hybridization, microarrays) are labor-intensive and potentially time-consuming, it is important to understand their limitations. For example, using a differential display procedure (which is probably the most sensitive among the above mentioned methods) we detected less than a 2-fold change in the expression of mRNA encoding cytochrome b following chronic, but not acute treatment with imipramine (N.-Y. Hung, M. Strakhova, R.T. Layer and P. Skolnick, J. Mol. Neurosci., 1997:9:167–176) based on analysis of Northern blots. This effect was restricted to cerebral cortex and was not observed following chronic treatment with non-antidepressant drugs (e.g., haloperidol and morphine). However, differential display is biased toward highly abundant RNA species and may be unable to detect differences in rare messages. Conversely, methods like suppression subtractive hybridization are capable of detecting changes in rare transcripts but lack the sensitivity of differential display and related techniques. Moreover, both the functional and morphological organization of the central nervous system presents complexities that may not be encountered in other disciplines. Advantages and disadvantages of various approaches and their applicability to research in biological psychiatry will be discussed.

196. MOOD STABILIZERS INCREASE NEUROGENESIS AND NEURITE OUTGROWTH

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It has become increasingly appreciated that the long term treatment of MDI involves the strategic regulation of gene expression in critical neuronal circuits. We have undertaken an extensive series of experiments using differential display to identify genes regulated by both Li and VPA. These are two structurally highly dissimilar agents; although they likely do not exert their therapeutic effects by precisely the same mechanisms, identifying the genes which are regulated in concert by these two agents, when administered in a therapeutically relevant paradigm, may provide important leads about the molecular mechanisms underlying mood stabilization. Several novel candidates for the therapeutic actions of mood stabilizers have been identified, including an mRNA binding protein, which increases the levels of a kinase known to play a critical role in cytoskeletal remodeling. We have also found that lithium produces a marked increase in the expression of the neuroprotective protein bel-2 in frontal cortex, hippocampus and striatum. Accompanying these effects, lithium not only robustly protects neurons from a variety of insults, but also increases neurogenesis in the dentate gyrus of adult rodents. Consistent with such neurotrophic effects, lithium also increases the levels of NAA (N-acetylaspartate, a marker of neuronal viability) in the brains of patients with MDI. We have also found that VPA robustly increases neurite outgrowth in cultured human neuroblastoma cells. Taken together, our data suggest that chronic lithium and VPA bring about persistent morphological changes in the brain, effects, which may play a major role in their long term therapeutic effects.

Supported by NIMH, Stanley Foundation, NARSAD and Joseph Young Sr. Awards

197. REGULATION OF MOOD STABILIZER REGULATED GENES

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Mood stabilizers such as lithium and valproate are highly effective treatments for bipolar disorder (BD). Despite many years of investigation, the mechanism of their therapeutic action is not yet clear. Recently, an increasing body of evidence has demonstrated effects of both drugs on signal transduction pathways. These signaling molecules trigger changes in gene expression which are thought to contribute to the effects of chronic treatment with these drugs. Differential display PCR and cDNA microarray were used to identify genes regulated by chronic treatment with lithium and valproate in rat cerebral cortex and rat C6 glioma cells. The expression of a variety of genes were altered by chronic treatment with lithium including: CNPase II, c-jun, M-ras, TGF-beta type II receptor, IGF-I-R alpha and presenilin-1 gene expression, suggesting novel targets for lithium that may be relevant to its mechanism of action. We also found that chronic treatment with valproate increased both mRNA and protein levels of 78-kilodalton glucose-regulated protein (GRP78). Since GRP78 performs molecular chaperone activities, participates in protein trafficking, and binds Ca²⁺ in the endoplasmic reticulum as well as protecting cells from the deleterious effects of damaged proteins, the present findings suggest that valproate treatment may regulate one or more of these processes. A number of novel cDNAs have also been identified which are being characterized and studied further with 5' RACE-PCR and library screening. These results may further our understanding of the mechanism of action of mood stabilizers, and identify new targets for genetic studies and therapeutic strategies in BD.

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198. PROGRAMS OF GENE EXPRESSION IN HUMAN FIBROBLASTS FROM PATIENTS WITH MAJOR DEPRESSION

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Results from our laboratory have provided compelling evidence that human fibroblasts, a nonneuronal tissue, provide a relevant model of signal transduction in affective disorders: (1) they express neuronal genes encoding aminergic receptors, G proteins, and the effector enzymes that produce second messengers and protein kinases; (2) transfected with the luciferase transporter gene pAD neo2-C12-BGL fibroblasts illustrate the amplification mechanism of signal transduction mediated by the beta adrenoceptor i.e., the cyclic AMP-PKA-CREB cascade; (3) fibroblasts from patients with major depression show a blunted beta adrenoceptor mediated PKA response and a significant reduction in nuclear CREB-P versus fibroblasts from normal control subjects; (4) in addition to their effects on receptor mediated signal transduction cascades in fibroblasts, antidepressants affect the cytoplasmic-nuclear trafficking of transcription factors (e.g. GR). Previously we have hypothesized that transcription factors modify programs of gene expression, the ultimate effect of agonist-receptor activation. Presently we are utilizing the Differential Display technology (developed by Liang and Pardee in 1992) to compare the simultaneous expression of approximately 10,000 genes in fibroblasts...
from human subjects—clinically depressed versus normal controls. To date fifty-six arbitrary 13-mer upstream primers in combination with 3 one-base anchored oligo-T primers (approximately 150 reactions) have indicated a number of (apparently) differentially expressed genes in the two groups. Following an additional series of reactions (bringing the total to approximately 240) candidate genes will be sequenced, compared to national databases for identification, and subjected to reverse Northern analysis for “false positives”. Competitive PCR will then be utilized to quantitate differences in expression.

