

Interactive monoaminergic basis of anxiety and depression

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There ought to be advantages associated with reviewing current notions on anxiety and depression disorders in close proximity, *e. g.*, mixed anxiety-depression is a very common syndrome in the aged whereby a large majority of patients seek G. P. help (Boulenger and Boyer, 1994), and the enterprise has been explored quite recently (Graeff *et al.*, 1996) in relation to the major receptor-complex involved, the 5-HT system. As evident from the papers presented in this section, the syndrome described here was to a great extent synonymous with another that seems to be acquiring much treatment-preponderance, the serotonin syndrome (Lejoyeux *et al.*, 1993; Sternbach, 1991). The interactive monoaminergic basis of anxiety and depression was spun around the centrifugal forces of serotonin, its sub-receptor profile, the increasingly implicated hypothalamic-pituitary-adrenal axis and related gender differences and possibly the beta-adrenoceptors.

1.1. Anxiety disorders

The chapter by Rodgers and Cao (Chapter 2) traces the historical and controversial background to the role of the multiple 5-HT receptors in anxiety disorders and thus focuses predominantly on the preclinical findings (*cf.* Griebel *et al.*, 1997). The frameworks for this type of behavioural pharmacological approach to the identification of potential and valid compounds for the eventual treatment of broad or specific spectra of anxiety disorders have been described previously by the group (*e. g.*, Cole and Rodgers, 1994; Rodgers and Cole, 1993; Rodgers *et al.*, 1997) and others (Green and Hodges, 1991) as presented in the definitive review by Rodgers and Cole (1994). Constraints upon adequately stable indications have been rife: the paucity of pharmacological tools, the rudimentary nature of 5-HT receptor pharmacology, the dominance by ligands functioning as full/partial ago-

nists at 5-HT_{1A} sites, the naivety of prevailing animal models, the disappointing limitations in predictive clinical efficacy should all be considered. The authors have primarily applied an ethoexperimental analysis of the mouse elevated plus-maze paradigm in demonstrating that the full agonists cause primarily an inhibition of motor behaviour, the partial agonists induce under the most favourable circumstance only weak anxiolytic effects, whereas there are available a diversity of 5-HT_{1A} antagonists that evidence robust and anxiolytic effects in the laboratory. It seems unlikely that the experimental anxiety reduction was due to concomitant antagonism at 5-HT_{1A} and α_1 and/or $\beta_{1/2}$ -adrenoceptors (but see also Cao and Rodgers, 1997a).

The interactive involvement of monoaminergic systems in anxiety disorders was not explicitly addressed either in the above analysis or in the remaining chapters that were designed to cover this approach. Despite this, the preclinical analyses of the Rodgers groups into the neuropharmacological effects of an exceedingly wide range of putative and available compounds indicate evidence on a broad neurotransmitter-pathway front. The relative implications for noradrenergic and GABAergic pathways have been reviewed (*e. g.*, Johnston, 1991). As reviewed too by Cole *et al.*, (1995), α_2 -adrenoceptor antagonists like yohimbine and idazoxan induce anxiogenic effects in patients with panic disorder (Albus *et al.*, 1992; Krystal *et al.*, 1992) whereas clonidine, α_2 agonist reduced anxiety measures in these patients (Coplan *et al.*, 1992). The eventual role of the 5-HT₃ receptors in anxiety remains controversial, despite much early evidence in favour, reviewed by Rodgers *et al.*, (1995). As suggested by these authors, the efficacy of 5-HT₃ antagonists appears to be determined by the particular type of disorder and the particular test/treatment conditions employed. GABAergic subreceptor influences upon both anxiety-generation and alleviation have been comprehensively examined and described in the paper by Dalvi and Rodgers (1996). The relative role of DA receptor subtypes in anxiety has been studied too (Rodgers *et al.*, 1994): the results appear somewhat rudimentary, at least with regard to compounds like SKF38393, SCH23390 and quinpirole, but in spite of these sulpiride seems to offer unambiguous indications of anxiolytic action. These results suggest potential anxiety-alleviating effects of DA D₂ antagonism by sulpiride although raclopride would perhaps be of greater suitability. The possible influence of the DA D₄ receptor-mediation of purported anxiolytic effects of clozapine (Moore *et al.*, 1994; Szezwczak *et al.*, 1995) was examined by Cao and Rodgers (1997b) applying the selective D₄ receptor antagonists, L-745,870 and L-741,742, in the mouse plus-maze. Both compounds failed to induce behavioural alterations thereby casting shadows on eventual D₄ modulation.

