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REVIEW

VARIABILITY IN THE EFFECTS OF 5-HT-RELATED COMPOUNDS IN EXPERIMENTAL MODELS OF ANXIETY: EVIDENCE FOR MULTIPLE MECHANISMS OF 5-HT IN ANXIETY OR NEVER ENDING STORY?

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Variability in the effects of 5-HT-related compounds in experimental models of anxiety: evidence for multiple mechanisms of 5-HT in anxiety or never ending story? G. GRIEBEL. Pol. J. Pharmacol., 1996, 48, 129–136.

To date, more than two thousand experiments have investigated the behavioral effect of 5-HT-interacting drugs in animal models of anxiety disorders. Most of them have focused on the involvement of drugs interacting with 5-HT_{1A}, 5-$HT_{2A/2C}$ and 5-HT_3 receptors. Although numerous results are in line with the classic 5-HT hypothesis of anxiety, suggesting that decreased anxiety is related to decreased activity in central 5-HT neurons and vice versa, paradoxical drug effects have often been found. To explain this variability, several authors point to a determining role of the experimental paradigms used. In fact, an overview of the behavioral data arising from the vast literature indicates that conditioned procedures as well as more ethological-based tests are equal in revealing anxiolytic-like effects of drugs targetting 5-HT_{1A}, 5-HT_{2A} or 5-HT_{2C} receptor subtypes. Furthermore, results obtained in ethologically-based animal models of anxiety with drugs stimulating 5-HT transmission are most consistent with the classic 5-HT hypothesis of anxiety in that they showed an increase in animals' emotional reactivity. Finally, anxiolytic-like effects of 5-HT_3 receptor antagonists are in great part revealed by models based on spontaneous behaviors. Taken together, these observations lead to the conclusion that different 5-HT mechanisms, mediated by different receptor subtypes, are involved in the genesis of anxiety.

Key words: *5-HT (serotonin), anxiety, animal models, review*

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Since the initial study of Aprison and Ferster [1], who revealed potential anxiogenic-like effects of the 5-HT precursor, 5-hydroxytryptophan, in a pigeon conflict procedure, more than two thousand experiments have been carried out to investigate the behavioral effects of 5-HT-interacting drugs in experimental models of anxiety. The identification and characterization of several 5-HT binding sites in brain tissue, in particular in limbic areas, and the synthesis of highly selective ligands for these receptor subtypes, have been the starting point in the mid eighties for numerous studies investigating the behavioral action of 5-HT-related drugs in anxiety models (Fig. 1). Several theories have been developed concerning the role of the 5-HT system in anxiety. Among these, that of Iversen [28], suggesting that anxiety is related to increased activity in central 5-HT neurons, has been the most acknowledged. In support of this view is the observation that some benzodiazepines decrease 5-HT turnover in the brain. However, the picture is overall less clear. The behavioral effects of drugs decreasing the activity of the central 5-HT system are often more variable than the effects of standard anxiolytics and not all findings are accounted for by this hypothesis. There are many instances in which compounds decreasing 5-HT neurotransmission produce effects opposite to those of standard anxiolytics, suggesting an anxiogenic-like action. Moreover, in some studies, drugs known to possess a 5-HT-stimulating action displayed anxiolytic-like properties, while in others they potentiated animals' emotional reactivity. Finally, a great number of studies found no evidence for anxiolytic- or anxiogenic-like effects of drugs modulating central 5-HT neurotransmision [15]. The reasons for this variability in drug effect remain in great part unknown, but certainly include some factors (such as species differences, sex of the animals, environment in which a test is conducted) which have been widely assessed in many recent reviews [3, 16, 18, 20–22, 34, 38].

The objective of the present article is to provide an overview of the developments in research involving the 5-HT system and anxiety. The emphasis will be given to a review of animal models used to evaluate these drugs. Results obtained with some of the most widely studied compounds, including fluoxetine, buspirone, mCPP and ondansetron, will be illustrated graphically with attention given to the types of behavioral procedures used. For the sake of convenience, anxiety models in the present review have been divided into tests based on unconditioned responses, and models based on conditioned reactions (for more details, see [15]).

