BASIC

30. 13-CIS-RETINOIC ACID (ROACCUTANE) MAY INDUCE DEPRESSION BY ALTERING COMPONENTS OF SEROTONINERGIC NEUROTRANSMISSION

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Neurological symptoms, including depression and psychosis, have been reported in adults ingesting excess vitamin A or taking vitamin A supplements. Roaccutane (13-cis-retinoic acid, 13-cis-RA) a synthetic retinoid, is an effective oral treatment for severe recalcitrant nodular acne. Although the epidemiological evidence is contradictory, its use in patients has also been linked with psychiatric side effects including suicidal ideation and depression (Hull & D'Arcy 2003, Am J Clin Dermatol 4:493). In summary, the depressive symptoms occur in 5-10% of patients, develop soon after starting drug treatment (days-weeks), resolve after drug discontinuation (in some cases; days-months) and recur following drug rechallenge. We have recently shown that enhanced depression-related behaviour is evident in adolescent mice chronically treated with 13-cis-RA (O'Reilly et al. 2006, Neuropsychopharm 31:1919). Retinoids bind to intracellular receptors, recognize specific promoter elements and regulate gene transcription. A number of neuronal genes have been identified containing retinoic acid response elements but their importance in depression-related behaviours has not been analyzed. Here we have examined whether 13-cis-RA treatment can regulate components of serotoninergic signalling using a conditionally immortalized cell line derived from dorsal raphe neurones (RN46A-B14) that expresses tryptophan hydroxylase, 5-hydroxytryptamine (5HT), 5HT1A receptors and 5HT transporters. Our data indicate that retinoids alter the expression of components of the serotonin signalling pathway which, in vivo, may impair serotoninergic transmission thereby altering depression-related behaviours.

31. PROTEOMIC INVESTIGATION OF THE VENTRAL RAT HIPPOCAMPUS LINK PROTEINS TO ESCITALOPRAM TREATMENT RESISTANCE AND STRESS RESILIENCE IN THE CHRONIC MILD STRESS RAT MODEL OF DEPRESSION

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Background: Depression is a complex and heterogeneous disorder. Several research groups have focussed at unravelling the neurobiology of depression and quite a few hypotheses have evolved during the last 50 years ranging from monoamine availability in the synaptic cleft to neuronal plasticity. Objectives: Development of depression as well as recovery is most likely accompanied by a change in protein expression and it was warranted to quantitatively investigate protein differences independent of any of the established hypotheses. The ventral part of hippocampus was chosen as the region of interest due to dorsoventral differentiation and previous cell proliferation studies showing an escitalopram stimulated increase in ventral cytogenesis which correlated to recovery from behavioural deficits. Methods: Two-dimensional differential in-gel electrophoresis (2D DIGE) was employed to compare the ventral hippocampal proteomes between groups in the chronic mild stress (CMS) model of depression. The CMS paradigm induces anhedonic-like behaviour by exposing rats to a series of mild stressors. A significant decline in the consumption of a sucrose solution is observed in stressed animals compared to non-stressed animals. This is reversed by antidepressant treatment. Six different groups emerge from our model; resilient (stress resistant), drug-responders, drug-nonresponders, stress vehicle, unchallenged drug, unchallenged vehicle. Results: 28 candidate proteins were detected of which 13 was successfully identified using tandem mass spectrometry. The identified proteins were functionally classified as axonal guidance proteins, cytoskeleton organisers, vesicle transport members and molecular chaperones. Conclusion: Although these results are preliminary, the data reflect essential functionality of neuronal adaptations and support the novel hypothesis of cellular plasticity.

