effects, treatment optimization and development of new drugs. Several studies have demonstrated that clinical treatment with classical antipsychotics induces a high degree of D2dopamine receptor occupancy. For classical antipsychotics, distinct thresholds in D2occupancy have been shown for antipsychotic effect, prolactin increase and extrapyramidal side effects (EPS) respectively. The atypical antipsychotic clozapine induces a significantly lower striatal D2occcupancy as compared to classical antipsychotics. The hypothesis of a 'limbic selectivity' for clozapine was recently tested with high resolution PET and the high affinity radioligand [11C]FLB457. The finding of a low D2occupancy that was maintained also in extrastriatal regions did not support the hypothesis of a preferential limbic D2occupancy. PET studies of the novel antipychotics risperidone and olanzapine have shown D2occupancy levels similar to those induced by classical antipsychotics. Further studies are needed to test whether D2occupancy thresholds for clinical effects differ between classical and novel antipsychotics.

S04.5

PET and antipsychotic drugs – future

J. Tedroff*. *A Carlsson Research AB, Department of Medicine, Göteborg, Sweden*

For many years PET using displacement studies of PET ligands bound to neuroreceptors has studied the pharmacological action of antipsychotic drugs. Using this approach it has been demonstrated that antipsychotic effects can be achieved by a number of neuroreceptor blocking properties.

During recent years, studies using electrical deep brain stimulation in neurological conditions, have demonstrated that electrical inhibition of very small localized intracerebral targets indeed can affect the function of vast areas of the brain. In a similar manner antipsychotic drugs may, despite different or selective receptor binding properties, affect certain functional domains of the brain, which are common for antipsychotic effects. To visualize such effects PET data have to be analysed differently, employing analysis of connectivity across brain networks such as the corticostriatal pathways. Using this approach it can be demonstrated marked differences between the healthy and schizophrenic states of brain connectivity. Typical and atypical antipsychotic drugs affect these deviations towards a more normalised state, albeit with some differences. Analysis of brain network connectivity in disease and of drugs are likely to expand understanding of the functional effects underlying the antipsychotic properties of various drugs.

S05. Personality disorders – an update

Chairs: L. Ekselius (S), J. Livesley (CDN)

S05.1

Developmental pathogenesis of personality disorder

J. Livesley*. *University of British Columbia, Department of Psychiatry, Vancouver, Canada*

Multiple biological and psychosocial variables are associated with the development of personality disorder. Each variable appears to have a small effect and none appear to be either necessary or sufficient to cause personality disorder. Under these circumstances it seems more appropriate to refer to the factors that predispose to the development of personality disorder than to refer to causes.

Behaviour genetic studies indicate that genes and environment contribute to the aetiology of personality disorder and that all personality traits are heritable. It is not possible to distinguish between traits that are largely influenced by genetic factors and traits that are largely environmental in origin. Multiple genetic factors appear to be involved that differ in effect. Some influence the development of specific traits whereas others have wider effects influencing the development of clusters of traits. The broader genetic dimensions appear to be responsible for the clusters of traits that define the different patterns of personality disorder. Each genetic factor appears to involve multiple genes each contributing a small amount of phenotypic variance.

A similar picture emerges from studies of the psychosocial origins of personality disorder. Multiple factors are related to personality disorder including family dysfunction, deprivation, and trauma but none are invariably associated with personality disorder and specific links between different kinds of adversity and specific forms of disorder have not been identified.

These results reveal a complex picture of the aetiological of personality disorder. They suggest that studies of single variables or groups of related variables are unlikely to contribute to understanding pathogenesis. They also suggest the need to re-think our concept of the environment. The environment is not something independent of the individual. Instead individuals shape the environment to which they respond. A theory of the pathogenesis of personality disorder needs to explain the interaction between genetic predisposition and environmental adversity. In particular, it needs to explain the way genetic predisposition and the emerging personality shape the environment to which the individual responds and how this environment in turn influences gene expression and the emerging personality.

S05.2

Personality – different genes or differences in gene activation?

J. Hallman*, H. Garpenstrand, M. Damberg, L. Oreland. *Uppsala University, Uppsala, Sweden*

Monoamine oxidase (MAO) activity in platelets correlates with personality (e.g. sensation seeking, impulsiveness). Low platelet MAO, as well as the personality traits associated with these, have been associated with e.g. type 2 alcoholism, criminality and violent behaviour. The transcription factor family AP-2 is a regulatory factor for prenatal development of monoaminergic nuclei as well as of monoamine turnover in the adult rat forebrain. The gene encoding AP-2b includes a polymorphic region, which is associated with e.g. personality as well as with impulsive binge-eating disorder. In both male and female AP-2β genotypes homozygous with regard to a [CAAA]5 repeat display significantly lower platelet MAO activity than the other genotypes. Thus, it seems likely that the personality disturbances, linked to low platelet MAO, should be associated with the presence of this AP-2β gene allele. In this way, common transcriptions factors regulate the expression of midbrain monoamine structures as well as that of platelet MAO, thereby explaining the association between platelet MAO and personality (see Damberg et al., Mol. Psych.. 6, 503, 2001).

