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Mood and neuropsychological function in depression: the role of corticosteroids and serotonin

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ABSTRACT

Background. Depressed patients show deficits on neuropsychological tests. However, the basis of these impairments and their relationship with mood disturbance remains unclear.

Methods. This paper reviews the literature regarding the relationship between mood disturbance and neuropsychological impairment in depression and the evidence for serotonergic and hypothalamic–pituitary–adrenal (HPA) axis involvement in these two domains.

Results. Mood disturbance and neuropsychological impairment both occur in depression, but have no clear relationship in time or degree. Impairment of post-synaptic 5-HT_{1A} receptor function may result in the symptom of low mood in depression. Depressed patients demonstrate abnormalities in the functional control of the HPA axis with a resultant hypercortisolaemia, which may impair neuropsychological function. These processes may be related given the extensive interactions between the serotonergic system and the HPA axis.

Conclusions. We argue that there is a neurobiological cause of impaired neuropsychological function in depression. The complex relationship between neuropsychological function and mood may be a result of interactions between the serotonergic system and the HPA axis, particularly in the hippocampus with involvement of serotonergic 5-HT_{1A} and glucocorticoid receptors. A primary dysfunction in these receptors will produce a lowering of mood and neuropsychological impairment respectively. Either dysfunction will result in a secondary impairment of the alternate system. Thus, the affective and psychological changes of depressive illness are likely to have complex relationships in time and severity to one another and the illness as a whole may result from a range of primary aetio-pathologies.

THE BASIS OF DEPRESSIVE NEUROPSYCHOLOGICAL IMPAIRMENT AND ITS RELATIONSHIP WITH MOOD

Depressed patients, of all ages, show deficits on neuropsychological tests, particularly those connected with learning and memory (Elliott *et al.* 1996). Theoretical psychological frameworks have previously been invoked to explain this impairment and it has been suggested that poor motivation and an inability to sustain effort on memory tasks lead to apparent impairment on neuropsychological testing (Cohen *et al.* 1982). However, detailed neuropsychological testing suggests that reduced effort is not the major determinant of impaired performance as the impairments are not simply related to task difficulty (Austin *et al.* 1992). If neuropsychological impairments were secondary to low mood, one would expect the degree of neuropsychological dysfunction to correlate with this. Early studies supported this view (Stromgren, 1977; Cohen *et al.* 1982), but it has been challenged by recent studies (Abas *et al.* 1990; Brown *et al.* 1994; Ilsley *et al.* 1995). In addition, neuropsychological impairments persist in elderly recovered depressives (Abas *et al.* 1990; Ferrier *et al.* 1991; Bahrainian *et al.* 1995) and in

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younger depressed patients selective attentional deficits continue beyond recovery of the disturbance in mood (Trichard *et al*. 1995). These findings support the notion that impaired neuropsychological function is not simply an epiphenomenon of depressed mood and that psychological factors alone are unlikely to account for the neuropsychological impairment. Depressed mood and neuropsychological impairment may occur in parallel as a result of a common neurobiological disturbance in depressive illness. However, we shall argue that the situation is more complex and that these two symptoms may result from disturbances in two different systems between which there is a close interaction.

THE SEROTONERGIC SYSTEM AND DEPRESSION

The monoamine theory of depression (Schildkraut, 1965; Ashcroft *et al*. 1966; Coppen, 1967) is three decades old, but understanding of the pathophysiology of depression and how changes in brain 5-HT systems might influence human behaviour mood cognition remains elusive. Rapidly lowering brain tryptophan concentrations (and hence 5-HT) may lead to a small but significant lowering of mood in healthy subjects (Young *et al*. 1985), though this has been disputed by other groups (Abbott *et al*. 1992; Oldman *et al*. 1994). This discrepancy may be because lowering of mood in response to tryptophan depletion is only apparent in subjects with a vulnerability to depression, such as patients with a strong family history of depression (Benkelfat *et al*. 1994) and euthymic subjects on no treatment but with a history of recurrent depression (Smith *et al*. 1997). The consequences of rapid lowering of 5-HT on the functional activity of the serotonergic system remains to be determined. Deakin & Graeff (1991) have suggested that 5-HT neurones in the raphé that project onto post-synaptic 5-HT_{1A} receptors in hippocampus maintain adaptive behaviours in the face of aversive stimuli. They further hypothesize that a failure of this system leads to helplessness in animals and depression in humans. This model would predict the mood lowering effect of tryptophan depletion in humans is a result of reduced transmission through post-synaptic 5-HT_{1A} receptors in hippocampus.

