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 studies 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.

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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 amnergic 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...