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PREDATOR-ELICITED FLIGHT RESPONSES IN SWISS-WEBSTER MICE: AN EXPERIMENTAL MODEL OF PANIC ATTACKS

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Abstract

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1. The nosological status of panic disorder is still a matter of debate. Nevertheless, evidence is emerging that panic attacks have a different pattern of drug responsiveness from other forms of anxiety.
2. Several experimental animal models of panic attacks have been developed. These vary in the extend to which they meet criteria for face validity, predictive validity and construct validity, normally applied to such models.
3. In the present review, the authors examine the possibility that predator-elicited flight responses in Swiss-Webster mice might serve as an experimental model for the screening

of panic-modulating drugs.
4. Drug effects on flight responses clearly indicate that this model has good predictive validity as panic-promoting agents increase flight reactions, while panicolytic drug challenge induces opposite effects. In addition, drugs devoid of any effect on panic attack, also do not alter flight behavior.
5. These findings strongly suggest that the model of predator-elicited flight responses in Swiss-Webster mice is useful for the investigation of panic-modulating drugs.

Keywords: animal model, antipredator defense, benzodiazepine receptor ligands, flight, panic, serotonin receptor ligands, serotonin reuptake inhibitors, swiss-webster mouse

Abbreviations: anxiety/defense test battery (A/DTB), benzodiazepine receptor ligand (BZPR), conditioned suppression of drinking (CSD), diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV), fear/defense test battery (F/DTB), generalized anxiety disorder (GAD), mouse defense test battery (MDTB), panic attack (PA), panic disorder (PD), periaqueductal grey (PAG), serotonin (5-HT), serotonin reuptake inhibitor (SRI), ultrasonic vocalization (USV)

1. Introduction

Panic attack (PA) is the central pathologic feature of panic disorder (PD). It involves sudden onset of intense apprehension, fearfulness, or terror, often accompanied by such physiological symptoms as shortness of breath, sweating, dizziness, and palpitations. (DSM-IV, 1994). In contrast, generalized anxiety disorder (GAD) is characterized by persistent anxiety with apprehensive expectation (DSM-IV, 1994).

An interesting array of pharmacological agents has been used to treat both psychopathologies. Antipanic therapy is almost always chronic in nature. Many antipanic agents are also antidepressants, although not all antidepressant agents are effective against panic. Treatments effective against GAD, such as the traditional benzodiazepines receptor (BZPR) full agonists, the barbiturates and the 5-HT_{1A} receptor agonists, often are of limited utility in the treatment of PD. For instance, most studies suggest that classic BZPR agonists require high and motor-impairing doses to alleviate PA (Dunner et al., 1986; Pollack and Rosenbaum, 1988). In fact, only some of the second-generation BZPR agonists, like alprazolam or clonazepam, have been reported to be effective antipanic agents (Chouinard et al., 1982; Sheehan et al., 1984; Shehi and Patterson, 1984; Beaudry et al., 1986; Pollack et al., 1986; Spier et al., 1986).

Many animal models of emotional psychopathology involve exposure of subjects to external or internal stimuli which are assumed to be capable of inducing the relevant emotional state in humans. For animal models of panic, pharmacological provoking agents like the α_2-adrenoceptor antagonist yohimbine (Charney et al., 1984), the 5-HT direct agonist mCPP (Charney et al., 1987)

or even flumazenil, a BZPR antagonist (Nutt et al., 1990) have been used. Although experimentally induced and naturally occuring PA share many features, their exact relationship is still unknown (Nutt and Lawson, 1992). Animal models of anxiety often respond with an anxiogenic-like profile to these agents, but they also show a similar response to drugs which induce anxiety in human volunteers (Gentil et al., 1990; Duka and Dorow, 1995) but which do not provoke panic-like reactions, such as the BZPR inverse agonist Ro 15-3505 (Lister, 1988; Belzung et al., 1988; Sanger and Cohen, 1995). This brings into question the validity of such procedures to reveal a specific panic profile of panic provoking agents.

