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5-HT-Related Drugs and Human Experimental Anxiety

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ZUARDI, A. W. *5-HT-related drugs and human experimental anxiety*. NEUROSCI BIOBEHAV REV **14**(4) 507–510, 1990.— Clinical observations and double-blind studies demonstrated an anxiolytic effect of drugs that facilitate serotonergic transmission on several anxiety disorders. There is a latency of several weeks for their anxiolytic effect to take place. There may be, in addition, a biphasic effect, i.e., an acute anxiogenic effect followed by an anxiolytic effect after chronic use. In addition, acute administration of m-chlorophenylpiperazine (MCPP), an agonist of 5-HT-1 receptors, increased anxiety in normal volunteers as well as in patients with panic or obsessive-compulsive disorders. Studies in healthy volunteers have been performed in our laboratory to explore the acute effect on human anxiety of drugs that selectively influence 5-HT neurotransmission. We observed that acute administration of chlorimipramine enhanced the rise in anxiety induced in healthy volunteers by speaking in front of a video camera. With a similar experimental design, we also demonstrated an anxiogenic effect of metergoline, a nonselective 5-HT receptor blocker. It is suggested that the proanxiogenic effect of acute administration of 5-HT uptake inhibitors may be due to impaired 5-HT neurotransmission.

Serotonin Human anxiety Experimental anxiety

HUMAN anxiety may represent a set of phenomena not necessarily correlated with a single biological substrate. Anxiety may be a normal emotion in man, a symptom observed in different physical diseases, or a separate pathological condition. The nosological classification of mental disorders made by the American Psychiatric Association (1) distinguished several types of anxiety disorders, among them generalized anxiety disorder (GAD); panic disorder (PD) with or without agoraphobia; obsessive-compulsive disorder (OCD); and other phobias (single and social). For the first three anxiety disorders there is strong evidence of serotonergic involvement (20), chiefly with respect to the therapeutic response observed with the use of drugs that interfere with serotonergic systems.

As regards GAD, a new class of drugs related to serotonin has proved to be as effective as the benzodiazepines (27). The first of these drugs, buspirone, has a high affinity for 5-HT-1A receptors, in addition to its dopaminergic effects. Two buspirone analogs therapeutically effective on GAD, namely gepirone and ipsapirone, are even more specific for the 5-HT-1A receptor than the parental drug (8).

In PD, the therapeutic effect of drugs that inhibit serotonin reuptake such as chlorimipramine (22), zimelidine (12), fluvoxamine (11) and fluoxetine (15) is well known. Certain drugs therapeutically effective on PD, such as imipramine and chlorimipramine, inhibit the reuptake of both serotonin and noradrenaline. However, their therapeutic effect seems to be related to serotonergic blockade, since a double-blind study has shown a decrease in the frequency of panic attacks with fluvoxamine, a specific inhibitor of serotonin reuptake, but not with maprotiline, a specific inhibitor of noradrenaline reuptake (10).

In OCD, the drug most extensively studied has been chlorimipramine. From the initial observations (30) to more recent controlled studies (2, 18, 23, 29), the therapeutic effect of chlorimipramine on OCD has been consistently observed. This effect was not observed with other antidepressants such as nortriptyline (29), amitriptyline (2) and desmethylimipramine (32). In addition, clinical improvement of this disorder has been obtained with drugs that inhibit serotonin reuptake with more specificity than chlorimipramine, such as zimelidine (21), fluoxetine (13) and fluvoxamine (14).

Thus, we conclude that drugs that seemingly facilitate serotonergic neurotransmission relieve the symptoms of GAD, PD and OCD, even though their effects are not necessarily the same in the various pathologies. In this respect, preliminary results have suggested that buspirone is less effective than serotonin reuptake blockers in PD (28).

Curiously, however, the serotonin reuptake blockers as well as buspirone-like drugs show a latency of 2 to 6 weeks for the therapeutic effect to occur, depending on the type of anxiety disorder. In addition, some experimental results have shown a worsening of the anxiety symptoms at the beginning of treatment, especially with the serotonin reuptake blockers in PD (20). Thus, an anxiogenic effect of acute drug administration may occur.