At present it impossible to study the functional activity of hippocampal 5-HT_{1A} receptors in man. However, the endocrine responses to L-tryptophan are believed to be an indicator of post-synaptic 5-HT_{1A} function, probably in hypothalamus (Smith *et al*. 1991). Five studies have reported a blunted growth hormone (GH) response to L-tryptophan in depressed patients compared to controls (see Power & Cohen, 1992). One prospective study has also shown that the GH response returns to normal on recovery from depression (Upadhyaya *et al*. 1991). Neuroendocrine studies using 'specific' $5HT_{1A}$ agonists have been somewhat less consistent (Cowen, 1996), probably since they also have activity at other receptor sites. However, a study with ipsapirone, a relatively selective probe, demonstrated a reduction in the putative 5-HT_{1A} receptor-mediated responses in depressed patients compared to controls (Lesch *et al*. 1990).

Further support for Deakin & Graeff's model (1991) and a role for hippocampal 5-HT_{1A} receptors comes from studies of the mechanism of action of antidepressants. *In vivo* studies in rodents have demonstrated that a range of antidepressants and electroconvulsive shocks, when given chronically but not acutely, attenuate the function of autoinhibitory 5-HT_{1A} receptors on serotonergic neurones in the raphé nuclei (Goodwin *et al*. 1985; Maj & Moryl, 1992). Attenuation of these autoreceptors enhances serotonergic transmission generally, including to the hippocampus. An overall effect of antidepressants in enhancing 5-HT transmission through hippocampal 5-HT_{1A} receptors has also been put forward by Blier & de Montigny (1994) using *in vivo* electrophysiological techniques in rats, though they argue for differing antidepressant mechanisms.

Rapid depletion of plasma tryptophan, with a presumed decrease in central 5-HT concentrations, causes a return of depressive symptoms in antidepressant treated patients (Delgado *et al*. 1990), supporting a role of 5-HT in the action of antidepressants. Chronic treatment of depressed patients with a variety of antidepressants, including tricyclic antidepressants (TCAs) (Charney *et al*. 1984; Price *et al*. 1989; Cowen *et al*. 1990), MAOIs (Price *et al*. 1985) and selective

serotonin reuptake inhibitors (SSRIs) (Price *et al*. 1989), enhances the prolactin responses to L-tryptophan again suggesting increased neurotransmission at 5-HT_{1A} receptors.

Although SSRIs potently inhibit 5-HT uptake, acute administration of these drugs leads to little or no increase in 5-HT levels at post-synaptic sites (Bel & Artigas, 1992). This is a result of increased levels of 5-HT in the raphé activating somatodendritic 5-HT_{1A} receptors leading to a decrease in the firing rate of the 5-HT neurones. Chronic administration of SSRIs leads to a decrease in the functional activity of somatodendritic 5-HT_{1A} receptors and therefore the firing rate of raphé cells normalizes and for each impulse reaching the terminal there is a larger increase in 5-HT in the synapse due to the continuing blockade of the uptake mechanism (Bel & Artigas, 1993). Co-administration of a 5-HT_{1A} antagonist with an SSRI will therefore lead to an acceleration of the action of antidepressants (Artigas, 1993; Artigas *et al*. 1996), because the effects of the early increase in 5-HT in the raphé, which leads to a reduction of the firing rate of the 5-HT neurones, will be blocked. Support for this acceleration comes from two double blind controlled studies (Perez *et al*. 1997; Tome *et al*. 1997), although there has been one negative result (Berman *et al*. 1997). It will be of great interest to see the effect of more selective 5-HT_{1A} antagonists than pindolol when these become available.

In summary, there is evidence from both human and animal studies supporting the view that an impairment of post-synaptic 5-HT_{1A} function leads to a lowering of mood and that antidepressant treatments reverse this impairment.