2. Criteria for an Animal Model of Panic Attacks

Evaluation of animal models of psychiatric disorders typically proceeds along three lines: predictive validity, face validity, and construct validity (Willner et al., 1992). Predictive validity refers to the sensitivity of the model to specific drug challenge. In the case of PA, these models must be specifically sensitive to the effects of clinically proven, panic-modulating agents. Face validity refers to the phenomenological similarity between the model and the disorder. This implies, for instance, that a model of panic produces reactions in animals that are analogous to PA in humans. Construct validity implies that the cause of behavioral change in the animal is sufficient to cause a similar response in man (Treit, 1985).

The central issue in assessing the face validity of a simulation of PA is the degree to which the simulation is realistic. Clearly, a valid animal model should demonstrate a resemblance to the clinically defined symptoms of the disorder. PA is defined in the DSM-IV diagnostic system (1994) by the presence of at least 4 of 13 somatic or cognitive symptoms, including palpitations, sweating, feeling of choking, fear of dying or paresthesias. It is clear that most, if not all, of these symptoms, which often rely on verbal report, can hardly be modelled in animals. Nonetheless, Martin (1993) recently set up an experimental paradigm in which rats are treated with panicogenic drugs, then briefly exposed to an uncontrollable and aversive situation and finally, are subjected to an avoidance task in a shuttle box. The behavioral deficits induced in these rats are described as homologous to those observed in PA, particularly in patients who are inhibited in cognitive and behavioral processes. Although this approach seems interesting, discrepancies between the pharmacological data and the clinical observation were found in this model. For instance, acute buspirone, a 5-HT_{1A} partial agonist, has been found active, while clinical reports invariably failed to show an antipanic efficacy of this compound (Schweizer and Rickels, 1988; Pohl et al., 1989). Indeed, panic may even be exacerbed by buspirone (Frazer and Lapierre, 1987; Chignon and

Lepine, 1989; Norman and Judd, 1989).

The difficulties of modelling PA-like symptoms in animals have led several authors to develop animal models of PA based on predictive validity only. For instance, Fontana and Commissaris (1988) and Fontana et al. (1989) claim that the conditioned suppression of drinking (CSD), a modified version of the Geller-Seifter and Vogel conditioned conflict tests, might serve as an animal model for the study of antipanic drugs, as chronic treatment with such agents (imipramine, desipramine, amitryptyline and phenelzine) resulted in an increase in the number of shocks accepted, while acute treatment with these agents induced no change in this measure compared to baseline levels. More recently, Molewijk et al. (1995) suggested, on the basis of drug effects, that conditioned ultrasonic vocalizations (USV) elicited by reintroducing adult rats into the environment in which they previously received inescapable footshocks, also may serve as screening methods for antipanic challenges. However, major discrepancies between the outcomes in animal studies and the clinical findings were found in both models. For example, in Molewijk's paradigm (USV), 5-HT_{1A} receptor full and partial agonists (i.e. flesinoxan, buspirone, ipsapirone) potently reduced ultrasound emission. However, as mentioned above, clinical results with buspirone did not reveal a reduction in the frequency of PA. Furthermore, Westenberg et al. (1992) demonstrated that treatment with flesinoxan in PD patients did not reduce the occurrence of PA. In fact, this treatment produced a substantial increase in anxiety. Finally, in the USV paradigm, the panic-promoting drug yohimbine was also found to decrease ultrasound emission, thereby clearly indicating that the USV test is of limited utility in the screening of panic-modulating drugs. The main concern regarding the CSD procedure is that only a few drugs have been tested in this paradigm. Among these, only antipanic agents have been used. Therefore, it is not known whether the CSD is specifically sensitive to such compounds or if it also detects effects of non panicolytic drugs, including anti-GAD agents. Finally, a last but not least concern with both procedures, is that neither of them is bidirectionally sensitive to changes in response induced by panicogenic treatment. For example, it is now widely acknowledged that acute treatment with 5-HT reuptake inhibitors (SRIs) (imipramine, fluvoxamine) results in a transcient increase in the frequency of PA in PD patients (Westenberg and Den Boer, 1993b). Despite this clinical effect, neither the CSD nor the USV procedure were able to detect a panicogenic-like action after acute SRI drug challenge. In summary, although both models yield some interesting outcomes, it would be excessive to claim that they are specifically sensitive to panic-modulating drug treatment.

