abnormality may underlie the observation of increased impulsive and aggressive behaviors in individuals at risk for suicidal behavior. That biobehavioral characteristic crosses diagnostic boundaries. Most recently, we have reported that serotonergic abnormalites in postmortem brain tissue related to major depression differ significantly in their localization compared to the serotonergic abnormalities associated with suicide. Thus, major depression involves a diffuse change in serotonin transporter binding throughout the prefrontal cortex and temporal cortex, whereas suicidal behavior involves an alteration in serotonin transporter binding in the ventral prefrontal cortex only. Future studies addressing more detailed aspects of the serotonergic and other neurotransmitter systems are required to further differentiate syndromal correlations from temperament and personality correlations in high risk patients.

S33.04
SUICIDE AND YOUNG PEOPLE

B.S. Runeson

No abstract was available at the time of printing.

S34. Imidazolines: novel markers for depression and potential targets of new antidepressants

Chairs: A. Halaris (USA), J.E. Piletz (USA)

S34.01
MIDAZOLINE RECEPTORS: POTENTIAL MARKERS FOR DEPRESSION AND TARGETS OF ANTIDEPRESSANT DRUG DEVELOPMENT

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Imidazoline binding sites (I-sites) have been characterized using radioligands like ^{3}H-clonidine. At least two I-sites, I_1 and I_2, have been defined based on differential binding affinities, subcellular localizations and regional brain distributions. Human platelets possess both subtypes and immunologically-related 33 kDa and 45 kDa proteins. Platelet I_1 sites are elevated in depressed patients but downregulated after desipramine, fluoxetine, citalopram, clomipramine and imipramine. We used I receptor binding protein (IRBP) antiserum to quantify I receptors on platelets of depressed patients before and after bupropion. Western blots revealed increased IRBP-immunodensity in a 33 kDa protein band in untreated patients. This band has been positively correlated with I_1 binding sites on platelets. After 6 weeks of treatment, IRBP-immunodensity was downregulated predominantly in treatment responders. Non-responders showed no elevation in IRBP at pretreatment and no downregulation at posttreatment. IRBP-immunodensity was negatively correlated with plasma bupropion concentrations. Thus, a 33 kDa IRBP on platelet plasma membranes is elevated in depression and normalized in treatment responders. We also determined associations between clusters of depressive symptomatology and platelet parameters. Two of the Hamilton Depression clusters, the endogenomorphic and retardation dimensions, showed significant correlations with binding parameters. Thus, platelet I_1 might become a potential marker for affective symptomatology and/or a specific marker for unipolar depression and this could lead to the development of compounds targeting these receptors and exerting antidepressant efficacy.

S34.02
CLONING OF A CANDIDATE IMIDAZOLINE RECEPTOR CDNA FROM HUMAN HIPPOCAMPUS

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Pharmacologically distinguishable imidazoline receptors (IR) and alpha2-adrenoceptors (alpha-2AR) share several common properties in the brainstem. We recently cloned a candidate IR1 cDNA from the human hippocampus using two IR-selective antisera (DNA & Cell Biology, 2000). The clone, designated imidazoline receptor antisera-selected (IRAS-1) cDNA, encodes a 167 kD protein. Transfection of IRAS-1 cDNA into CHO (Chinese hamster ovary) cells resulted in high affinity IR1 sites labeled with [125I]-p-iodoclonidine (PIC). Using phaeochromocytoma PC-12 cells, we also selected a stably-transfected subclone that exhibits a 2-fold increase in IR1-like Bmax. The transfected CHO and PC-12 subclones both showed a 167 kD anti-IRAS band as well as smaller bands (~85 kD). But, transient trasfections into COS-7 and Sf9 cells failed to result in an increase in IR1 binding sites, suggestive that host cell processing of IRAS-1 is critically important for IR1 binding site. Furthermore, CHO cells permanently transfected with human alpha-2AR cDNA were transiently co-transfected with IRAS-1 cDNA. These co-transfectants produced both alpha-2AR and IRAS-1 (immunologically) at expected levels, but there was a surprising 3-fold increase in alpha-2AR binding. Thus, IRAS-1 not only encodes IR1 binding sites in a host-cell specific manner, but also may interact with alpha-2AR to increase their binding capacity for PIC. It is possible that IRAS and alpha-2AR interact with each other in certain brain cells to mediate sympathetic outflow in a coincident detection manner.

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S34.03
BRAIN AND PLATELET IMIDAZOLINE RECEPTORS IN MOOD DISORDERS

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Major depression has been associated with alterations of imidazoline receptors (I_1- and I_{2B}-IR) and related IR proteins in brain and platelets. The immunodensity of a 45-kDa IR (putative membrane I_1-IR) is increased in brains of suicides and depressed suicides, and also in platelets (45- and 35-kDa IR) of depressed patients. Similarly, I_1-sites (^{125}I-p-iodoclonidine binding) and the levels of a 33-kDa IR are increased in platelets of depressed patients (Halaris, Piletz and colleagues). In brains of depressed suicides, the abundance of a 30-kDa IR (putative glial I_{2B}-IR) is down-regulated in parallel with a reduction of ^{3}H-idazoxan binding (I_{2B}-IR), which is in line with recent histopathological studies showing reduced glial density in brains of depressed patients. IR proteins (35- and 45-kDa peptides) are not altered in platelets of euthymic patients with bipolar affective disorder. Antidepressant drugs induce down-regulation of 45-kDa IR protein and I_1-sites in platelets of depressed patients and up-regulation of I_{2B}-sites in rat brain. To foster the knowledge of IR a new IR antibody was