THE SEROTONERGIC SYSTEM AND NEUROPSYCHOLOGICAL IMPAIRMENT

The role of the 5-HT system in neuropsychological function is unclear. In rats, inhibition of 5-HT synthesis improves learning (Brody, 1978), but in mice the opposite effect is seen (Valzelli & Pawlowski, 1979). Post-training administration of 5-HT antagonists to mice enhances learning and memory (Altman & Normile, 1986), though others have disputed this (Kubo *et al*. 1988). McEntee & Crook (1991) argue that stimulation of 5-HT activity impairs learning and memory, while impairment of 5-HT neurotransmission enhances it. However, many of the studies reviewed by McEntee & Crook used non-selective 5-HT ligands and 5-HT may have varying effects at different receptor subtypes.

Little is known about the role of 5-HT in cognition in young healthy or depressed subjects. Treatment with the 5-HT_{2C} agonist M-chlorophenylpiperazine has been found to impair recent memory in Alzheimer's disease patients and elderly controls, but most significantly in the former (Lawlor *et al*. 1989*a*, *b*). Depletion of the 5-HT precursor tryptophan (and hence brain 5-HT levels) in healthy volunteers produces mild selective neuropsychological impairments particularly affecting the retrieval of learnt material (Park *et al*. 1994). However, the 5-HT receptors involved in this effect are unclear. No evidence exists that post-synaptic 5-HT_{1A} receptors play a direct role in the genesis of the neuropsychological impairment in depression.

THE HPA AXIS AND DEPRESSION

The HPA axis has been hypothesized as being of aetiological importance in depressive illnesses (Murphy, 1991; Dinan, 1994). Many depressed patients have a loss of normal diurnal variation of plasma cortisol with hypercortisolaemia seen throughout the day (Sachar *et al*. 1973; Murphy, 1991). Imaging studies demonstrate an enlargement of the adrenal cortex in depressed patients compared to healthy subjects (Nemeroff *et al*. 1992; Rubin *et al*. 1996). This hyperplasia correlates with cortisol levels in depression (Nemeroff *et al*. 1992), and, along with the normalization of cortisol levels, appears to disappear following recovery (Rubin *et al*. 1996). MRI studies have also revealed an enlargement of the pituitary gland in depressed subjects (Krishnan *et al*. 1991; Axelson *et al*. 1992).

Abnormality in the regulatory feedback mechanism may explain the overactivity of the HPA axis seen in depressed patients, since a lack of dexamethasone suppression of cortisol secretion is observed (Carroll *et al*. 1981; Rush *et al*. 1996). However, the specificity of this test has been called into question (Coppen *et al*. 1983). Certainly non-suppression is also seen in patients with schizophrenia (Munro *et al*. 1984), dementia (Spar & Gerner, 1982), alcohol problems (Costa *et al*. 1996), anorexia nervosa (Gerner &

Gwirtsman, 1981) and bulimia nervosa (Mitchell *et al*. 1984; O'Brien *et al*. 1988) with little correlation to co-morbid depressive symptoms. However, the DST continues to be of some interest in that it is reported that the DST tends to normalize with effective treatment (Carroll, 1986) and continued non-suppression is associated with a poorer prognosis including an increased risk of relapse (Nemeroff & Evans, 1984).

Impaired feedback control of the HPA axis may be due to an abnormality in corticosteroid receptor plasticity. Despite a hypercortisolaemia, depressive patients generally do not demonstrate Cushingoid features, possibly because of a reduction in the function of corticosteroid receptors. Support for this idea has come from a study of β-endorphin/β-lipotrophin secretion. In control subjects intravenous hydrocortisone causes an increased secretion of these pituitary peptides, but this is attenuated in depressed subjects (Young *et al*. 1991). In addition in healthy subjects, metyrapone, which inhibits cortisol synthesis, causes an up-regulation of lymphocyte corticosteroid receptor levels, but this response is absent in depressed patients (Rupprecht *et al*. 1991). The primary abnormality in depression may thus be an impairment of corticosteroid receptor function (Barden *et al*. 1995).