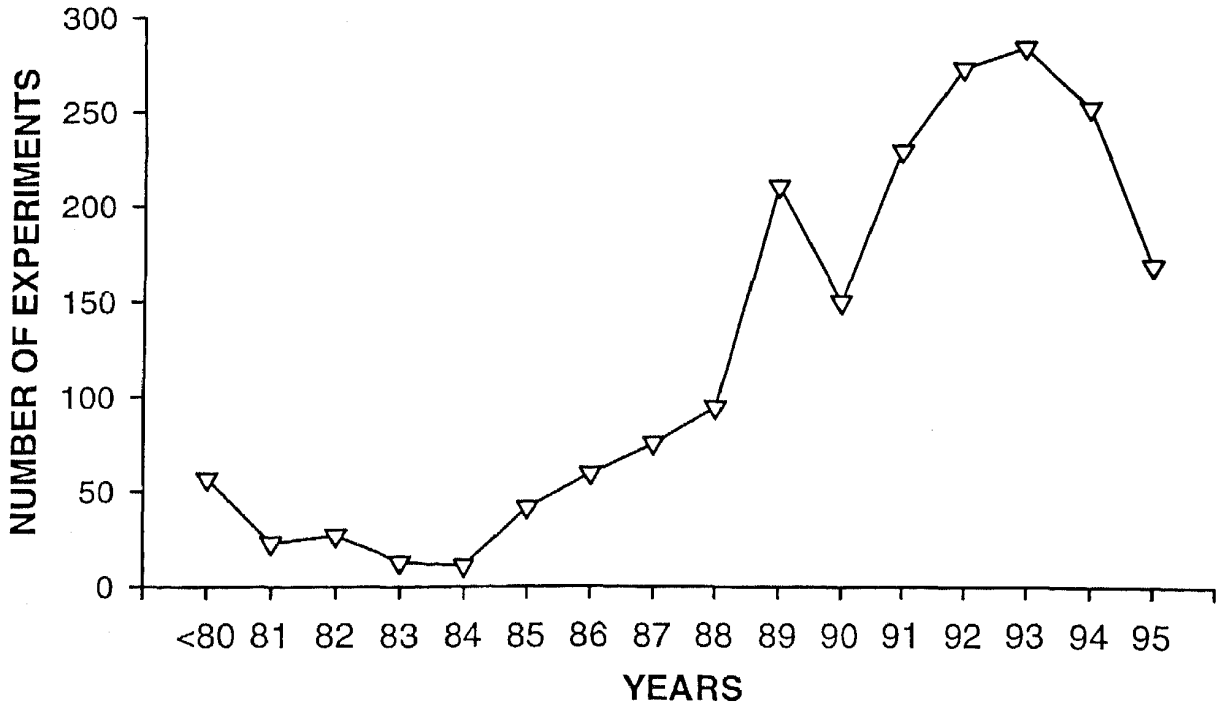

Fig. 1. The number of 5-HT/anxiety experiments in articles published from 1961 to 1995 (sources are Medline and Current Contents)

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Behavioral effects of the acute administration of 5-HT reuptake inhibitors (SRIs) in animal models of anxiety: the case of fluoxetine

SRIs were originally developed as antidepressants, but many studies have revealed that these compounds present therapeutic potential beyond the treatment of depression. SRIs provide an effective treatment for obsessive-compulsive disorders (OCD) and panic attacks (PA). Studies investigating the effects of SRIs in patients suffering from generalized anxiety disorder (GAD) have not been performed, but there are indications that patients suffering from social phobia may respond favorably as well. In addition, it is now widely acknowledged that SRIs often induce a transient increase in anxiety in PA patients at the beginning of the treatment [40].

Although the initial work of Cook and Davidson [7] suggested that the non selective SRI imipramine was devoid of any effect in a Geller-Seifter conflict test, several investigators have more recently reported an activity of SRIs in experimental models of anxiety [15]. Among these, much attention has been paid to the selective SRI fluoxetine which produced variable effects in such procedures (Fig. 2). The drug was found to potentiate anxious responses in 46% of the studies, while 31% revealed an opposite effect. Analysis of the different experimental procedures used provides evidence that some models are more sensitive than others to the behavioral action of SRIs, including fluoxetine. As summarized in Figure 2, tests based on spontaneous responses more often revealed a modification in the behavioral responses than did conditioned paradigms. In addition, results from ethologically-based models seem more consistent with the "classic" hypothesis of 5-HT function in anxiety as 86% of the experiments revealed an anxiogenic-like profile of fluoxetine, whereas only half of the investigations using conditioned paradigms showed such an activity.