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produced. Rabbit liver membranes were solubilized with CHAPS and IR purified using a ReactiGel-amiloride resin. The purified protein (I_2-type) was used to immunize rabbits, and the IgG fraction was used after purification. The antibody immunoprecipitated the binding of ^{3}H-2-BFI (I_2-IR) in rabbit liver. Western blot analysis of human brain membranes (prefrontal cortex) with this antibody (AMI, 1:12,000 dilution) resulted in the labeling of a unique protein of about 77 kDa (putative I_2-IR). In a well-defined population of depressed suicides, the immunodensity of this 77 kDa IR protein in the prefrontal cortex was marginally increased (41±21%, n = 10, $p > 0.05$) compared to that in matched controls. This increase was clearly apparent in antidepressant-free (69±29%, n = 6, $p < 0.05$) but not in antidepressant-treated (1±20%, n = 4) depressed suicides. These preliminary data suggest that this putative I_2-IR, in contrast to the 30-kDa IR protein, is up-regulated in brains of depressed suicides and down-regulated by antidepressant drugs. The functional relevance of altered IR in the pathogenesis of mood disorders (e.g. modulation of monoaminergic neurones by IR) is unknown, but brain $I_{1/2}$-IR appear to be targets for the effects of antidepressant drugs.

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S34.04

IMAGING NORADRENERGIC AND NON-ADRENERGIC BINDING OF [^{3}H]CLONIDINE IN BRAINS FROM PSYCHIATRICALLY CHARACTERIZED HUMANS

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Clonidine is a partial agonist at brain α_2-adrenoceptors (α_2AR), and also has high affinity in homogenate binding assays for non-adrenergic imidazoline-binding sites (I-sites). This study utilized receptor autoradiography to compare the density distributions of binding of [^{3}H]clonidine to α_2AR and I-sites and in sections of human brain. The α_2-adrenoceptor component of [^{3}H]clonidine binding was masked with either norepinephrine (α_2AR agonist) or with methoxy-idazoxan (selective α_2AR antagonist) and the remaining I-sites were displaced with the imidazoline compound, cirazoline. Densities of [^{3}H]clonidine binding to α_2AR and I-sites, determined in adjacent tissue sections, were positively correlated across 27 brain regions ($p = 0.0003$; $r^2 = 0.385$). Despite this significant correlation, closer inspection within the hippocampus, using quantitative transepts drawn across hippocampal images, revealed α_2AR enrichments in the CA-1 and inner molecular layer of the dentate gyrus, areas not enriched in I-sites. Competition curves were generated for I-sites in caudate sections using 10 ligands reported to distinguish between I_1 and I_2 subtypes. The rank-order of affinities was cirazoline > harmane > BDF6143 > idazoxan = tizanidine (affinities of agmatine, efaroxan, moxonidine, norepinephrine, and oxymetazoline were too low to be reliable). [^{3}H]clonidine binding to α_2AR and to I-sites in 6 layers of the left, rostral orbitofrontal cortex (area 47) were measured in 7 psychiatrically normal control subjects and 8 subjects with major depression, of whom diagnoses were confirmed by retrospective psychiatric autopsy. Ratios of α_2AR/I-site binding were significantly higher (approximately 2-fold) across all layers of the cortex of control subjects relative to major depressive subjects. In conclusion, (1) the distribution of non-adrenergic [^{3}H]clonidine binding sites in human brain sections is correlated with, but distinct from, α_2AR, (2) the pharmacology of these sites is distinct from α_1AR, α_2AR, I_1 or I_2 sites as previously defined in membrane binding assays, and (3) major depression is associated with an abnormality in the ratio of α_2AR/I-sites in the orbitofrontal cortex.

S34.05

NEW APPROACHES TO IMIDAZOLINE RECEPTORS

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In view of the potential role of imidazoline receptors in both psychiatric (depression, addiction) and neuropsychiatric (Alzheimer's, Huntington's) disorders, there is a great need to have selective and potent probes for them. Our group has been working in this field for a number of years and have characterised a series of high affinity, high specificity ligands such as 2-BFI and BU224. The pharmacological actions of these compounds are intriguing in that, to varying degrees, they increase the release of noradrenaline and dopamine in 5HT in brain. We have previously shown 2-BFI to have efficacy in the Porsolt forced swim test. In a rat model of opiate withdrawal, we noted that BU224 could alleviate some symptoms of the syndrome such as diarrhea (Hudson et al., 1999). This suggests that these compounds may have some utility as therapeutic agents. More recently, we have synthesized a high affinity irreversible ligand of these receptors which offers the promise of studying the effects of long term ablation of imidazoline receptors on neurochemistry and behaviour (Coates et al., 2000). Moreover, it will allow us to identify the imidazoline proteins and therefore proceed towards purification and cloning. The implications of this for psychiatry will be discussed.

S35. Somatoform disorders and related disorders: the clinical concepts and the neurobiological basis

Chairs: M. Ackenheil (D), N. Sartorius (CH)

S35.01

SOMATOFORM DISORDERS AND CONCURRENT CONCEPTS IN INTERNAL MEDICINE

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Around the world and across different cultures, medically unexplained somatic symptoms are characteristic of psychosocial distress and indicative of somatoform disorders. However, when a medically unexplained somatic symptom (or a syndrome) is explained (which is sometimes due to the advancement of our medical knowledge and more often due to the reclassification of our existing knowledge), it tends to move from the area of psychiatry to the area of internal medicine. The most recent examples include Chronic Fatigue Syndrome, Fibromylagia and Irritable Bowel Syndrome.

In this paper we will discuss the concept of somatoform disorder and compare it to concurrent concepts in internal medicine including the above-mentioned conditions. Our discussion points will be based on a comparative analysis of symptom profiles and diagnostic features of these disorders and for such purpose we will use the data collected in the International Study of Somatoform Disorders-a large epidemiological project carried out by the World Health Organisation in eleven countries spaning four continents.