A basic research-drug development account of the involvement of the 5-HT_{1A} receptor in anxiety disorder is outlined by Manzanares *et al.*, (Chapter 6), not least of all because of the widespread and preference distribution of these receptors in limbic regions of the brain (Remy *et al.*, 1996). In describing the background medicinal chemistry the authors have offered a rationale for the preclinical development and synthesis of 5-HT_{1A} receptor agonists and antagonists based upon a bulk of preclinical neuropharmacology in the main. Eventually the search for these enti-

ties led to the synthesis of an agonist, B-20991, and an antagonist, EF-7412. Pharmacological characterisation of B-20991 was carried out on the basis of several analyses: regulation of body temperature, 5-HT_{1A} receptor-mediated behaviour, neurochemical activity (5-HT/5-HIAA as well as DA/DOPAC assays of the hypothalamus), transduction mechanisms were studied through inhibition of forskolin-stimulated adenylylate in cultured transfected HeLa cells, locomotor activity in an open-field and the assessment of anxiolytic action through the social interaction and light/dark box test models, the consensus of the tests being that the compound was an agonist of the 5-HT_{1A} receptor at the somatodendritic and postsynaptic sites possessing a potential anxiolytic action. The pharmacological profile of the putative antagonist was assessed through indexing its effects upon thermoregulation and its antagonistic potential against the corticosterone-elevating effect of the agonist. In addition the anxiolytic profile was tested in the light-dark box test although no anxiolytic action was forthcoming. This negative result, and even that of the 5-HT_{1A} agonist, B-20991, must certainly be assimilated in the context of the chapter by Rodgers and Cao (Chapter 2) which would expect one to anticipate quite a different outcome (see also Barf *et al.*, 1996).

1.2. Depressive disorders

The chapter by van Praag (Chapter 5) presents the notion of depression as a 5-HT-related, anxiety and/or aggression-driven, stressor-precipitated concept that incorporates some degree of disadvantageous hypothalamic-pituitary-adrenal (HPA) mobilisation and comprises the following elements: (1) the serotonergic disturbances observed in some populations of depressed patients, particularly those with decreased cerebrospinal 5-HIAA and blunted hormonal responses to 5-HT agonists, (2) a 5-HT-related condition consisting of some dysfunction of anxiety and/or aggression, characterised psychopathologically as anxiety/aggression-driven. This account takes into consideration important aspects of an individual's personality in that anxiety and aggression (anger) are assigned core status in the stress syndrome thus envisioned. The underlying serotonergic disturbance is associated with an oversensitivity for stressful events (see also van Praag, 1996), thereby providing the neurobiological background for a trait pathology that leads to the major depressive condition and persists during remission. One prediction from this account is that a full agonist of the 5-HT_{1A} receptor that allows a combined anxiolytic-anti-aggression should exert an efficacious therapy in depression. Curzon's chapter (Chapter 3) reviews that basis for implicating the role of 5-HT in depression: the availability of tryptophan for 5-HT synthesis, the activity of the HPA system in this regard (Cowen, 1993), the decreased responsiveness to serotonergic compounds and implications of sex differences in 5-HT function. He describes the complexity of interactive monoaminergic effects in depression by recourse to the neuropharmacology of tianeptine, a compound that enhances 5-HT uptake and decreases 5-HT availability (Oluyomi *et al.*, 1997). The compound has been shown both to block the stress-induced release of central NA and to increase basal

dialysate DA to a more marked degree in the nucleus accumbens than in the striatum. As indicated, both the acute and chronic administration of antidepressants affect the responsiveness of the mesotelencephalic DA system (Willner, 1995), as well as vulnerability to the disorder (Loas, 1996). The chapter by Cowen (Chapter 4) reviews functional 5-HT abnormality in depression from 5-HT neurocrine challenge tests in patients; the consensus being patients with major depression have a dysfunctional presynaptic 5-HT (but see also van Praag *et al.*, 1987). Tryptophan depletion techniques, that lower 5-HT levels in healthy subjects, also lower mood in those subjects, male or female, with a vulnerability factor (family history of depression), and induced relapse in recently recovered patients. The clinical antidepressant action of the SSRIs is discussed with regard to 5-HT_{1A} receptor function both as autoreceptors on the cell body and at postsynaptic receptors in terminal fields, where they reduce their responsiveness (see below and Berman *et al.*, 1997).

