S06.4

Substance P (NK1) receptors in mood disorders and schizophrenia

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The Substance P receptor has been implicated in stress responses and anxiety traits in the rodent, and neurokinin-1 receptor antagonism may have antidepressant and anxiolytic effects. This suggests that the function and/or expression of the neurokinin-1 receptor might be affected in subjects with mood disorders. We have measured neurokinin-1 receptor densities in the anterior cingulated cortex in subjects with major depression, bipolar disorder, schizophrenia and controls using quantitative autoradiography with [125I]-substance P. The anterior cingulate cortex was chosen for initial analysis since recent neuroimaging studies and neuropathological data suggest its involvement in mood disorders. Neurokinin-1 receptor densities were higher in the superficial than in deep laminae. These densities increased with age and declined with prolonged autopsy interval. No differences were seen between the four groups. However, the ratio of superficial to deep laminar binding was lower in the subjects with major depression compared with all other groups. This change in the laminar ratio of [125I]-substance P binding, may reflect alterations in specific neural circuits expressing the neurokinin-1 receptor.

S06.5

Clinical update: substance P antagonists in patients with major depression

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Evidence with the novel compound MK-0869, suggests that Substance P (NK1) antagonists (SPAs) provide a unique antidepressant mechanism. We investigated another selective NK1 antagonist, "Compound A" in outpatients with major depression with melancholia. Double blind; placebo-controlled; male or female, aged 18–60, scoring = 25 points on the HAMD-17, 4 on the CGI-S. "Compound A" once daily in the evening (n=66), or matching placebo (n=62) for 6 weeks. For patients receiving "Compound A," the improvement in HAMD-17 total score was 10.7 points, compared with the mean 7.8 point improvement in patients receiving placebo ($p < 0.009$). Compared with placebo, the mean CGI-I improved significantly ($p < 0.009$). Depressed mood also improved to a greater extent in the active group compared with placebo. "Compound A" was generally well tolerated. The incidence of sexual side effects was similar to placebo; the incidence of GI adverse effects was low. Antidepressant actions have been observed with two highly selective NK1 antagonists (MK-0869 and "Compound A"). NK1 antagonism is an authentic and generally well tolerated antidepressant mechanism.

S06.6

NK-1 receptor antagonists: a review of preclinical and clinical data

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Anatomical and pharmacological studies of the substance P (SP) system have suggested that it plays a role in pain, inflammation, emesis and most recently in depression and anxiety. Published clinical data support a role for NK-1 receptor antagonists as antiemetic agents and antidepressants with potential efficacy against anxiety. Surprisingly, the clinical data, albeit limited, provide modest support for efficacy against pain and inflammation. We have described a number of compounds e.g. CP-99,994 and CP-122721, that exhibit high affinity for the NK-1 receptor present in human, guinea pig, hamster and ferret, but greatly diminished affinity for the rodent NK-1 receptor. Thus, it has been necessary to develop novel assays using species other than the rat and/or identify compounds with greater affinity for the rodent receptor.

The activity of selective NK-1 receptor antagonists in behavioral and biochemical models of anxiety, depression, pain and emesis will be reviewed. In addition, clinical results from a double blind placebo controlled trial with CP-122,721 in patients with moderate depression will be presented.

S07. Future directions for research on fetal life and psychiatric disorders

Chairs: T. McNeil (S), J. Waddington (GB)

S07.1

Obstetric complications and schizophrenia – a meta-analysis of population-based studies

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Obstetric complications have long been postulated to increase the risk for later schizophrenia but case-control studies attempting to investigate this association have yielded conflicting results due to methodological problems. Although the large, recently-published population-based studies were expected to give definitive results they have also produced contradictory and largely negative findings for individual obstetric complications. Meta-analysis provides a method for integrating quantitative data from multiple studies in order to improve the estimates of effect size, increase statistical power, and make sense out of studies with conflicting conclusions. The methodological similarities of the population-based studies and their standardised fashion of reporting results lend themselves to this approach. Relevant papers were identified by MEDLINE search, examination of reference lists of published papers and through personal contact with researchers in the field. Meta-analysis of 8 population-based studies that met our inclusion criteria revealed that three groups of complications were significantly associated with schizophrenia: (1) Complications of pregnancy (bleeding, diabetes, rhesus incompatibility, pre-eclampsia); (2) Abnormal fetal growth and development: (low birthweight, congenital malformations, reduced head circumference) and (3) Complications of delivery (uterine atony, asphyxia, emergency caesarian section). Pooled estimates of effect sizes were generally around 2 with the largest effect for diabetes during pregnancy. There was evidence for significant heterogeneity in the results for low birthweight and asphyxia. We consider these results in the light of previous research and discuss why it is so difficult to investigate obstetric complications as a risk factor for schizophrenia.

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