Raised corticotropin releasing hormone (CRH) concentrations in cerebrospinal fluid (Banki *et al*. 1992) together with a blunted ACTH response to CRH in depressed patients (Nemeroff *et al*. 1988) have led to hypotheses of abnormalities in hypothalamus being central to depression (Nemeroff, 1996). Animal studies have demonstrated that CRH administration can lead to decreased appetite, disrupted sleep and psychomotor alterations (Kalin *et al*. 1983; Heinrichs *et al*. 1995) leading to the proposal that excess CRH acts on extra-pituitary sites to produce some of the symptoms of depression (Nemeroff, 1996). However, other than findings of high rates of depression in Cushing's syndrome patients (Cohen, 1980; Kelly *et al*. 1983), there is little evidence (or hypothesized mechanisms) that raised concentrations of corticosteroids mediate a lowering of mood in depression. Acute administration of cortisol to depressed patients causes a transient elevation in mood (Goodwin *et al*. 1992) and so the relationship between HPA axis abnormalities and low mood in depression is unclear.

Antidepressant treatments may normalize HPA axis function via an indirect effect of actions on serotonergic systems, given the multiple interactions between 5-HT and the HPA axis (discussed below). Chronic treatment with antidepressants has also been demonstrated to have effects on corticosteroid receptor (specifically the glucocorticoid type – see below) mRNA levels in rat brain (Pepin *et al*. 1989), an effect mirrored by increases in corticosteroid receptor binding sites (Reul *et al*. 1994). These effects are seen in cultured fibroblast cells in the absence of serotonergic neurones (Pepin *et al*. 1992). An increase in central corticosteroid receptors would lead to increased negative feedback on the HPA axis and consequently decreased cortisol levels. However, antidepressants differ in their effects on corticosteroid receptor numbers (Seckl & Fink, 1992; Budziszewska *et al*. 1994), and the original findings have not been replicated by all groups (Budziszewska *et al*. 1994).

THE HPA AXIS AND NEUROPSYCHOLOGICAL IMPAIRMENT

In rats there is an association between high corticosterone levels and impairments in memory and learning (Sapolsky *et al*. 1986). Corticosteroid antagonists also impair spatial learning in rats (Oitzl & De Kloet, 1992). These discrepant findings may reflect a 'bell-shaped' dose–response curve frequently seen with corticosteroids (see below – Sapolsky, 1992). High levels of endogenous corticosteroids in Cushing's disease are associated with significant impairments of memory (Starkman & Schteingart, 1981), which correlate with the plasma level of cortisol and ACTH (Starkman *et al*. 1986). Neuropsychological difficulties are reversed by treatment of the underlying disorder causing the Cushing's syndrome (Mauri *et al*. 1993). Healthy volunteers given corticosteroids show neuropsychological impairments on a range of neuropsychological tests (Carpenter & Gruen, 1982; Reus, 1984; Wolkowitz *et al*. 1990; Newcomer *et al*. 1994; Young *et al*. 1994*b*), some of which, such as errors of commission in tests of learning, parallel the findings in depressed patients (Wolkowitz *et al*. 1990). Healthy volunteers subjected to stress exhibit raised cortisol levels

with a correlated impairment in declarative memory (Kirschbaum *et al*. 1996). In the elderly, there is an association between HPA axis dysfunction and cognitive impairment (O'Brien *et al*. 1994). It is argued that this may be the result of glucocorticoid induced hippocampal cell death (Sapolsky *et al*. 1986) and that this may be an important mechanism of neuropsychological impairment and not only in normal ageing but in dementia and depression in old age (O'Brien, 1997).

In non-elderly depressed patients the link between corticosteroids and cognition is less clear. Rubinow *et al*. (1984) reported a positive correlation between neuropsychological impairment and urinary cortisol and several groups have found greater neuropsychological impairment in depressives who do not suppress cortisol in response to dexamethasone, compared with those who do (Brown & Qualls, 1981; Reus, 1982; Winokur *et al*. 1987; Wolkowitz *et al*. 1990). This, however, has been disputed (Caine *et al*. 1984; Silberman *et al*. 1985). Wauthy *et al*. (1991) found a significant correlation between neuropsychological impairment and cortisol levels and have suggested that some of the previous discrepancies may be the result of different methods of assessing HPA function. An alternate explanation relates to the neuropsychological tests used. A recent study has suggested that, in depressed patients, there is a positive correlation between plasma cortisol and effortful processing but a negative correlation with automatic processing (Bemelmans *et al*. 1996). Studies to date have used a whole variety of different neuropsychological tests involving varying degrees of automatic and effortful processing. The few studies that have correlated neuropsychological function with cortisol levels directly have involved small numbers of patients. There is, therefore, a need for further studies examining the relationship between neuropsychological impairment and HPA axis function in depressed patients using investigations other than the dexamethasone suppression test and employing varied and precise neuropsychological tools.