Behavioral effects of the acute administration of 5-HT receptor ligands in animal models of anxiety: drugs acting at 5-HT_{1A}, 5-$HT_{2A/2C}$ and 5-HT_3 receptors

At the present time, the 5-HT receptor family can be split into seven groups: 5-HT_1-like, 5-HT_2-like, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7. Within the 5-HT_1 family, five subtypes have been described, i.e. 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}. The 5-HT_2 group can be further divided into 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} [25]. Of these, at least the 5-HT_{1A}, 5-$HT_{2A/2C}$ and 5-HT_3 receptors have been implicated in anxiety.

5-HT_{1A} receptor agonists: the case of buspirone and gepirone

Both buspirone and gepirone act as partial agonists at these binding sites. The former is now widely approved for the treatment of GAD, while a few studies have reported possible clinical efficacy of the latter in the acute treatment of GAD [31, 33, 35, 39]. The amount of data that has been accumulated on the effects of these agents in the various anxiety procedures is vast. Out of 284 experiments with buspirone, 201 (70.8%) revealed that the drug produced anxiolytic-like responses, while 59 (20.8%) failed to show any activity of the compound. Finally, a few studies (8.5%) demonstrated that the acute administration of buspirone in animals potentiated animals' emotional reactivity (Fig. 2). With regards to gepirone, a quite similar pattern of outcomes has emerged from the 61 experiments in which the drug's anxiety-modulating action has been evaluated.

Interestingly, contrary to a common opinion suggesting that conditioned paradigms are less sensitive to the action of 5-HT_{1A} receptor agonists than unconditioned models, buspirone and gepirone are more often found to induce "anxiolysis" in the former (75.8 and 96.7%, respectively) than in the latter (64.8 and 57.1%, respectively) (Fig. 2). However, it must be emphasized that negative results ("anxiogenesis" and "inactive") have been obtained mostly in the elevated plus-maze in rats [15]. Figure 3 shows that only 30% of the studies revealed an anxiolytic effect of these anti-GAD agents in the elevated plus-maze test in rat. The reasons for these paradoxical responses have been extensively assessed in several recent papers by Handley and McBlane [19, 30]. In any case, when disregarding the effects of 5-HT_{1A} receptor agonists in this model, tests based on conditioned reactions are equal in revealing anxiolytic-like effects of these compounds.

5-$HT_{2A/2C}$ receptor ligands: the case of ritanserin and mCPP

In general, compounds claimed to be selective ligands for the 5-HT_{2A} receptor show similar affinity for 5-HT_{2C} receptors [24, 26], which is not surprising, given the very close structural similarity of these two receptors [23]. Among these, ritanserin and mCPP have been the subject of several clinical investigations showing that both drugs modulate anxiety-related responses.

Challenge tests with mCPP, an agonist at these binding sites, have demonstrated anxiogenic responses

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in PA, GAD and OCD, and healthy controls [39]. In line with the clinical observations, studies in animals showed that mCPP elicited anxiogenic-like effects in more than 70% of the experiments, while only a few (13.7%) revealed an opposite action (Fig. 2). Paradoxical anxiolytic responses of mCPP have been described mostly in studies using tests based on conditioned responses (82.1%), indicating that these models are of limited utility in the evaluation of behavioral effects of such agents.

Ritanserin is an antagonist at 5-$HT_{2A/2C}$ receptors. It has been found to attenuate anxious responses in