S05.3

Genetics and suicidal behaviour

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Although a familial aggregation of suicide has been observed by many psychiatrists, the reason for this has until recently been

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thought to reside in the shared socio-cultural and psychological environment, rather than in a shared genetic endowment. Even Franz Kallman, one of the major proponents of the idea of a genetic background of psychiatric disorder, considered a genetic background to suicide unlikely. Accummulating evidence for an association between low serotonin function and an increased risk of suicidal behaviour has, however, made a genetic background for suicide more plausible. Family and twin studies using modern techniqes and controlling for psychiatric illness support the idea that vulnerability to suicidal behaviour is to some extent under genetic control. Several genetic polymorphisms involved in serotonin transmission have been studied for a possible association with suicide. Among them, an modest excess of the tryptophan hydroxylase 17779C allele has repeatedly demonstrated in association with suicide, most recently in a study of surviving cotwins whose monozygotic twin had committed suicide. These, and some studies involving other genetic markers will be briefly reviewed in the presentation.

S05.4

Treatment outcome of personality disorders

P. Tyrer. *UK*

No abstract was available at the time of printing.

S06. Substance P (NK1) receptors – possible role in stress, anxiety and affective disorders

Chairs: T. Hökfelt (S), E. Brodin (S)

S06.1

Anatomy of substance P and NK1 receptors in the brain

T. Hökfelt*. *Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden*

Substance P has a wide distribution in the CNS, including cortical and limbic brain regions, suggesting involvment in multiple functions. Regions with a particular dense substance P innervation include the medial amygdaloid nucleus, the zona reticulata, substantia nigra and the spinal trigeminal nucleus/spinal dorsal horn. There are at least 30 different cell groups expressing substance P in the rat brain. Substance P coexists with classic transmitters, for example with serotonin in the descending system to the spinal cord, but not in the dorsal raphe 5-HT neurons, which project to the forebrain. However, in the human brain a high proportion of the serotonin neurons in the dorsal raphe nuclei has detectable substance P expression. So far three substance P receptors have been identified. The NK-1 receptor has a wide distribution in the rat CNS and is internalized upon stimulation with the ligand. Such internalization can in fact be used as an index of endogenous substance P release. This approach has opened up new possibilities to study substance P functions in the CNS.

S06.2

Pharmacology – a historical overview

E. Brodin*. *Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden*

Recent studies indicate that neurokinin 1 (NK1) receptor antagonists may be an alternative to selective serotonin uptake inhibitors (SSRI) and other drugs in the treatment of affective disorders. It has been suggested that the antidepressant effect of NK1-receptor antagonists does not involve monoaminergic mechanisms. However, there are preclinical evidence for interactions between substance P (SP), the most important endogenous ligand at NK1-receptors, and serotonin (5-hydroxytryptamine, 5-HT) in limbic structures, the periaqueductal grey (PAG) and other brain regions. Acute and subchronic treatment with SSRI:s and tricyclic antidepressant drugs induce changes of tissue levels of SP, and the other tachykinin neurokinin A, in

these brain regions in the rat. These interactions may involve separate SP- and serotonin-containing pathways or pathways from the dorsal raphe region coexpressing SP and 5-HT. Interestingly, subchronic SSRI treatment and electroconvulsive stimulation have similar effects on SP-levels in the rat cerebral cortex in rats. In addition to these neurochemical data, there are electrophysiological results demonstrating SP/monoamine/-interactions which may be of importance for the antidepressant effect of NK1-receptor antagonists as well as other antidepressant drugs.Preclinical evidence also indicate that SP and NK1-receptors play a key role in the adaptation to stress, a wellknown aetiological factor behind the development of affective disorders. Acute stress induce marked changes in tissue levels of SP in limbic structures and the PAG in the rat that correlate in time with plasma corticosterone levels. Mice lacking the NK1 receptor have been shown to be less aggressive and less anxious than wild type controls and NK1-receptor antagonists have anxiolytic properties in animal models. In our own experiments we have found that the 5-HT1A-receptor agonist 8-OH-DPAT, at low dosage, which also has anxiolytic effect, counteracts stress-induced tachykinin release in the limbic system.

S06.3

Diminished anxiety- and depression-related behaviors in substance P-deficient mice

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While the role of substance P (SP) in nociceptive signaling is now well established, its role in the regulation of higher brain functions remains poorly understood. Limbic structures, including the amygdala, contain a high density of SP terminals and NK1 receptor sites, suggesting that SP may be involved in the modulation of emotional behaviors. Indeed, recent clinical and pharmacological studies, and the analysis of NK1 receptor mutant mice suggested that the NK1 receptor modulates emotional responses. In this study, we have analyzed SP-deficient mice (Tac1-/-) in animal models of anxiety and depression. Tac1-/- animals were more active in the forced-swim and tail-suspension test, and displayed a reduced activity change after bulbectomy. Thus, SP deficient mice behaved like wild type animals treated with antidepressants. Tac1-/- also showed a marked reduction of anxiety and stress related responses in the O-maze test, the Thatcher-Britton conflict paradigm, and the social interaction test. Our results suggest a significant role of SP/NKA in the regulation of emotional states and provides further evidence that the NK1 receptor might be a useful pharmacological target in the treatment of affective disorders.

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