The search for animal models of PA also led some authors to examine the possibility that beside the core symptoms of PA, additional subsidiary symptoms may be modelled in animals. In the DSM-IV (1994), PA is described as often accompanied by an "urge to escape" (pg. 394) and PD

patients "usually report an urgent desire to flee from wherever the attack is occurring" (pg. 394). It has been suggested that panic may be the result when 'flight or fight' mechanisms are strongly aroused but no perceived route for escape is available (Ashcroft et al., 1993). In addition, electrical stimulation of the hypothalamic-periaqueductal grey (PAG) fight-flight system in man elicits symptoms and autonomic changes that closely resemble panic (Sano et al., 1972). Based on these observations, several authors have suggested that PA might be due to the spontaneous activation of hypothalamic-PAG fight-flight mechanisms (Deakin and Graeff, 1991; Deakin et al., 1991; Graeff, 1991). To illustrate this idea, Graeff (1991) developed a procedure in which the activation of the rat dorsal PAG leads to behavioral defense manifestation (i.e. flight, jump escape) identified as panic-like. He concluded that this situation has face validity as an animal model of PA. Unfortunately, this model revealed paradoxical drug effects. For example, the 5-$HT_{2A/C}$ receptor blocker trazodone caused dose-dependent increases in the threshold of aversive dorsal PAG electrical stimulation (Jenck et al., 1989a), but failed to improve PA in a clinical trial (Charney et al., 1986). Even more clearly, mCPP which has been reported to produce PA in human (Charney et al., 1987), displayed a marked antiaversive action in this test (Jenck et al., 1989b).

Two ethological-orientated models of PA based on flight/escape responses of mice exposed to a predator have also been proposed. One has emerged from the work of Hendrie and Neill (1991), who demonstrated that mice exposed to cries of certain bird species (most of which were rodent predators) displayed behavior largely defense/escape orientated and identified as panic-like. These authors further showed that only panicolytic drug treatment (i.e. chronic imipramine and alprazolam) were able to reduce these responses. The predictive validity of this model is limited, however, as high doses of classic BZPR agonists (i.e. chlordiazepoxide, diazepam) and acute imipramine did not significantly change escape behavior. The second model is based on the work of Blanchard and colleagues (1993b) on antipredator defense in rats. These authors developed two test batteries, a Fear/Defense Test Battery (F/DTB) measuring defensive behaviors to present, approaching predators, and an Anxiety/Defense Test Battery (A/DTB) measuring reactions to potential threat. Both batteries have been used in conjunction with administration of potentially anxiolytic drugs (for more details see Blanchard et al., 1993b). These tests have recently been adapted for use in mice and a preliminary pharmacological study demonstrated that the panic-promoting agent yohimbine produces an increase in flight from an approaching/contacting human (Blanchard et al., 1993a). To further demonstrate the validity of this model for the screening of panicogenic and antipanic compounds, the authors investigated the behavioral outcome after administration of an array of psychoactive drugs on flight responses of mice exposed to a threat stimulus.