Nordström and Åsberg (Chapter 5) pursue the theme of depression into the final consequence and thereby have outlined a major suicide risk hypothesis. Some critical factors would appear to be: a morbid escalation of the biological propensity (Roy *et al.*, 1995) and the circumstantial prerequisites (Nordström *et al.*, 1995), the affective disorder situation, a critical vulnerability to suicide risk, dangerous personality traits in addition to a deficiency in serotonin and its major metabolite, 5-HIAA. Two major areas of risk, on the basis of survival analysis studies, have been discussed: 1) current suicide attempt analysis predicted a 12% one-year suicide risk in depressed patients; and 2) low CSF 5-HIAA levels in depressives predicts a suicide risk of 17% within one year of an attempted suicide. The authors discuss an analysis of vulnerability developed from entities such as anxiety dysregulation, aggression dyscontrol and impulsive disinhibition in the context of reduced serotonin-availability. In these analyses, particular focus should once again be placed upon the serotonergic system in relation to the HPA axis and the blunted prolactin response (see also Curzon, van Praag and Cowen). The contribution of specific 5-HT receptor subtypes was not touched upon although Arranz *et al.*, (1994) found that there were significant decreases in post mortem 5-HT_{1D} binding affinity of brains from depressed suicides and in the number of binding sites in brains of nondepressed suicides with an unchanged number of 5-HT_{1A} binding sites and unchanged affinity in the suicide groups. The seriousness of the condition in clinical depression, and particularly in treatment-resistant depression, is further exacerbated by volume of evidence, presented in the chapters of Sluzewska (Chapter 9) and Dantzer (Chapter 8), for wide-ranging alterations of the body's immune response system.

The natural history of major depression has been characterised by its incidence, recurrence and duration of episodes wherein onset consists of incidence and the prodrome, and chronicity of episodic durations and recurrence after recovery (Eaton *et al.*, 1995). Recent reviews of depressive states pertain to the accounts presented above, particularly Curzon and van Praag, as follows: female-male prevalence rate that also shows similar recurrence rate, episode duration and recovery rate (*cf.* Eaton *et al.*, 1989, 1997), all of which serves to highlight the prevailing

rudimentary nature of gender differences in the understanding of depression and its neuropharmacological therapy. Even less information exists regarding the treatment of depression in children and adolescents despite its morbidity and mortality and the paucity of controlled studies (Boulos *et al.*, 1992; Emslie *et al.*, 1997). As discussed in the chapters by Sluzewska (Chapter 9) and Dantzer (Chapter 8) with regard to immune response functioning, treatment-resistance and poor outcome indicate a sizeable problem: poor outcome has been identified for 20% of presenting major depressives (Keller *et al.*, 1994).