32. EARLY SOCIAL ENVIRONMENT SHAPES ADULT BRAIN NGF AND BDNF LEVELS AND SOCIAL AND EMOTIONAL BEHAVIOUR IN MICE

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During early postnatal development, important processes that shape the mammalian brain are taking place. This highly plastic period offers the possibility to epigenetic factors to affect brain structure and function. Indeed, the early social environment is crucial for brain and behaviour development, as shown by the disrupting effects of its impoverishment or deterioration. Children who experience severe perturbations in care are at higher risk for the emergence of behavioural problems or psychiatric disorders later in life. In order to study the effects of the early experiences on adult brain function and behaviour, we exposed mouse pups to an early social enrichment: Communal Nesting (CN). CN, which consists in a single nest where three mothers keep their pups together and share care-giving behaviour from birth to weaning, mimics the natural ecological niche of the mouse species. At adulthood, mice reared in CN display higher propensity to interact socially and better social skills when compared to mice reared in standard laboratory conditions. Furthermore, mice reared in CN show higher NGF and BDNF levels in selected brain areas, including hippocampus and hypothalamus, and increased rate of newly generated brain cells. With regard to emotional behaviour, we found that the ability to exploit social cues in facing challenging situations at adulthood changes according to the early social experiences. Overall, these findings confirm the crucial role played by early social experiences in shaping adult social and emotional behaviour and suggest a role for neurotrophins as factors mediating the long-term effects of experiences on brain function.

33. MUTATION OF TRYPTOPHAN HYDROXYLASE-2 SUPPRESSES THE EFFECTS OF CITALOPRAM ON EXTRACELLULAR SEROTONIN

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Background: The G1463A single nucleotide polymorphism (SNP) of human tryptophan hydroxylase-2 (TPH-2) gene, the enzyme responsible of brain serotonin (5-HT) synthesis, is associated with poor response to selective serotonin reuptake inhibitors (SSRIs). Likewise, SNP of the mouse TPH-2 (C1473G) is associated to reduced brain 5-HT synthesis and no response to SSRIs in the forced swimming test (FST), in inbred mice carrying the 1473G allele such as DBA/2J and BALB/c. Objectives and methods: In vivo microdialysis was used to investigate whether the impairment of 5-HT synthesis influenced basal and citalopram-induced rise of extracellular 5-HT in the medial prefrontal cortex (mPFC) and the dorsal hippocampus (DH) in strains of mice carrying allelic variants of TPH-2. As the 5-HT precursor tryptophan restored the effect of citalopram in the FST in "non-responder" mice, we investigated whether boosting 5-HT synthesis enhanced the effect of citalopram on extracellular 5-HT. Results: Mice carrying the mutation of TPH-2 had less extracellular 5-HT in the mPFC (-40%) and DH (-20%) and a reduced response to citalopram (1,25-20 mg/kg). Tryptophan (300 mg/kg) transiently increased extracellular 5-HT by about 50% in the mPFC DBA/2J mice but had no effect on citalopram-induced rise of extracellular 5-HT in the mPFC and DH. Conclusions: The TPH-2 mutation suppresses the extracellular 5-HT availability and the response to citalopram. Tryptophan could be a useful strategy to restore the therapeutic effect of SSRIs.

34. EARLY RISK FACTORS FOR NEUROPSYCHIATRIC DISEASES: COMPARATIVE APPROACHES TO INVESTIGATE INTERACTIONS BETWEEN GENES AND ENVIRONMENT

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In humans, both genetic and experiential factors can shape individual vulnerability to psychiatric illness. However, the quality and quantity of experience predisposing an individual towards psychopathology and the specific neural substrates affected are still open questions. Among the many factors involved in brain development and function, neurotrophins appear as good candidates for mediating long-term effects of experience on brain function. We have used a comparative approach using both rodents and primates (rhesus macaques) to test the hypothesis that changes in the levels of neurotrophins (i.e., NGF and BDNF) during critical periods of brain development, as a result of different rearing experiences, might affect the ability to cope with stress and lead to behavioural changes at adulthood. We have shown that, in rodents, neurotrophins are sensitive to manipulations of the mother-infant relationship and, more in general, of the rearing environment and can be sensitive to the animal's ability to cope with social stress. We have recently measured levels of NGF and BDNF in rhesus macaques exposed to early stress (reared in the presence of peers, rather than by the mother) both in the cerebrospinal fluid and in the peripheral circulation. Data indicate that plasma levels of neurotrophins are increased by peer rearing, suggesting that these markers of brain plasticity might also be a peripheral measure of early adversity in primates, possibly underlying