3. The Mouse Defense Test Battery

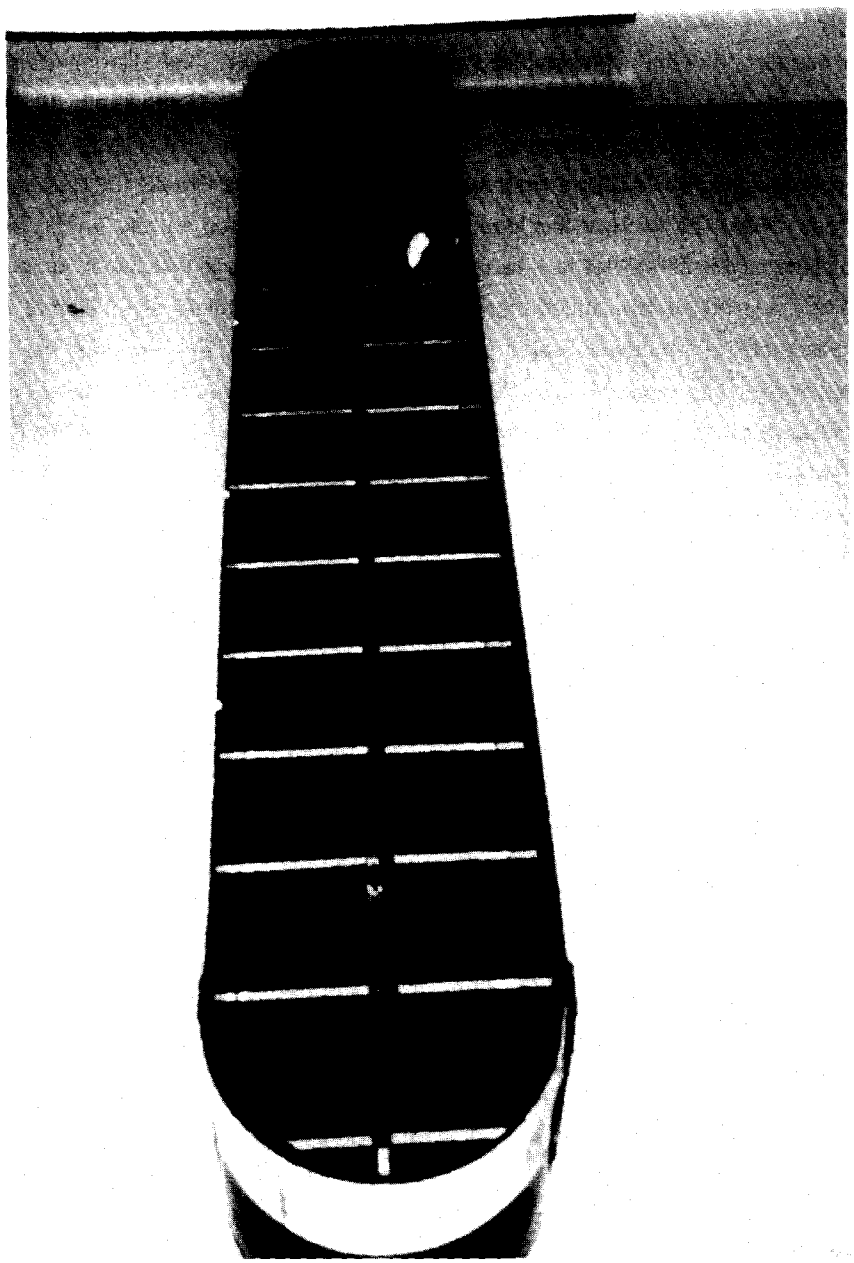

Fig 1. The oval runway (0.40 m wide, 0.30 m high, and 5.0 m in total length) in which tests were conducted. It consists of two 2 m straight segments joined by two 0.4 m curved segments and separated by a median wall (2.0 x 0.30 x 0.06).

Defensive behaviors constitute the reactions of animals to the host of life-threatening dangers encountered in every natural environment, from predators, from conspecific attack, and from threatening features of the environment (Blanchard et al., 1993b). Among these responses, flight/avoidance, freezing and defensive threat/attack have been the most intensively investigated in an experimental context. For instance, we demonstrated in several recent studies, that Swiss-Webster mice exposed to a nonpainful threat stimulus (i.e. rat) displayed strong defensive behaviors. Among these, flight/avoidance and defensive threat/attack responses were predominant (Griebel et al., 1995c; Griebel et al., 1995a).

The MDTB is run in a (mouse-scaled) oval runway based on that used in the rat F/DTB. However, specific situational and behavioral components of the A/DTB, involving reactivity to stimuli associated with potential threat rather than to the actual presence of an approaching predator, have been incorpored into the mouse battery (Griebel et al., 1995c; Griebel et al., 1995a). Figure 1 shows the oval runway in which tests were conducted. It consists of two 2 m straight segments joined by two 0.4 m curved segments and separated by a median wall. The apparatus was elevated to a height of 0.80 m from the floor to enable the experimenter to easily hold the rat, while minimizing the mouse's visual contact with him. Subjects were placed into the runway for a 3-min. familiarization period. Then, a hand-held anaesthetized Long-Evans rat was introduced into the runway and brought up to the subject. The experimenter stood adjacent to the runway while holding the anaesthetized rat. Approach was terminated when contact with the subject was made or the subject ran away from the approaching stimulus. If the subject fled, avoidance distance (the distance from the stimulus to the subject at the point of flight) and the number of avoidances after five approaches were recorded. Immediately after these approaches, the hand-held rat chased the subject for a distance of 15 m and flight speed was recorded.

