Sleep-endocrine effects of growth hormone-releasing hormone (GHRH) in major depression.

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Studies in normal human subjects and animals suggest that the neuropeptide growth hormone-releasing hormone (GHRH) is a common regulator of the sleep EEG and nocturnal hormone secretion. In healthy volunteers GHRH prompts an increase in the amount of slow wave sleep (SWS) and in growth hormone (GH) secretion and blunting of cortisol release. Inhibition of GHRH may contribute to sleep-endocrine aberrances during depression. We tested the effects of pulsatile application of 4 x 50 μg GHRH on the sleep EEG and simultaneously investigated nocturnal hormone secretion in 10 inpatients (4 females, 6 males) with the acute episode of major depression. In contrast to the effects of placebo, after GHRH GH secretion increased distinctly and rapid-eye-movement (REM) density decreased during the second half of night. No other significant changes in sleep-endocrine activity, including SWS, cortisol and ACTH secretion, could be observed. We assume that hypothalamic-pituitary-adrenocorticol system activity and slow wave sleep are inert to the influence of GHRH during acute depression. Cortisol and ACTH remained unchanged even in a subsample of five younger (aged 19-28 years) patients. This observation is in contrast to our recent finding that cortisol secretion is blunted in young normal volunteers after GHRH. But on the other hand, GHRH is capable of stimulating GH and inducing a decrease in REM density in these subjects.

Plasma Levels of Tricyclic Antidepressants and Clinical Response

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Eighteen subjects with "endogenous" depression-11 women and 7 men were include in the study. They met DSM-III-R criteria for major depression. In the course of the treatment with tricyclic antidepressants (TCA) 3 patients (17%) become manic, 1 patient (5%) was not in compliance with the drug chosen. The remaining patients - 8 women (57%) and 6 men (43%) were with mean age 51 (SD = 17.38) and 36.2 (SD = 15.27) years respectively. After one week placebo period the patients randomly assigned to 2.5 mg/kg body weight Amitriptylin-AMI or Imipramine-IMI with mean daily doses 175 mg (SD = 53.03) for AMI and 204, 2 mg (SD = 66.8) for IMI. Mean plasma study states levels were 223.27 ng/ml (SD = 128.6) for AMI and 253.21 ng/ml (SD = 148.31) for IMI. Seven of 10 responders-R (71%) had therapeutic plasma levels-pharmacokinetic R. Three of them had plasma levels outside the established therapeutic range. Three of the 4 nonresponders-NR had plasma levels outside the therapeutic range, but one was within it-pharmacodynamic NR. Comparing the R and NR group within and without the therapeutic range we found $\chi^2 = 9.3$ and $p < 0.001$. In conclusion the clinical response of the patients with "endogenous" depression depends strongly upon the plasma study states level.

LOCALIZATION OF THE DOPAMINE D4 RECEPTOR IN RAT BRAIN -- AN AUTORADIOGRAPHIC STUDY USING [3H]-YM 09151-2.

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Neuroleptic treatment of schizophrenia provides a reduction in psychotic episodes and is accompanied by unwanted extrapyramidal side effects. Clozapine is atypical in that it does not produce these side effects. Typical antipsychotics have high affinity for dopamine D_2 receptors, whereas atypicals, such as Clozapine, have D_4 selectivity. Location of mRNA in rat brain show that D_2 message is highest in the nigrostriatal areas, whereas D_4 is distributed in cortical and limbic regions. The D_4 selectivity of Clozapine and mRNA location indicate that D_4 receptor antagonism may provide antipsychotic efficacy without extrapyramidal side effects. This study identifies for the first time the D_4 receptor protein in autoradiographic blocking studies with [^{3}H]-YM-09151-2 ([^{3}H]-YM), a D_2, D_3, and D_4 ligand. Blocked studies demonstrated that Raclopride, a D_2/D_3 compound, and D_4 selective compounds Clozapine and (+)Apomorphine showed inhibitions in similar brain regions of D_2 and D_4 mRNA distribution, respectively. The study also investigated [^{3}H]-Raclopride ([^{3}H]-RAC) autoradiography to further contrast D_2 location from D_4. [^{3}H]-RAC showed similar binding in regions blocked by cold Raclopride in [^{3}H]-YM autoradiography. These findings reveal that the D_4 receptor is located in dopaminergic structures involved in cognition and emotional stability while avoiding extrapyramidal structures which affect motor functioning.

EXPRESSION OF A NOVEL TRK C RECEPTOR ISOFORM WITH TRUNCATED EXTRACELLULAR DOMAIN IN FETAL AND ADULT MONKEY BRAINS

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The Trk family of receptor tyrosine kinases has been identified as the high affinity receptors for neurotrophins such as NGF, BDNF, NT-3 and NT-4. As part of our effort to study the development of mesencephalic dopamine neurons in primate, we sought to examine the pattern of expression of *trk* A, *trk* B and *trk*C gene transcripts in midbrains of developing and adult African green monkeys. Using the technique of RT-PCR with two degenerate oligo primers corresponding to conserved amino acid (a.a.) sequences in the extracellular domain and in the tyrosine kinase domain, we showed that the expressions of *trk* A, *trk*B and *trk* C mRNAs were differentially regulated during fetal development in monkey midbrain. In addition, nucleotide sequence analysis of the PCR products revealed a novel isoform of the *trk* C gene transcript which contains a 24 b.p. deletion in the extracellular region adjacent to the transmembrane domain. The deletion results in a substitution of the residue valine for the a.a. sequence Glu-Ser-Thr-Asp-Asn-Phe-Ileu-Leu-Phe (equivalent to a.a. 402-410 of the published porcine Trk C sequence) present within the extracellular domain of the monkey Trk C receptor. Furthermore, we showed by RNase protection assay that these two *trk* C isoforms were co-expressed in a similar manner in both developing and adult monkey brains. Our data thus indicate that an additional isoform of the Trk C receptor tyrosine kinase exists in primate and may provide additional specificity of response to different members of the family of neurotrophins. Supported in part by PHS grant MH-14092 and the Axion Research Foundation.