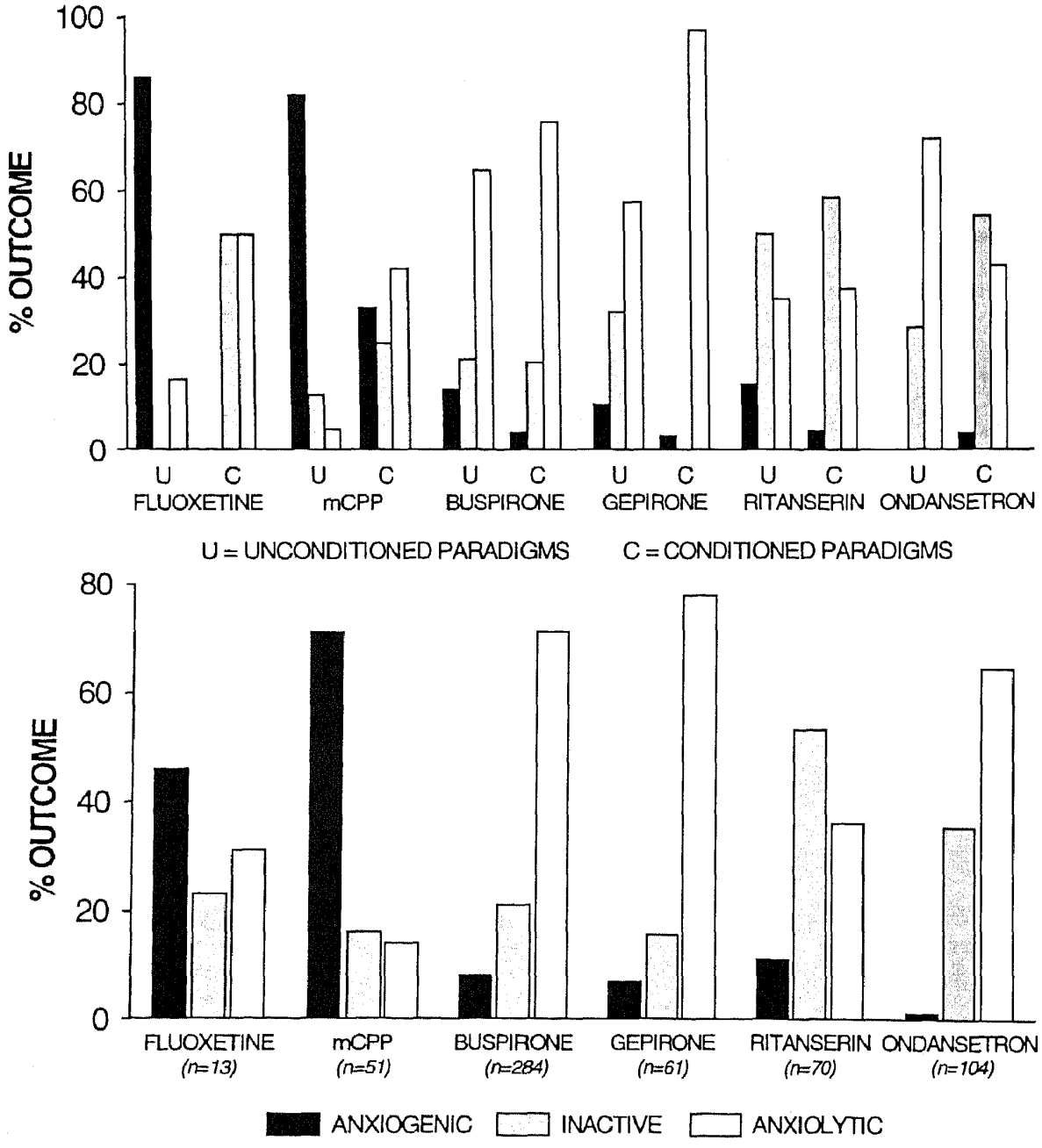

Fig. 2. Illustration of the outcomes of the most studied compounds modulating 5-HT neurotransmission after a single dose in animal models of anxiety disorders

GAD [5, 6] and PA [17], although this latter effect was not confirmed in a double-blind placebo-controlled study comparing ritanserin to fluvoxamine [12]. To date, 70 studies investigated the behavioral action of ritanserin in experimental models of anxiety. Most of them (53%) failed to reveal any anxiety-modulating effect of the drug. Only 36% found it "anxiolytic" and in 11% of the cases, ritanserin displayed an anxiogenic-like profile (Fig. 2). A detailed analysis of the procedures indicates that none of these effects is revealed in any particular model (Fig. 2). Thus, the reasons for this apparent difference in anxiety-modulating action of ritanserin and related compounds remain to be determined.