4. Drug Effects on Flight Reactions in the Mouse Defense Test Battery

Figures 2 to 4 summarize the effects of various psychoactive drugs on flight responses of Swiss-Webster mice exposed to a natural threat stimulus (the hand-held rat) in the oval runway. The authors mainly focussed on three different classes of drugs: BZPR ligands, direct 5-HT receptor ligands and SRIs.

4.1. Benzodiazepine Receptor Ligands

The effects of two full agonists (chlordiazepoxide at 5, 10 and 25 mg/kg; alprazolam, acutely at 0.05, 0.5 and 1 mg/kg, and chronically at 0.5, 1 and 2 mg/kg), a partial agonist (Ro 19-8022 at 0.5,

1 and 2 mg/kg), an inverse agonist (Ro 19-4603 at 0.025, 0.05 and 0.1 mg/kg) and the antagonist flumazenil (at 5, 10 and 20 mg/kg) have been investigated in the MDTB (Griebel et al., 1995b; Griebel et al., 1994).

Figure 2 indicates that acute injection of chlordiazepoxide and alprazolam failed to reduce avoidance distances, frequency of avoidances or flight speed at non sedative/myorelaxant doses. This was in contrast to chronic alprazolam which decreased avoidance distances at doses devoid of any effect on locomotor activities. In addition, flumazenil strongly increased rat-subject distance needed to elicit avoidance.

Assuming that flight is an index of panic-like reactions, the present findings with these three reference compounds are in agreement with clinical data indicating that: 1) classic BZPR agonists may be of limited utility in the management of PD as high doses are required to alleviate PA; 2) chronic treatment with alprazolam improves PA; 3) flumazenil is somewhat anxiogenic in volunteers (Darragh et al., 1983; Schopf et al., 1984; Duka et al., 1986; Higgitt et al., 1986; Lavie, 1987) and that it increases the frequency of PA in PD patients (Nutt et al., 1990).

With regards to the BZPR inverse agonist Ro 19-4603, the MDTB data indicate that this potential anxiogenic drug (Belzung et al., 1990) induced effects which are opposite to those observed with chronic alprazolam and closely resemble those obtained with flumazenil as it increased predator-subject distance leading to avoidance. By contrast, Ro 19-8022 strongly decreased flight/avoidance responses at all doses (0.5 to 2 mg/kg) while the 0.5 mg/kg dose also reduced the distance between the subject and the predator at which flight occurred. The compound also consistently reduced flight speed in the chase/flight test. Since these effets were obtained at doses at which no evidence of an increase in falls was obtained, the action of this BZPR partial agonist reflects specific reductions in activation of defense-related flight systems.

4.2. 5-HT Receptor Ligands

4.2.1. 5-HT_{1A} Receptor Ligands. Several ligands selectively or preferently acting at these binding sites have been assessed (Griebel et al., 1995d; Griebel et al., 1995c): 8-OH-DPAT, a full agonist (0.05-10 mg/kg); gepirone, a partial agonist (2.5-10 mg/kg) and S 21187, a recently synthetized 5-HT_{1A} receptor antagonist (2.5-10 mg/kg) (Guardiola-Lemaître et al., 1993). Figure 3 shows that drug effect on flight was minimal with only S 21187 producing a slight decrease in the number of avoidances and flight speed when facing the predator. In this context, and in view of the flight/panic hypothesis, one can propose that: 1) 5-HT_{1A} receptor agonists are ineffective