In summary, there is support for the notion that the neuropsychological impairment seen in depression is as a result of the concomitant hypercortisolaemia. If this is the case and the lowering of mood is primarily as a result of an impairment of transmission through post-synaptic 5-HT_{1A} receptors, how are these two sets of symptoms linked in depression?

SEROTONERGIC–HPA AXIS INTERACTIONS

There is a large degree of interaction between corticosteroids and 5-HT (reviewed by Chaouloff, 1993; McAllister-Williams & Young, 1998). Central to these interactions are hippocampal 5-HT_{1A} receptors (McAllister-Williams & Young, 1998).

Serotonergic effects on HPA axis function

Serotonergic mechanisms exert an excitatory influence on the entire HPA axis (Chaouloff, 1993). For example, local application of 5-HT into the hypothalamus produces a dose-dependent increase in CRH release (Holmes *et al*. 1982; Nakagami *et al*. 1986; Calogero *et al*. 1989). 5-HT_{2A} and 5-HT_{2C} receptors are primarily involved in the mechanism of this 5-HT mediated CRH release, although 5-HT_{1A} receptors may also be involved (Calogero *et al*. 1989). 5-HT has also been shown to elicit ACTH release directly from the pituitary (Spinedi & Negro-Vilar, 1983) by activation of 5-HT_{1A} and 5-HT_{2A} receptors (Calogero *et al*. 1990; Rittenhouse *et al*. 1994).

5-HT also has effects on corticosteroid receptors. Neurotoxic lesions of serotonergic neurones in rats leads to a reduction of corticosteroid receptor mRNA expression in hippocampus (Seckl & Fink, 1991), while the application of 5-HT increases corticosteroid receptor sites (Mitchell *et al*. 1992). In rat hippocampus this effect is mediated by 5-HT_{1A} receptors and involves an increase in corticosteroid receptors of the mineralocorticoid type (Budziszewska *et al*. 1995 – see below). Thus, the 5-HT system acting through 5-HT_{1A} receptors may be able to modulate the negative feedback control of the HPA axis.

Corticosteroid effects on serotonergic function

Corticosteroids play a modulatory role on central serotonergic function. There is a complex relationship between the amplitude of the corticosteroid stimulus (or the dose of exogenously administered corticosteroid) and the response of the 5-HT system. In many circumstances this response is 'bell-shaped' illustrating a key role

of corticosteroids in maintaining homeostasis (Sapolsky, 1992) and results from the activation of two populations of corticosteroid receptors, mineralocorticoid (MR) and glucocorticoid (GR). MRs are found in the limbic system (including the hippocampus), while GRs are widely distributed, but enriched in the hippocampus, hypothalamus and in the cell bodies of monoaminergic (including serotonergic) neurones (Reul & de Kloet, 1985; Harfstrand *et al.* 1986; Aronsson *et al.* 1988). MRs display a 10-fold higher affinity for corticosterone relative to GRs. This results in high MR occupancy, even in conditions of low circulating levels of corticosterone. GRs, conversely, are only extensively occupied at times of high corticosterone levels, such as at the time of peak circadian levels and during stress. The expression of GRs and MRs shows a diurnal variation, with both receptor subtypes being more prominent at the nadir of corticosteroid levels (Holmes *et al.* 1995*a*). Many experiments involving the administration of corticosteroids are difficult to interpret because the degree of corticosteroid receptor occupancy by endogenous corticosteroids prior to administration of the exogenous compound is unclear.

Corticosteroids have a variety of effects on serotonergic metabolic pathways. These include inducing tryptophan catabolism through effects on hepatic tryptophan pyrrolase activity (Knox & Auerbach, 1955), enhancing precursor availability (Neckers & Sze, 1975), and increasing 5-HT synthesis by affects on tryptophan hydroxylase (Azmitia & McEwan, 1969). However, these effect appear to primarily affect 5-HT turnover, rather than levels *per se* (Azmitia *et al.* 1970).