This suggestion is strengthened by the finding that the 5-HT-1 receptor agonist, m-chlorophenylpiperazine (MCPP), causes an anxiogenic effect when acutely administered. Table 1 summarizes the acute effects of MCPP on normal volunteers and on patients with panic or obsessive-compulsive disorders. In most studies, acute MCPP administration increased subjective anxiety as well as physiological indexes such as plasma levels of cortisol, prolactin and growth hormone. In some studies on normal volunteers, there was little or no increase in anxiety, a fact possibly related to the dose used. However, MCPP doses that were unable to provoke alterations in normal controls (or only induced smaller effects on

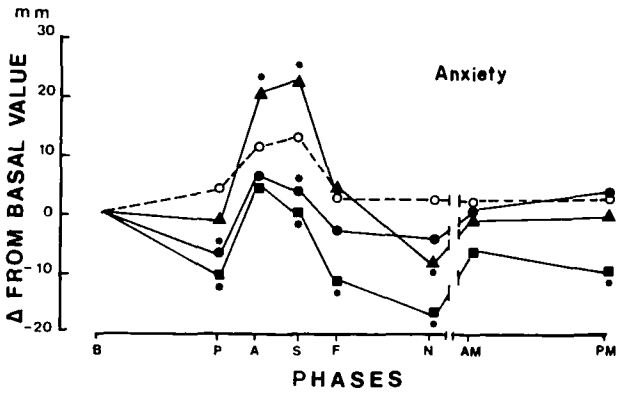

FIG. 1. Effect of chlorimipramine (▲ 25 mg), maprotiline (■ 50 mg), lorazepam (● 1 mg) and placebo (○) on subjective anxiety of health volunteers submitted to a simulated public speaking test, assessed by the visual analog mood scale (VAMS) of Norris. Points in the figure are the means of 10 volunteers. Measures were taken before drug intake (B) and at prestress (P), anticipation of public speaking (A), speech performance (S), poststress (F), in the evening (N), and on next day morning (AM) and afternoon (PM). The medication was given immediately after B. The asterisks indicate significant differences from placebo, $p<0.05$. For sake of clarity, the time scale in the abcissa was expanded during the SPS test (P-S).

them), showed an anxiogenic effect on patients with PD or OCD (19,34). These results suggest that patients may be more sensitive to the acute effects of MCPP, in agreement with hypotheses that the increase in anxiety may be related to a supersensitivity of 5-HT receptors (19,33). In any case, MCPP also induces anxiety in healthy volunteers (6, 7, 31).

In order to evaluate whether acute administration of a 5-HT reuptake blocker could induce anxiety in normal volunteers, we tested the effects of chlorimipramine (25 mg) on anxiety induced by speaking in front of a video camera. Considering that chlorimipramine and chiefly its metabolite, desmethylchlorimipramine, also blocks the reuptake of noradrenaline, another group of volunteers was treated with maprotiline (50 mg), a selective noradrenaline reuptake blocker that apparently exerts little or no influence on central 5-HT neurotransmission. Two additional groups of volunteers received lorazepam (1 mg) and placebo, respectively. The study was double blind and the effects of the drugs were assessed by means of self-rating scales and physiological measures. We observed that chlorimipramine facilitated the increase in anxiety scores caused by simulated public speaking, whereas lorazepam and maprotiline decreased anxiety (Fig. 1). This effect of chlorimipramine is not likely to be related to noradrenaline, since maprotiline caused an opposite effect on anxiety. Thus, the proanxiogenic effect of acute chlorimipramine administration may be due to interference with serotonergic neurotransmission (17).