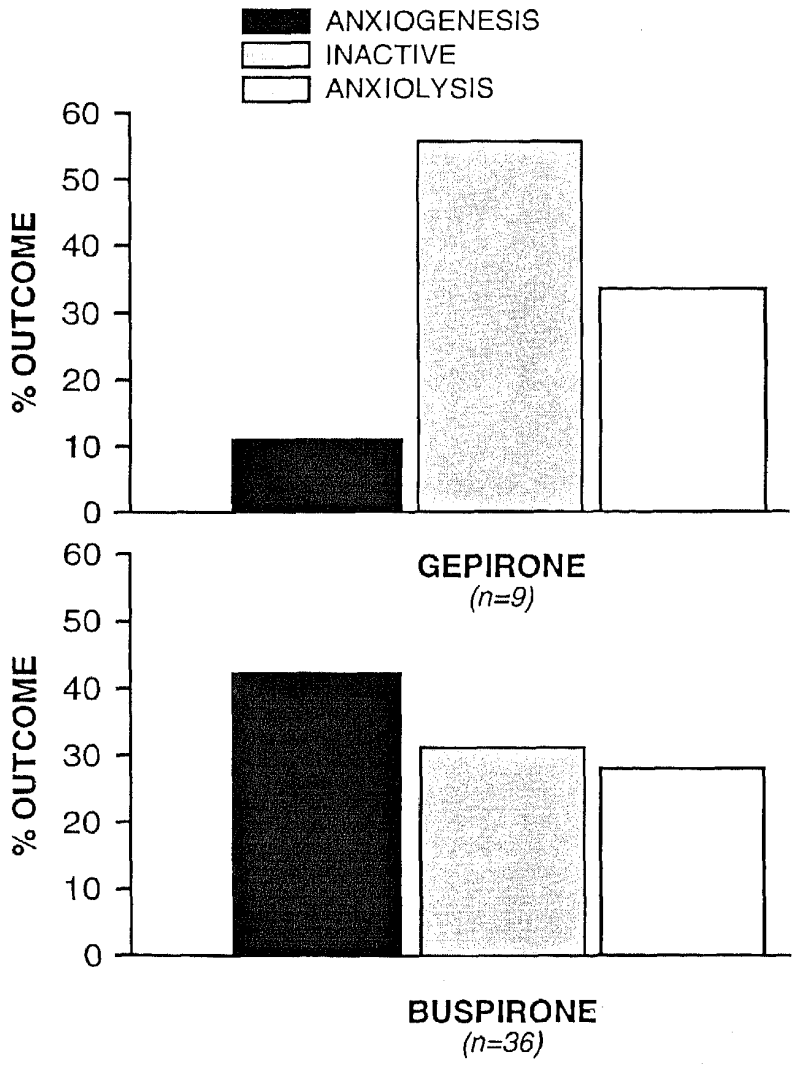

Fig. 3. Behavioral outcome of two 5-HT_{1A} receptor partial agonists in the elevated plus-maze test

The intriguing effects of 5-HT_3 receptor antagonists in animal models of anxiety disorders

To date, only a few data on the anxiolytic activity in humans of 5-HT_3 receptor antagonists have been published. Two recent reports indicate potential efficacy of ondansetron and tropisetron in the treatment of GAD [8, 29]. Other studies, however, found no indication of evidence of anxiolytic activity of BRL 46470 on PA induced by mCPP [14] and of ondansetron in GAD [35].

The lack of clear-cut findings at the clinical level contrasts strongly with the vast and expanding literature relating behavioral effects of 5-HT_3 receptor antagonists in experimental models of anxiety. Incontestably, the most widely studied agent in this group is ondansetron. Approximately 100 experiments were carried out with this drug. Most of them (64.4%) demonstrated an efficacy of ondansetron in reducing anxiety-related responses in animals. Figure 2 shows that negative outcomes ("anxiogenic" and "inactive") are in great part revealed by models based on conditioned responses (57.6% versus 28.2% in unconditioned models). Interestingly, when an anxiolytic-like effect had been detected, it was revealed over a wide dose range, with minimum dose levels in the nano/picogram range. Similar findings have been revealed with several other 5-HT_3 receptor antagonists such as MDL 72222, tropisetron, granisetron or zacopride [15].