Many groups have observed increases of 5-HT_{1A} receptor binding, mainly in hippocampus, following adrenalectomy that are reversed by administration of corticosterone (de Kloet *et al.* 1986; Martire *et al.* 1989; Burnet *et al.* 1992; Mendelson & McEwen, 1992*a*; Chalmers *et al.* 1993; Kuroda *et al.* 1994; Tejani-Butt & Labow, 1994; Chalmers *et al.* 1994; Zhong & Ciaranello, 1995; Nishi & Azmitia, 1996; Le Corre *et al.* 1997). This effect of corticosterone is mediated via GRs (Chalmers *et al.* 1994) influencing 5-HT_{1A} receptor transcription (Zhong & Ciaranello, 1995; Nishi & Azmitia, 1996). Adrenalectomy appears to have an opposite effect of decreasing raphé 5-HT_{1A} receptor binding sites (Tejani-Butt & Labow, 1994). In non-adrenalectomized animals, Mendelson & McEwen (1991) have shown that chronic stress produces elevated corticosteroid levels and a transient increase in hippocampal 5-HT_{1A} receptors, through chronic exogenous corticosterone causes a more prolonged down regulation (Mendelson & McEwen, 1992*b*). A complication regarding previous findings related to 5-HT_{1A} receptors is that two recent studies have shown that adrenalectomy increases 5-HT_7 receptor mRNA in hippocampus (Le Corre *et al.* 1997; Yau *et al.* 1997) and these receptors have a similar pharmacology to the 5-HT_{1A} subtype (Tsou *et al.* 1994; To *et al.* 1995). Changes in 5-HT receptors, as a result of alterations in HPA axis activity, may be of physiological relevance. In rats, repeated stress has been found to decrease hippocampal 5-HT_{1A} receptor numbers (Watanabe *et al.* 1993; Flugge, 1995), though this is not a universal finding (Holmes *et al.* 1995*b*), possibly reflecting different methods of inducing stress in animals.

In dorsal raphé GR agonists cause a reduction in the functional activity of 5-HT_{1A} autoreceptor mediated inhibition of cell firing (Lanfumey *et al.* 1993; Laaris *et al.* 1995), an effect likely to be on receptor–effector coupling since there is no change in the number of 5-HT_{1A} receptors (Laaris *et al.* 1995). Hippocampal single cell electrophysiological studies have demonstrated that MR activation decreases post-synaptic 5-HT_{1A}-mediated hyperpolarization (Joëls *et al.* 1991; Beck *et al.* 1996), while selective GR agonists block this MR effect, though GR agonists alone have no effect (Joëls & de Kloet, 1992). Thus, the effects of corticosteroids on post-synaptic 5-HT systems vary with circadian variation in plasma levels and the relative balance between MR and GR activation (Joëls & de Kloet, 1994). *In vivo* models of somatodendritic 5-HT_{1A} function (hyperphagia in rats, Haleem, 1992, and hypothermia in rats and mice, Young *et al.* 1992, 1994*a*) are attenuated by corticosterone administration, in agreement with electrophysiological data (Lanfumey *et al.* 1993; Laaris *et al.* 1995). Putative post-synaptic 5-HT_{1A} mediated behaviours may be reduced (rat forepaw treading, Haleem, 1992) or enhanced (rat open field activity, Berendsen *et al.* 1996), probably reflecting varying degrees or

MR and GR activation. Hydrocortisone has been shown to attenuate buspirone induced cortisol release and hypothermia in man (Young *et al*. 1994*c*) and the GH response to L-tryptophan (Lunn *et al*. 1996). These results suggest that corticosteroids have similar effects on post-synaptic 5-HT_{1A} receptors in man as in rodents.

It, therefore, appears that inhibitory somatodendritic 5-HT_{1A} receptor function is reduced by GR activation, leading to an enhancement of 5-HT neurotransmission generally, while the effects of corticosteroids on post-synaptic receptor function depends on the level of circulating corticosteroid differentially activating MR or GR receptors.