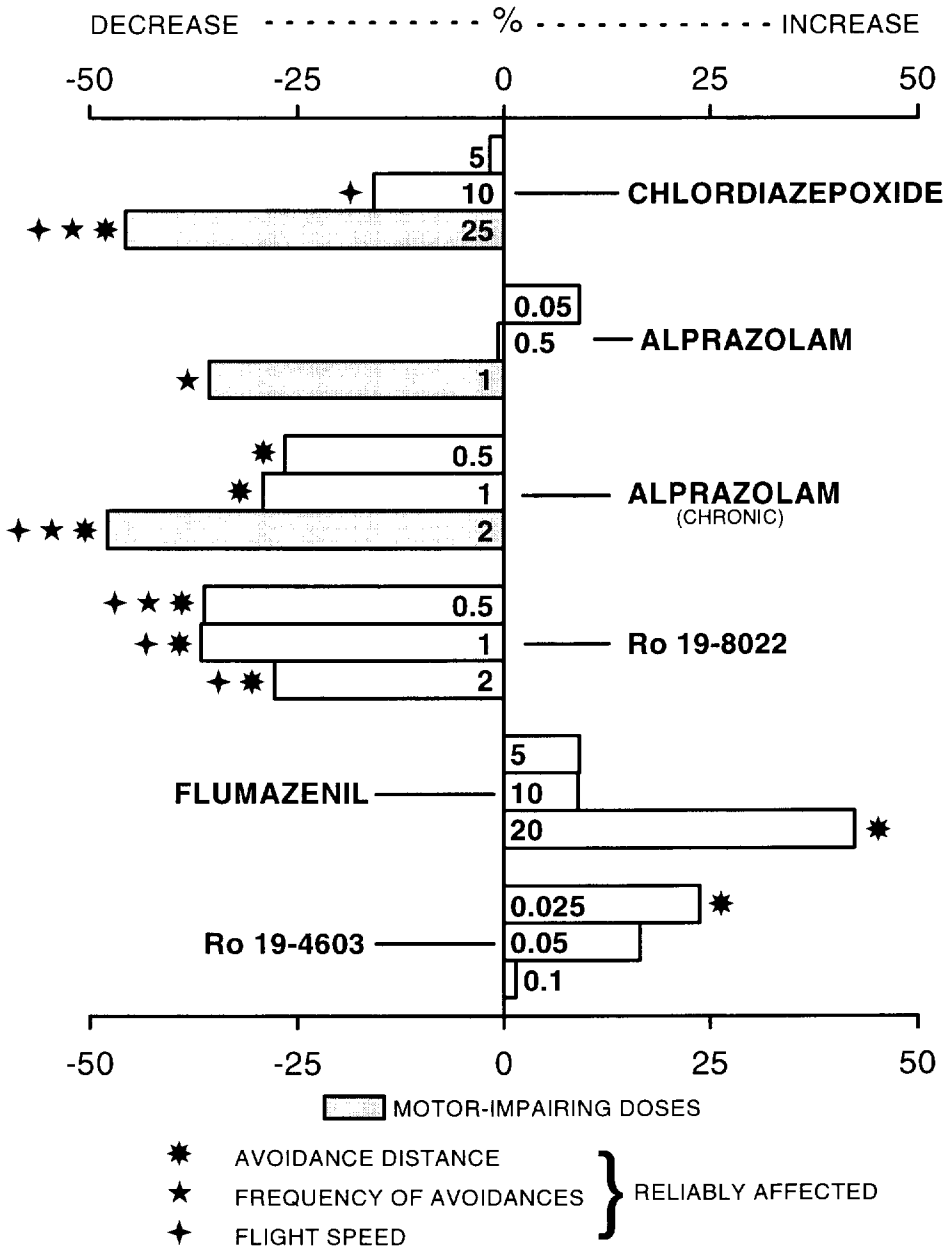

Fig 2. Effects of various benzodiazepine receptor ligands on three flight measures in the Mouse Defense Test Battery.

in reducing PA; 2) 5-HT_{1A} receptor antagonists may have some efficacy in the treatment of PA.