**Biological and Psychologic Consequences of Bereavement and Depression**

Friday, May 12, 2:30 PM–5:00 PM
Location: Comiskey
Chair: Trey Sunderland
Co-Chair: Ni A. Khin

199. STUDIES OF TRAUMATIC GRIEF: CRITERIA, RISKS, OUTCOMES

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In the DSM-IV, a single paragraph is devoted to “Bereavement,” bereavement is listed among “conditions or problems . . . related to . . . mental disorders” (i.e., a “V” code), and attention is focused almost exclusively on symptoms of depression (e.g., psychomotor retardation, worthlessness, excessive guilt). According to the DSM-IV, clinicians should diagnose bereaved individuals with Major Depressive Disorder if they endorse the specified depressive symptoms 2 months or longer after the loss. These guidelines negate substantial evidence that symptoms apart from those of depression—symptoms of Traumatic Grief (TG)—may constitute a separate pathological component of bereavement-related psychological distress.

This presentation will provide an overview of results suggesting that Traumatic Grief is a distinct syndrome deserving a separate place in the DSM. Results will be presented which demonstrate that symptoms of TG: 1.) form an independent factor from symptoms of depression and anxiety, 2.) have risk factors, clinical correlates and a response to pharmacotherapy distinct from those associated with depression, 3.) predict substantial morbidity (e.g., high blood pressure, suicidality), and 4.) often persist for years, even after controlling for baseline severity of depressive symptomatology and other important confounding influences. While these findings suggest the need for separate diagnostic criteria for TG, no standardized criteria exist. To promote the development of uniform criteria, a panel of leading experts in bereavement and in psychiatric nosology convened and, ultimately, agreed upon a working criteria set for TG. Preliminary results that test the performance of the proposed consensus criteria will be presented, and future directions discussed.

200. BIOPSYCHOLOGICAL PROFILE OF NORMAL, BEREAVED AND POST-BEREAVED DEPRESSED ELDERLY

N.A. Khin (1), L. Bauer (1), E. Cannon-Spoor (1), T. Fleisher (2), M. Brown (2), J. Bock (1), R. Lasser (1) and T. Sunderland (1)

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Our longitudinal study follows a cohort of elderly bereaved spouses and controls prospectively from psychological, biological and immunological perspectives over 13 months, to find possible links between bereavement, biologic markers of depression and immunologic function. Currently, data has been collected from 50 subjects comprising 38 bereaved subjects and 12 non-bereaved married controls. Both the bereaved and control groups consist of older adult (age 70), well-educated (16 yrs) and cognitively intact individuals. Preliminary results indicate that considerable elevations on baseline measures of depression (Geriatric Depression Scale, Hamilton Depression and Inventory of Complicated Grief) along with elevated serum cortisol levels are predictors of subsequent conversion to major depression during the next 6 months. Nine of 38 (23.7%) elderly subjects became depressed during bereavement. Demographic variables such as age, gender, education, length of marriage and cognitive functioning showed no significant differences between groups. Routine baseline immune measures such as WBC, lymphocyte counts, number of T/B cells subsets identified by immunophenotype (i.e., CD4 & CD8) were found to be similar among the groups. Similarly, no differences were found in Complement C3/C4 levels and autoantibodies. Delayed type hypersensitivity skin tests revealed significant difference in total induration diameters between the depressed and non-depressed individuals. Results of in vivo antibody response to immunizations are pending. While the number of subjects in this study is still relatively small, we have not yet seen evidence of baseline immunologic measures which predict eventual depression in elderly bereaved subjects. This baseline biologic data will be crucial in establishing a possible predictive pattern of behavior and immunologic changes over time in the bereavement process.

201. IMPACT OF FAMILIARITY AND EMOTIONAL ATTACHMENT ON THE VISUAL PROCESSING OF FACES

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A significant body of literature documents the existence in humans of brain regions that respond preferentially to visual stimuli depicting faces. However, whereas most previous research has used anonymous faces as stimuli, our fMRI paradigms employ faces of individuals known to the subject, including people to whom the subject has a strong emotional attachment. Therefore, these studies are designed to bridge cognitive and affective neuroscience. In this presentation we describe preliminary results from three fMRI studies (the first completed, the other two ongoing). In experiment #1, subjects view faces of people from the following categories: unfamiliar, close friends and relatives (“personally familiar”), celebrities (“famous familiar”), and phase-scrambled faces. In experiment #2, mothers view faces of their own first-born child (current age 5–12), familiar (but unrelated) children, unfamiliar children, unfamiliar adults, and phase-scrambled faces. In experiment #3, bereaved spouses and a nonbereaved matched comparison group view the face of their spouse, living family members, unfamiliar people, and phase-scrambled faces. Subjects in all studies perform a one-back matching task. In experiment #1, stimuli are shown for 1 second and blocked by category, whereas in experiments #2 and #3, stimuli are shown for 1.5 seconds and are randomly distributed throughout the blocks. Data are acquired on a 1.5T scanner and analyzed using multiple regression. We hypothesize that personally familiar faces will activate regions in the anterior middle temporal gyrus and the temporal pole, as well as limbic areas including the amygdala and anterior cingulate gyrus.