*Pharmacology Biochemistry & Behavior*, Vol. 29, pp. 819–820. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

# $5HT_2$ Receptors, Depression and Anxiety

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DEAKIN, J. F. W. *$5HT_2$ receptors, depression and anxiety.* PHARMACOL BIOCHEM BEHAV 29(4) 819–820, 1988.— The distinction between non-psychotic depressive illness and anxiety states is blurred. Large scale trials in the neuroses indicate that benzodiazepines are ineffective in depression, and transiently and partially effective in anxiety. In contrast, tricyclic antidepressants are effective in both. All effective antidepressants decrease $5HT_2$ receptors number and this may mediate antidepressant efficacy. Our studies indicate that reduction of $5HT_2$ relative to $5HT_1$ neurotransmission would reverse the neuroendocrine abnormalities we have described in depression. Reduced $5HT_2$ neurotransmission may also be a mechanism of anxiolytic action in view of 5HT theories of punishment. There is clinical evidence for anxiolytic and antidepressant action of selective $5HT_2$ antagonists.

$5HT_2$ receptors Depression Anxiety Antidepressant drugs Tryptophan Prolactin Growth hormone

IT is a prevalent belief that anxiety and depressive neuroses are distinct conditions. This view has been fostered by the development and marketing of drugs which are effective in alleviating anxiety states—the benzodiazepines, and of other drugs effective in treating depression. In fact (a) few studies have demonstrated a natural boundary or point of rarity between anxiety and depressive states, (b) the therapeutic utility of benzodiazepines in anxiety states is less than once thought, and (c) tricyclic antidepressants are effective anxiolytics. Several studies illustrate these points.

Goldberg and colleagues [3] investigated neurotic symptoms in 238 patients attending their general practitioners with psychological problems. They were unable to demonstrate clearly separate groups of predominantly anxious and predominantly depressed patients. Latent trait analysis of symptom patterns showed that two statistically generated dimensions accounted for almost all the variance. One dimension had highest loadings with (was measured best by) anxiety symptoms and the other with depressive symptoms. However, the two dimensions were highly correlated ($r=0.7$) and anxiety symptoms were significant measures of the depression dimension and depressive symptoms had significant loading on the anxiety dimension. Other multivariate statistical studies have also failed to demonstrate discrete clinical categories within the neuroses. It is of course possible to make rules for the diagnosis of anxiety and depressive states as in DSMIII but the question is whether such rules reflect reality.

The reason that it is possible to discern separate dimensions of anxiety and depression may be that they have distinct psychological and neurochemical bases. Anxiety has been conceptualized as an abnormal sensitivity (or conditionability) to aversive stimuli which may be mediated by the excessive operation of neurochemical systems, including 5HT neurones, involved in the detection and behavioural consequences of such stimuli. Behavioural formulations of depression stress the loss of efficacy of rewards which may be mediated by defective functioning in catecholamine reward pathways. The reason that the two dimensions are correlated may be that lost efficacy of rewards and sensitivity to punishment are consequences of each other and that 5HT and catecholamine systems operate in reciprocal antagonism to each other.

In view of these studies we should not be surprised that tricyclic antidepressant drugs ameliorate both anxiety and depression. Klein [6] showed that imipramine was effective in patients with panic attacks. Recent studies suggest tricyclics may have a more general anxiolytic action. In a study of 178 neurotic out-patients, Johnstone [4] and colleagues compared the efficacy of amitriptyline, diazepam, their combination and placebo in a four week trial. The placebo response was large and few significant treatment effects on the various ratings emerged. Of the eight significant treatment effects, seven concerned amitriptyline. The therapeutic effects of amitriptyline were as great in the predominantly anxious as in the predominantly depressed. The presence of predominant anxiety symptoms did not predict responsiveness to diazepam. Similarly Kahn [5] *et al.* compared imipramine, chlordiazepoxide and placebo in neurotic out-patients. They analysed the results for the 156 anxious patients separately and found that the beneficial effects of chlordiazepoxide were few and confined to the first two weeks of treatment. In contrast, imipramine produced a sustained and more complete remission of anxiety.

Several antidepressants are effective $5HT_2$ receptor antagonists (e.g., amitriptyline, clomipramine) and all established antidepressants share the ability to decrease $5HT_2$ receptor binding after repeated administration. These phar-

macological actions may be relevant to their anxiolytic effects. Animal experiments suggest that 5HT neurones mediate the effects of punishment on behaviour. In some experimental models of anxiety the selective $5HT_2$ receptor antagonist ritanserin has anxiolytic effects. Furthermore, this drug has equivalent therapeutic effects to lorazepam in a placebo controlled trial in patients with anxiety. The fact that in animal models ECT increases $5HT_2$ receptor binding sites has been seen as a difficulty for the idea that antidepressant-induced down-regulation of $5HT_2$ receptors is involved in the efficacy of antidepressant drugs. However, antidepressants and ECT may have different mechanisms of action since the efficacy of ECT is restricted to severer forms of depression, in some studies to psychotic or delusional depressive illnesses. The latter may be quite distinct illnesses, with different aetiological mechanisms from other forms of depression. $5HT_2$ receptor down-regulation could thus be relevant to anxiolytic and antidepressant effects of drugs in non-psychotic depressive illnesses. It is intriguing that ECT is of doubtful efficacy in neurotic forms of depression and that the presence of anxiety symptoms is thought to predict a poor response to ECT. Perhaps this is because ECT does not down-regulate $5HT_2$ receptors. If $5HT_2$ receptor down-regulation is relevant to antidepressant efficacy of drugs then selective $5HT_2$ antagonists should have antidepressant effects. Evidence from placebo controlled trials suggests that indeed ritanserin has antidepressant actions in non-psychotic depressives.

Our neuroendocrine studies in depression also suggest that $5HT_2$ receptor down-regulation may be relevant to antidepressant activity. Infusions of the precursor tryptophan (LTP) evoke increased pituitary secretion of growth hormone (GH) and prolactin (PRL). The responses are clearly attenuated in depressed patients. The non-selective 5HT antagonist metergoline blocks PRL responses to LTP whereas ritanserin enhances them. We have suggested that the response is mediated by $5HT_1$ receptors and that effects of LTP on $5HT_2$ receptors antagonize the PRL response, hence the ability of ritanserin to enhance PRL response to LTP. In view of the effects of ritanserin, the ability of amitriptyline and desmethylimipramine to restore blunted PRL responses to LTP in depression [1,2] may be due to down-regulation of $5HT_2$ receptors.

The following theoretical account attempts to integrate the evidence discussed above. Anxiety and depression are separate but correlated dimensions of behaviour. Excessive neurotransmission through $5HT_2$ receptors enhances the behavioural effects of aversive stimuli and gives rise to symptoms of anxiety. There is secondary inhibition of catecholamine reward pathways, reducing the behavioural effects of rewards and giving rise to the symptoms of depression. Antidepressants inhibit $5HT_2$ neurotransmission giving rise to anxiolytic and secondary antidepressant effects. Antidepressants may also exert direct antidepressant effects through actions on catecholamine pathways. In contrast, ritanserin is a pure $5HT_2$ antagonist and may be expected to have primary anxiolytic effects with indirect antidepressant actions.

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