With regard to the first statement, both preclinical data and human studies provide evidence of a lack of efficacy of 5-HT_{1A} receptor ligands in flight/panic reactions. For instance, in Graeff's (1991) procedure in which the activation of the rat dorsal periaqueductal grey (DPAG) leads to behavioral manifestations identified as panic-like, 8-OH-DPAT and ipsapirone were ineffective (Jenck et al., 1989; Jenck et al., 1989b). Clinical data almost invariably failed to report an antipanic efficacy of 5-HT_{1A} receptor agonists (Rickels et al., 1982; Pohl et al., 1989; Robinson et al., 1989; Sheehan et al., 1990; Sheehan et al., 1993a; Sheehan et al., 1993b). The only exception recently emerged from an open-label trial showing that gepirone reduced frequency of panic attacks (Pecknold et al., 1993) in GAD patients. Nonetheless, double-blind placebo-controlled studies are needed to confirm these results.

As mentioned above, it has been reported that buspirone can exacerbate or trigger PA (Frazer and Lapierre, 1987; Chignon and Lepine, 1989; Norman and Judd, 1989). Similarly, another 5-HT_{1A} receptor agonist flesinoxan, has also been reported to exacerbate anxiety ratings in patients suffering from panic disorder (Westenberg et al., 1992). It was conjectured that the anxiogenic action of buspirone may result from an abnormally sensitized state of the postsynaptic 5-HT_{1A} receptors in such patients, thereby enhancing the postsynaptic agonist action of the compound (Norman and Judd, 1989). Consequently, some authors have recently hypothesized that 5-HT_{1A} receptor antagonists would have an anti-panic action (Fletcher et al., 1993). So far, nothing is known from a clinical viewpoint about a possible efficacy of 5-HT_{1A} receptor antagonists in the management of PD, but our data fit well with the theoretical rationale suggesting that blockade of central 5-HT_{1A} binding sites may be involved in the alleviation of PA.

4.2.2. 5-HT_{2A} Receptor Antagonist. The administration of pirenperone (0.5-2 mg/kg), a preferential antagonist at these receptors induced very specific effects on flight (Griebel et al., 1995c). The drug strongly reduced all flight parameters, including number of avoidances, avoidance distance and flight speed. The recognition that some antidepressants exert beneficial effects in panic and the finding that chronic treatment with most, but not all, antidepressants results in a downregulation of the postsynaptic 5-HT_{2A} receptors (Peroutka and Snyder, 1980) has led to the suggestion that selective 5-HT_{2A} receptor antagonists might have some efficacy in the treatment of panic (Westenberg and Den Boer, 1993a). However, no clinical study has yet evaluated the effect of selective 5-HT_{2A} receptor antagonists on PA. A pilot study (Humble et al., 1986) and an open trial study (Griez et al., 1988) found that ritanserin reduced PA, but three double-blind placebo-controlled studies (Deakin et al., 1990; Den Boer and Westenberg, 1990;

