.al J. Nutr. Bioc. 5:145-150, 1994), the isolation of a vitamin E analog from green barley leaf extract that stimulates release of prolactin and growth hormone from rat anterior pituitary cells in vitro. This molecule was identified as α-Tocopherol succinate, an analog of α-Tocopherol, or vitamin E. In the present study we tested the commercially available forms of α-Tocopherol and also succinic acid. Treatment of normal anterior pituitary cells with different forms of tocopherol (100μg/ml) and succinic acid (50-100μg/ml) caused significant increase ($p<0.01$) in prolactin and growth hormone release in only α-Tocopherol succinate-treated cells. α-Tocopherol, δ-Tocopherol, α-Tocopherol acetate, α-Tocopherol nicotinate, succinic acid disodium salt, and succinic acid butenedoic acid did not effect the prolactin and growth hormone release in vitro. Supported by a gift from Hagiwara Institute of Health, Hyogo, Japan.