The role of the hippocampus in serotonergic system–HPA axis interactions

The hippocampus inhibits most aspects of HPA activity including basal and circadian peak secretion as well as the onset and termination of responses to stress (Jacobson & Sapolsky, 1991). The removal of its input reduces, but does not abolish, the efficacy of corticosteroid inhibition (Sapolsky *et al*. 1990). However, the hippocampus is distinguished from other feedback sites, including the hypothalamus and pituitary, by the high expression of both MRs and GRs (Jacobson & Sapolsky, 1991), enabling it to modulate the HPA axis over a wide range of corticosteroid levels. Hippocampal MRs mediate inhibition of the HPA axis (Dallman *et al*. 1989) and basal activity may be controlled by this mechanism. The increased response of the HPA axis to stress after hippocampal damage or antagonism of hippocampal GRs (Feldman & Conforti, 1980; Sapolsky *et al*. 1984) suggests that these receptors also contribute significantly to HPA axis regulation.

Post-synaptic 5-HT_{1A} receptors influence HPA axis activity at a number of sites (see above). However, we are unaware of any work that has investigated the effect of selectively activating hippocampal 5-HT_{1A} receptors on HPA function. Such studies are of importance given the hypothesized action of antidepressants to enhance transmission through this receptor. Given that activation of 5-HT_{1A} receptors in hippocampus cause a hyperpolarization (Andrade & Nicoll, 1987; Colino & Halliwell, 1987) and thus inhibition of post-synaptic cells, it might be expected that activation of hippocampal 5-HT_{1A} would reduce HPA activity. This hypothesis remains to be tested. However, the evidence suggests that the integration of serotonergic–HPA axis interactions in hippocampus may be particularly important.

THE NEUROBIOLOGICAL INTERRELATIONSHIP BETWEEN LOW MOOD AND NEUROPSYCHOLOGICAL IMPAIRMENT IN DEPRESSION

The nature of the neurobiological impairment underlying depressive illness remains elusive. However, there is evidence that abnormalities in either the serotonergic system or the HPA axis can lead to some of the features of depression, including low mood and neuropsychological impairment. The evidence is less clear that an abnormality in one system alone can explain the full extent of the clinical features of depressive illness. Subtle abnormalities in the interactions between the HPA axis and the serotonergic system may lead to profound alterations in the functioning of both systems, and it may be this that results in a range of symptoms. One of the challenges we are now faced with is in translating the knowledge of 5-HT–HPA interactions into increased understanding of physiological and pathophysiological processes in man.

Hippocampal 5-HT_{1A} receptors are central to the myriad of 5-HT–HPA interactions. We suggest that an impairment of serotonergic transmission through this receptor may underlie the low mood seen in depression. In addition, the reduced activation of hippocampal 5-HT_{1A} receptors may decrease the inhibitory control of the HPA axis mediated by the hippocampus leading to hypercortisolaemia and a neuropsychological impairment.

An alternative hypothesis is that the primary neurobiological disturbance in depression is an abnormality of GRs (Dinan, 1994; Barden *et al*. 1995). If the function of GRs is decreased, the feedback control of the HPA axis would be impaired leading to a hypercortisolaemia, and in turn may lead to neuropsychological dysfunction. Reduced functional activity of GRs may increase the autoinhibitory action of somatodendritic 5-HT_{1A} receptors, decrease 5-HT_{1A} receptor numbers in hippocampus, and allow an increased MR attenuation of hippocampal

5-HT_{1A} receptor activation. Thus, the net serotonergic transmission through 5-HT_{1A} receptors in hippocampus would be reduced (by several mechanisms) with a probable lowering of mood. These hypotheses can be tested and such experiments may lead to more rational therapy.

Neuropsychological impairment in depression is not the epiphenomenon as it has sometimes been regarded. Given that there is no correlation between the severity of mood disturbance and neuropsychological impairment in depressive illness, it seems unlikely that one is simply the consequence of the other. Both may occur completely independently of one another. Alternatively, there may be a neurobiological explanation for their complex relationship. We suggest an explanation may lie in the fact that disturbances of serotonergic–HPA axis interaction might occur through several mechanisms and at different rates. Further studies are required to investigate serotonergic and HPA axis functions in tandem in depressed patients, examining how these relate to both low mood and neuropsychological impairment. Given the confounding effects of antidepressant medication on mood, serotonergic function (Blier & de Montigny, 1994), neuropsychological function (Knegtering *et al.* 1994; Bemelmans *et al.* 1996) and HPA axis function (Barden *et al.* 1995) it is imperative that these studies are conducted in drug-free subjects. Well designed studies of this nature seem likely to shed further light on the pathophysiology of depressive illnesses.

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