The last result supports the suggestion of a biphasic effect of 5-HT uptake inhibitors, i.e., an acute anxiogenic effect followed by an anxiolytic effect after chronic use. However, the relationship between drug-induced changes in anxiety and interference with serotonergic neurotransmission cannot be easily established. These drugs simultaneously affect autoreceptors and postsynaptic receptors. As indicated by the experimental evidence reviewed by Marsden (24), activation of somatodendritic autoreceptors reduces the firing rate of 5-HT raphe neurons and, as a consequence, decreases the release of 5-HT in terminal regions. In addition, autoreceptors situated on nerve terminals also are involved in the regulation of 5-HT release. Furthermore, postsynaptic 5-HT receptors in terminal regions belong to at least two subtypes, 5-HT-1A and 5-HT-2. Thus, the end effect of 5-HT uptake inhibitors on serotonergic transmission will depend on the balance among these multiple pharmacological actions. However, it is likely that the resultant consequence is not the same following acute as opposed to chronic drug administration.

TABLE 1

MCPP ACUTE EFFECT IN HEALTHY VOLUNTEERS AND PATIENTS WITH PANIC AND OBSESSIVE-COMPULSIVE DISORDER

Subjects	Dose (mg/kg)	Effect: Anxiety	Effect: Neuroendocrine*	References
Healthy Volunteers	0.25 PO	0	▲ Cortisol	19
	0.5 PO	△	▲ PRL, Cortisol	26
	0.5 PO	△	▲ PRL, Cortisol	34
	0.75 PO	—	▲ PRL, Cortisol; 0-GH	25
	0.1 IV	▲	—	31
	0.1 IV	▲	▲ PRL, Cortisol, GH	7
	0.1 IV	▲	▲ PRL, Cortisol, GH	6
Panic Disorder	0.25 PO	▲	▲ Cortisol†	19
	0.1 IV	▲	—	31
	0.1 IV	▲	▲ PRL, Cortisol, GH	6
Obsessive-Compulsive Disorder	0.5 PO	▲†	▲ PRL	34
	0.5 PO	▲	▲ PRL	33
	0.1 IV	▲	▲ PRL, Cortisol, GH	6

△ little increase; ▲ significant increase; 0 unchanged; — not evaluated.
*Plasma levels of cortisol, prolactin (PRL) and growth hormone (GH).
†Significantly higher in patients as compared to health control.

Electrophysiological studies in rats have shown that both fluoxetine and gepirone produce a decrease in efficacy of serotonergic transmission when administered acutely, but an increase when administered chronically. The acute effect may be due to the predominance of autoreceptor stimulation. With chronic use, the effects on postsynaptic receptors would predominate as a consequence of the reduced presynaptic effects. This probably occurs because of progressive desensitization of either somatodendritic autoreceptors, in the case of gepirone, or of terminal 5-HT autoreceptors, in the case of fluoxetine (3,4).

The participation of 5-HT-1A or 5-HT-2 postsynaptic receptor subtypes on anxiety may result in opposite effects (9). Contradictory results obtained with serotonergic receptor antagonists in human anxiety, apparently support this assertion. Thus, ritanserin, a selective 5-HT-2 receptor antagonist, has been shown to cause an anxiolytic effect in patients with generalized anxiety (5). On the other hand, in a study on normal volunteers we observed an anxiogenic effect of a nonspecific antagonist of serotonergic receptors, metergoline (16). From these results it may be suggested that specific blockade of 5-HT-2 receptors by ritanserin leads to an anxiolytic effect, whereas more extensive blockade of receptors, including 5-HT-1 and 5-HT-2, with metergoline produces an anxiogenic effect. Similar results are obtained with respect to prolactin secretion induced by L-tryptophan, which was blocked by metergoline and facilitated by ritanserin. This difference may be the consequence of antagonistic actions of 5-HT-1 receptors, responsible for prolactin secretion, and of 5-HT-2 receptors inhibiting hormone release. The same interpretation was suggested by Deakin (9) in respect to anxiety, postsynaptic 5-HT-1 receptors mediating an anxiolytic, and 5-HT-2 receptors an anxiogenic action.

The present interpretation of a biphasic effect of 5-HT uptake inhibitors on anxiety is apparently incompatible with other hypotheses about the role of serotonin in human anxiety (19, 24, 33). These contradictions show that the hypotheses formulated thus far are still insufficient to reconcile the available body of experimental evidence.

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