Conclusion

Although numerous reviews have extensively discussed the variability in response to 5-HT drug challenge in animal models of anxiety, it is still difficult to draw any coherent conclusion from the collection of data emerging from the vast preclinical literature. Certain authors point to a determining role of the experimental paradigms used. Variation in the effects might reflect differences in the degree to which the models themselves represent fear or anxiety [3, 18, 21, 22, 38]. These behavioral tests have been

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useful in the preclinical testing of benzodiazepine-type anxiolytics and in characterizing the effects of benzodiazepine antagonists, partial agonists, and inverse agonists [2, 38]. However, the validation of these paradigms has depended primarily on their sensitivity to benzodiazepines, and the recent introduction to clinical practice of the non-benzodiazepine anxiolytic buspirone has challenged the validity of these tests as general models of anxiety disorders. The possibility that these tests may be less sensitive to agents not acting at benzodiazepine receptors might at least in part explain these inconsistencies. Other authors suggest that this variability may also be due to a number of additional factors including administration routes [38], doses used [36], species differences [2], the sex of the animals [27], or the environment in which a test is conducted [16]. The most convincing explanation of these discrepancies has recently emerged from several papers of Handley and McBlane [18, 21, 22] who suggested that there is more than one 5-HT mechanism involved in anxiety models. It is obvious that all models are not equivalent. Thus, models based on spontaneous responses, such as the exploration tests, may reflect a type of anxiety linked with uncontrollable stress ("depressive anxiety") as animals are exposed by force to a novel and/or aversive environment from which they cannot escape, while those based on conditioning, especially the Geller-Seifter and Vogel's conflict tests, may reflect a type of anxiety associated with controllable aversive events ("anticipatory anxiety") [13]. Consequently, 5-HT modulation at 5-HT_3 target sites might be selectively involved in situations dealing with the so-called "depressive anxiety", whereas 5-HT_{1A}, and perhaps $5\text{-HT}_{2A/2C}$ receptors, may be involved in both types of anxiety-related responses.

Clearly, a better knowledge of the clinical outcomes after 5-HT drug challenge in anxiety disorders is necessary to shed more light on the mechanisms underlying these paradoxical drug effects. Unfortunately, after more than thirty years of preclinical research relating 5-HT and anxiety, it is very surprising to note that only one direct 5-HT-acting compound has become available in the treatment of GAD, namely buspirone. In addition, only SRIs have been successfully used in the chronic treatment of PA and OCD. It was hoped that the numerous studies initiated as far back as 1986 would shed more light on the issue of whether or not direct 5-HT receptor ligands (other than buspirone) possess clear-cut anxiolytic properties. Although a few studies have reported possible clinical efficacy of several 5-HT_{1A} partial agonists (i.e. gepirone and ipsapirone) in the treatment of GAD [4, 9–11] and/or PA [32], the total published evidence for efficacy is sparse and rests, at least in the case of gepirone, on no more than 100 patients. Whilst a number of studies involving new 5-HT_{1A}, 5-HT_{2A} and 5-HT_3 drugs have either been carried out or are underway, none has yet been published. Until proven otherwise, one can only presume that no clear-cut significant treatment differences between drugs and placebo were obtained. In line with this view is the recent report of Sramek et al. [37] revealing a lack of efficacy of the potent and highly selective 5-HT_{2A} receptor antagonist MDL 11,939 in GAD patients. This questions the validity of some preclinical results, and also suggests that more favorable attention must be given to the publication of non-significant effects.

At the present time, the "5-HT-anxiety" story is still promising. Nevertheless, positive clinical data need to support the vast, although variable, preclinical literature, otherwise interest in this research area will inevitably decrease and no compound will never replace the pioneer drug buspirone.

REFERENCES

1. Aprison M. H., Ferster C. B.: Neurochemical correlates of behavior. II. Correlation of brain monoamine oxidase activity with behavioural changes after iproniazid and 5-hydroxytryptophan administration. J. Neurochem., 1961, 6, 350–357.
2. Barrett J. E., Gleeson S.: Anxiolytic effects of 5-HT_{1A} agonists, 5-HT_3 antagonists and benzodiazepines: conflict and drug discrimination studies. In: 5-HT_{1A} Agonists, 5-HT_3 Antagonists and Benzodiazepines. Their Comparative Behavioural Pharmacology. Eds. Rodgers R. J., Cooper S. J., John Wiley & Sons, Chichester, 1991, 59–105.
3. Barrett J. E., Vanover K. E.: 5-HT receptors as targets for the development of novel anxiolytic drugs: models, mechanisms and future directions. Psychopharmacology, 1993, 112, 1–12.
4. Boyer W. F., Feighner J. P.: A placebo-controlled double-blind multicenter trial of two doses of ipsapirone versus diazepam in generalized anxiety disorder. Int. Clin. Psychopharmacol., 1993, 8, 173–176.
5. Bressa G. M., Marini S., Gregori S.: Serotonin S2 receptors blockage and generalized anxiety disorders. A double-blind study on ritanserin and lorazepam. Int. J. Clin. Pharmacol. Res., 1987, 7, 111–119.
6. Ceulemans D. L., Hoppenbrouwers M. L., Gelders Y. G., Reyntjens A. J.: The influence of ritanserin, a serotonin antagonist, in anxiety disorders: a double-blind placebo-controlled study versus lorazepam. Pharmacopsychiatry, 1985, 18, 303–305.
7. Cook L., Davidson A. B.: Effects of behaviorally active drugs in a conflict-punishment procedure in rats. In: The Benzodiazepines. Eds. Garattini S., Mussini E.,