Serotonin-availability, or lack of it in depressive states, is an important issue (see chapters by Curzon, Cowen and van Praag) as indicated in circumstances of reduced transmitter synthesis (Bel and Artigas, 1996; Delgado *et al.*, 1990). As indicated by Pérez *et al.*, (1997) and others (Adell and Artigas, 1991), antidepressant therapy may drive-up 5-HT concentrations in the vicinity of serotonergic cell bodies of the mid-brain to activate somatodendritic autoreceptors of 5-HT_{1A} type to induce a paradoxical reduction of 5-HT release in the major forebrain areas. Thus it was reasoned that combination of 5-HT_{1A} autoreceptor antagonists to selective serotonin reuptake inhibitors (SSRIs) might improve clinical efficacy (Artigas, 1993). For instance, it was shown preclinically that the mixed-adrenoceptor 5-HT_{1A} autoreceptor antagonist, pindolol, antagonised the SSRI-induced reduction of serotonergic neuronal activity thereby enhancing the action of this class of compound via enhanced 5-HT release that activated forebrain postsynaptic receptors (Dreshfield *et al.*, 1996; Romero *et al.*, 1996). Against this background, Pérez *et al.*, (1997) performed a randomised, double-blind, placebo-controlled trial to investigate the addition of pindolol (7.5 mg daily) or placebo to fluoxetine treatment (20 mg daily), applying the Hamilton and Montgomery-Åsberg depression-rating scales to assess the severity of depression. The dependent variables included (1) mean (\pm SD) changes from base line in Hamilton depression-rating scores, (2) cumulative percentage of patients with a sustained response, and (3) Kaplan-Meier estimated time to a sustained response, including survival analysis of the treatment combinations. Their results indicated that the pindolol-fluoxetine combination increased the proportion of responders to non-responders (75% versus 59%), the sustained response (69% versus 48%), and the proportion of patients in remission (60% versus 45%), as well as improving treatment efficacy as assessed by the decrease in Hamilton and Montgomery-Åsberg depression scores. This study confirms the results of open-labelled studies administering paroxetine and pindolol (Artigas *et al.*, 1994; Blier and Bergeron, 1995).

1.3. Seasonal Affective Disorder

The background strategy for the serotonin-availability-HPA abnormality condition in affective states, including mood disorders, utilises the hormones mobilised through serotonergic innervation as an index of serotonin efficacy in these disorders (Alper, 1990; Calogero *et al.*, 1990; van de Kar, 1991). Certain aspects, *e. g.*, tryptophan-usage and serotonin metabolism, of the condition, seasonal affective disorder, may serve to highlight the current status of depressive disorders. The

behavioural and neuroendocrine concomitants (Joseph-Vanderpool *et al.*, 1993; Lacoste and Wirz-Justice, 1989; Martikainen *et al.*, 1985) of the disorder as well as gender variations (Rybakowski and Plocka, 1992; Touitou *et al.*, 1983) have been important considerations. Serotonin agonists, *e. g.*, m-CPP a partially selective 5-HT_{2C} (previously 5-HT_{1C}) agonist (Jacobsen *et al.*, 1994; Kahn and Wetzler, 1991), or 5-hydroxytryptophan (Jacobsen *et al.*, 1987) have been applied to provoke hormonal responses associated with the disorder. Thus, García-Borreguero *et al.*, (1995) found that following m-CPP infusion untreated patients had exaggerated prolactin and cortisol responses in comparison to controls. Further, the abnormal serotonin function was restricted to winter with normalisation during the summer. In this respect, the seasonal changes in nocturnal core temperatures (notably 5-HT regulated) during sleep, assayed by Schwartz *et al.*, (1997) in seasonal affective disorder patients to the changes of seasons, could reflect characteristic seasonal disturbances of mood and energy. Recent findings by Neumeister *et al.*, (1997), however, refute a primary, direct role of serotonergic activity in the pathogenesis of the disorder. Drug-free depressed patients with seasonal affective disorder were given tryptophan depletion in a placebo-controlled, double-blind crossover study. Tryptophan depletion (reducing plasma total and free tryptophan levels by 79.0% and 87.5% respectively) failed to exacerbate the depressive syndrome, nor was winter-depression or seasonal-change associated with any significant alteration of pituitary size (via magnetic resonance imaging): there was a slight increase (+4.0%) for women across seasons, but a slight decrease (−4.3%) for men.

1.4. Posttraumatic Stress Disorder

The links between the material presented in this section and posttraumatic stress disorder (PTSD) are potentially interesting as sufferers report a cluster of anxiety-related symptoms, including hypervigilance, anxiety, fear and recurrent intrusive memories, affecting physiological, behavioural and cognitive response systems (*cf.* Jones and Barlow, 1990). Significantly, as in depressive and anxiety-related illness, PTSD has a higher incidence for female than male sufferers (Kessler *et al.*, 1995), possibly related to the differential susceptibility to depression (Breslau *et al.*, 1995; Kessler *et al.*, 1993; Nolen-Hoeksema and Girgus, 1994); thus, the gender-related, physiological and endocrine considerations outlined by Curzon (Chapter 3) and van Praag (Chapter 5) may undoubtedly be relevant in the mediation of this disorder too. As shown by Breslau *et al.*, (1997a) and Breslau *et al.*, (1997b), the risk for PTSD was twice as high for women than for men, uncontaminated by lifetime preexposure prevalence, number of traumatic events, preexisting comorbidity and family history. Physiological responses resemble neurochemical changes observed after inescapable shock (van der Kolk *et al.*, 1984), *i. e.*, predominantly noradrenergic (Aston-Jones *et al.*, 1994; Perry *et al.*, 1987), but also serotonergic (Kawahara *et al.*, 1993).