2009 Reproduction, representation et diffusion interdites. Loi du 01/07/92.

Randall L. O., Raven Press, New York, 1973, 379–404.
8. Costall B., Naylor R. J.: Anxiolytic potential of 5-HT_3 receptor antagonists. Pharmacol. Toxicol., 1992, 70, 157–162.
9. Csanalosi I., Schweizer E., Case W. G., Rickels K.: Gepirone in anxiety: a pilot study. J. Clin. Psychopharmacol., 1987, 7, 31–33.
10. Cutler N. R., Sramek J. J., Keppel Hesselink J. M., Krol A., Roeschen J., Rickels K., Schweizer E.: A double-blind, placebo-controlled study comparing the efficacy and safety of ipsapirone versus lorazepam in patients with generalized anxiety disorder: a prospective multicenter trial. J. Clin. Psychopharmacol., 1993, 13, 429–437.
11. Cutler N. R., Sramek J. J., Wardle T. S., Hesselink J. M., Roeschen J. K.: The safety and efficacy of ipsapirone vs. lorazepam in outpatients with generalized anxiety disorder (GAD): single site findings from a multicenter trial. Psychopharmacol. Bull., 1993, 29, 303–308.
12. den Boer J. A., Westenberg H. G.: Serotonin function in panic disorder: a double blind placebo controlled study with fluvoxamine and ritanserin. Psychopharmacology, 1990, 102, 85–94.
13. Gardner C. R.: Recent developments in 5HT-related pharmacology of animal models of anxiety. Pharmacol. Biochem. Behav., 1986, 24, 1479–1485.
14. Greenshaw A. J.: Behavioural pharmacology of 5-HT_3 receptor antagonists: a critical update on therapeutic potential. Trends Pharmacol. Sci., 1993, 14, 265–270.
15. Griebel G.: 5-Hydroxytryptamine-interacting drugs in animal models of anxiety disorders: more than 30 years of research. Pharmacol. Ther., 1995, 65, 319–395.
16. Griebel G., Moreau J.-L., Jenck F., Martin J. R., Misslin R.: Some critical determinants of the behaviour of rats in the elevated plus-maze. Behav. Process., 1993, 29, 37–47.
17. Griez E., Pols H., Lousberg H.: Serotonin antagonism in panic disorder: an open trial with ritanserin. Acta Psychiat. Belg., 1988, 88, 372–377.
18. Handley S. L.: 5-Hydroxytryptamine pathways in anxiety and its treatment. Pharmacol. Ther., 1995, 66, 103–148.
19. Handley S. L., McBlane J. W.: An assessment of the elevated X-maze for studying anxiety and anxiety-modulating drugs. J. Pharmacol. Toxicol. Method., 1993, 29, 129–138.
20. Handley S. L., McBlane J. W.: 5-HT drugs in animal models of anxiety. Psychopharmacology, 1993, 112, 13–20.
21. Handley S. L., McBlane J. W.: Serotonin mechanisms in animal models of anxiety. Braz. J. Med. Biol. Res., 1993, 26, 1–13.
22. Handley S. L., McBlane J. W., Critchley M. A., Njung'e K.: Multiple serotonin mechanisms in animal models of anxiety: environmental, emotional and cognitive factors. Behav. Brain Res., 1993, 58, 203–210.
23. Hartig P. R.: Molecular biology of 5-HT receptors. Trends Pharmacol. Sci., 1989, 10, 64–69.
24. Hoyer D.: Functional correlates of serotonin 5-HT_1 recognition sites. J. Recept. Res., 1988, 8, 59–81.
25. Hoyer D., Clarke D. E., Fozard J. R., Hartig P. R., Martin G. R., Mylecharane E. J., Saxena P. R., Humphrey P. P. A.: VII. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). Pharmacol. Rev., 1994, 46, 157–204.
26. Hoyer D., Waeber C., Schoeffter P., Palacios J. M., Dravid A.: 5-HT_{1C} receptor-mediated stimulation of inositol phosphate production in pig choroid plexus. A pharmacological characterization. Naunyn-Schmied. Arch. Pharmacol., 1989, 339, 252–258.
27. Hughes R. N.: Effects on open-field behavior of diazepam and buspirone alone and in combination with chronic caffeine. Life Sci., 1993, 53, 1217–1225.
28. Iversen S. D.: 5-HT and anxiety. Neuropharmacology, 1984, 23, 1553–1560.
29. Lecrubier Y., Puech A. J., Azcona A., Bailey P. E., Lataste X.: A randomized double-blind placebo-controlled study of tropisetron in the treatment of outpatients with generalized anxiety disorder. Psychopharmacology, 1993, 112, 129–133.
30. McBlane J. W., Handley S. L.: Effects of two stressors on behaviour in the elevated X-maze: preliminary investigation of their interaction with 8-OH-DPAT. Psychopharmacology, 1994, 116, 173–182.
31. Murphy D. L., Brooks A., Aulakh C., Pigott T. A.: Anxiolytic effects of drugs acting on 5-HT receptor subtypes. In: Serotonin, from Cell Biology to Pharmacology and Therapeutics. Eds. Vanhoutte P. M., Saxena P. R., Paoletti R., Brunello N., Jackson A. S., Kluwer Academic Publishers, Dordrecht, 1993, 223–230.
32. Pecknold J. C., Luthe L., Scott Fleury M. H., Jenkins S.: Gepirone and the treatment of panic disorder: an open study. J. Clin. Psychopharmacol., 1993, 13, 145–149.
33. Sacchetti E., Zerbini O., Banfi F., Tansella M.: Overlap of buspirone with lorazepam, diazepam and bromazepam in patients with generalized anxiety disorder: findings from a controlled, multicentre, double-blind study. Hum. Psychopharmacol. Clin. Exp., 1994, 9, 409–422.
34. Schreiber R., De Vry J.: 5-HT_{1A} receptor ligands in animal models of anxiety, impulsivity and depression: multiple mechanisms of action? Prog. Neuro-Psychopharmacol. Biol. Psych., 1993, 17, 87–104.
35. Schweizer E., Rickels K.: Serotonergic anxiolytics: a review of their clinical efficacy. In: 5-HT_{1A} Agonists, 5-HT_3 Antagonists and Benzodiazepines, Their Comparative Behavioural Pharmacology. Eds. Rodgers R. J., Cooper S. J., John Wiley & Sons, Chichester, 1991, 365–376.
36. Söderpalm B., Hjorth S., Engel J. A.: Effects of 5-HT_{1A} receptor agonists and L-5-HTP in Montgomery's conflict test. Pharmacol. Biochem. Behav., 1989, 32, 259–265.

2009 Reproduction, representation et diffusion interdites. Loi du 01/07/92.

37. Sramek J. J., Robinson R. E., Suri A., Cutler N. R.: Efficacy trial of the 5-HT_2 antagonist MDL 11,939 in patients with generalized anxiety disorder. J. Clin. Psychopharmacol., 1995, 15, 20–22.
38. Treit D.: Anxiolytic effects of benzodiazepines and 5-HT_{1A} agonists: animal models. In: 5-HT_{1A} Agonists, 5-HT_3 Antagonists and Benzodiazepines. Their Comparative Behavioural Pharmacology. Eds. Rodgers R. J., Cooper S. J., John Wiley & Sons, Chichester, 1991, 107–131.
39. Westenberg H. G. M., Den Boer J. A.: Serotonin in anxiety related disorders. In: Serotonin, from Cell Biology to Pharmacology and Therapeutics. Eds. Vanhoutte P. M., Saxena P. R., Paoletti R., Brunello N., Jackson A. S., Kluwer Academic Publishers, Dordrecht, 1993, 249–254.
40. Westenberg H. G. M., Den Boer J. A.: Serotonergic basis of panic disorder. In: Psychopharmacology of Panic, Oxford University Press, Oxford, 1993, 91–109.

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