Clinical evidence exists for chronic changes to noradrenergic, serotonergic and glucocorticoid systems in PTSD sufferers up to twenty-five years after the trauma

(Southwick *et al.*, 1992). Treatment results indicate that despite the lack of a consistent therapy (Friedman, 1988, 1991), selective 5-HT reuptake inhibitors, and in particular fluoxetine have been shown to be moderately efficacious (Arora *et al.*, 1993; Davidson *et al.*, 1991; McDougle *et al.*, 1991; Nagy *et al.*, 1993; van der Kolk *et al.*, 1994), 5-HT₁ agonists like buspirone have been applied (Schweizer and Rickels, 1994) and monoamine oxidase inhibitors, like brofaromine have not proven successful (Baker *et al.*, 1995) while selective NA uptake inhibitors risk an initial exacerbation of symptoms. The less-than-satisfactory efficacy of MAO_A inhibitors, in humans, like brofaromine and phenelzine in PTSD is somewhat in contrast to documented effects of these compounds in major depression. For instance, Celada *et al.*, (1992) showed that both drugs, administered over six weeks, increased 5-HT concentrations in platelet-free plasma by 254% in depressed patients, where the plasma 5-HT increase was more marked in responders than non-responders. Their results supported other such findings of antidepressant efficacy for these compounds in demonstrating a significant inverse relationship between plasma 5-HT and the Hamilton rating scale for depression (*ibid*). Brofaromine, a reversible and selective MAO_A inhibitor with 5-HT reuptake inhibition properties, was examined at a multicentre, double-blind, placebo-controlled study of 220 depressed patients (Chouinard *et al.*, 1993) and found to be more effective than placebo, and at least as efficacious as several other compounds, including phenelzine, tranylcypromine and imipramine. This pattern of treatment-compound efficacy may serve as one support for viewing PTSD as an anxiety rather than a depressive disorder.

In the interactive monoaminergic analysis of disorders a recent study employing yohimbine, as probe for noradrenergic activity, and meta-chlorophenylpiperazine (mCPP), as probe for serotonergic activity, was performed with PTSD patients ($n = 26$) and healthy subjects ($n = 14$) by Southwick *et al.*, (1997). Eleven (42%) of the PTSD patients experienced yohimbine-induced panic attacks showing significantly more, compared to controls, symptoms for anxiety, panic and PTSD unaccompanied by cardiovascular changes. Eight (31%) PTSD patients experienced m-CPP-induced panic attacks with significant increases in anxiety, panic and PTSD symptoms as well as increases in standing diastolic blood pressure. There was minimal overlap between yohimbine- and m-CPP-sensitive patients. It was concluded that there exist two neurological subgroups of patients with PTSD, one NA-sensitive, the other 5-HT sensitive (*ibid*). Note that the incidence of yohimbine-induced symptoms was lower than in the previous studies of Southwick *et al.*, (1993), 70%, and Bremner *et al.*, (1993), 60%. Chronic stress elevates the behavioural responses to m-CPP (Moreau *et al.*, 1993), and 5-HT_{2C} subreceptors appear to mediate this increased responsivity (Carver *et al.*, 1993). Thus, Southwick *et al.*, (1997) have suggested that a population of PTSD patients may have supersensitive 5-HT_{2C} receptors. Does the PTSD condition represent a trauma-induced receptor supersensitivity? Certainly, some aspects such as progression, seem to resemble the denervation-induced situation. It is likely that before a strategically-complete therapeutic may be embarked upon a number of basic neuropharmacological questions such as these will have to be confronted.

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