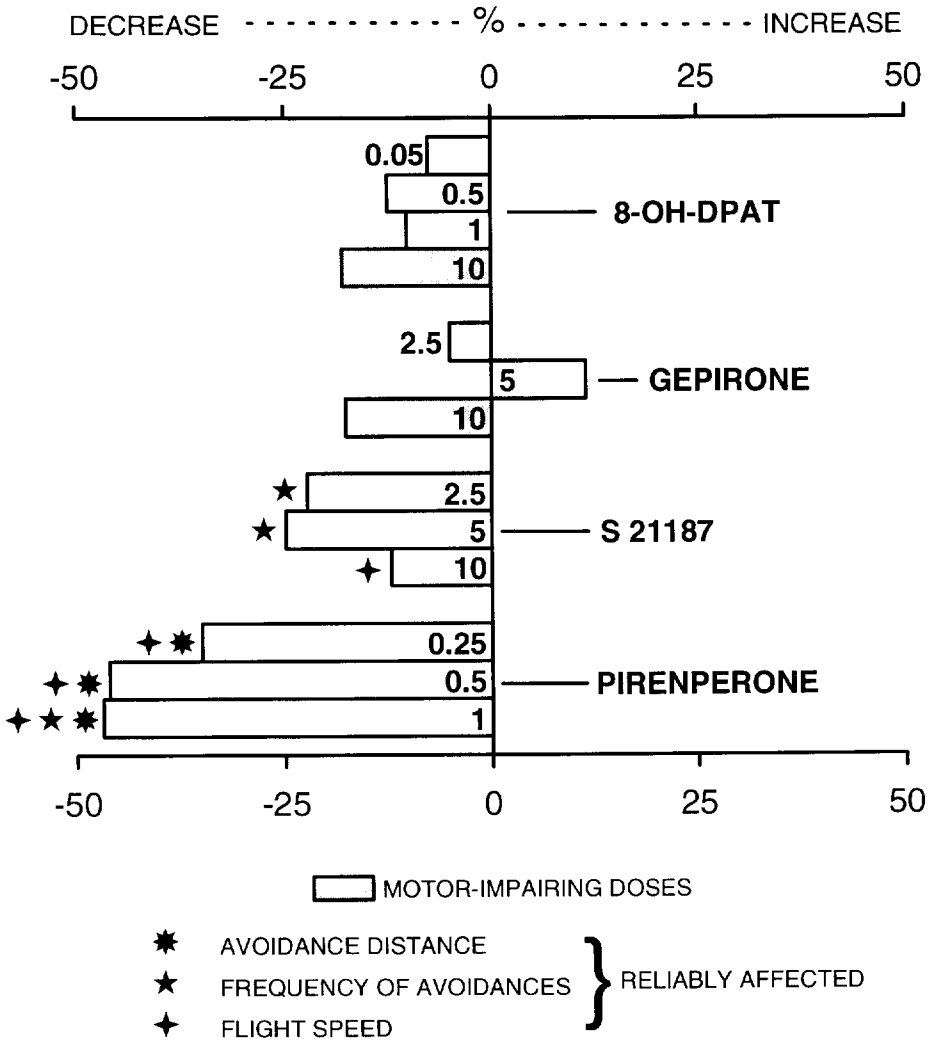

Fig 3. Effects of various 5-HT receptor ligands on three flight measures in the Mouse Defense Test Battery.

Westenberg and Den Boer, 1989) clearly reported that the drug either does not improve or even aggravates this condition. However, while ritanserin is a 5-HT_{2A} receptor antagonist, it is extremely nonselective with a nearly equal affinity for 5-HT_{2C} sites (Hoyer, 1991). Preclinical data are consonant with the view that ritanserin may not provide an accurate view of the effects of selective 5-HT_{2A} antagonists on panic. Jenck and coworkers (Jenck et al., 1989; Jenck et al., 1989b) showed that the preferential 5-HT_{2A} receptor blockers ketanserin and pirenperone dose-dependently increased the aversive threshold of DPAG stimulation, whereas mixed 5-$HT_{2A/2C}$ receptor antagonists, like ritanserin, cyproheptadine and mianserin, did not display a similar effect. These findings suggest a need for clinical trials with more selective antagonists at the 5-HT_{2A} receptor.

4.3. 5-HT Reuptake Inhibitors

Figure 4 shows that acute treatment with imipramine and fluoxetine potentiated flight reactions in response to an approaching or chasing predator. Thus, both treatments reliably increased the prey-predator distance at which flight occurred. In addition, acute imipramine also increased flight speed, indicating a strong action of the drug on the potentiation of flight responses. By contrast, after chronic treatment with either drug, flight-facilitating effects were not seen and in fact, a strong reduction in avoidance distances and/or avoidance frequencies was obtained.

These findings of a potentiation in flight reactions after a single acute dose of either SRI, are in agreement with the well described exacerbation in the severity and frequency of PA at the beginning of SRI medications, often accompanied by anxiety-related symptoms described as racing thoughts, nervousness, tremor, jitteriness or emotional discomfort (Westenberg and Den Boer, 1993b); second, the flight-reducing action after chronic treatment, fits well with the clinical efficacy of imipramine (Cassano et al., 1994; Mavissakalian and Perel, 1994; Rosenberg and Jensen, 1994; Mavissakalian et al., 1993; Roth et al., 1992; Woods et al., 1992) and fluoxetine (Fassio and Paoletti, 1993; Louie et al., 1993; Solyom et al., 1991; Schneier et al., 1990; Brady et al., 1989; Gorman et al., 1987) in the management of PA.

5. Conclusion

Several authors identify flight/avoidance reactions of rodents as panic-like (Graeff, 1991; Hendrie and Neill, 1991) and therefore suggest that an experimental model of flight responses

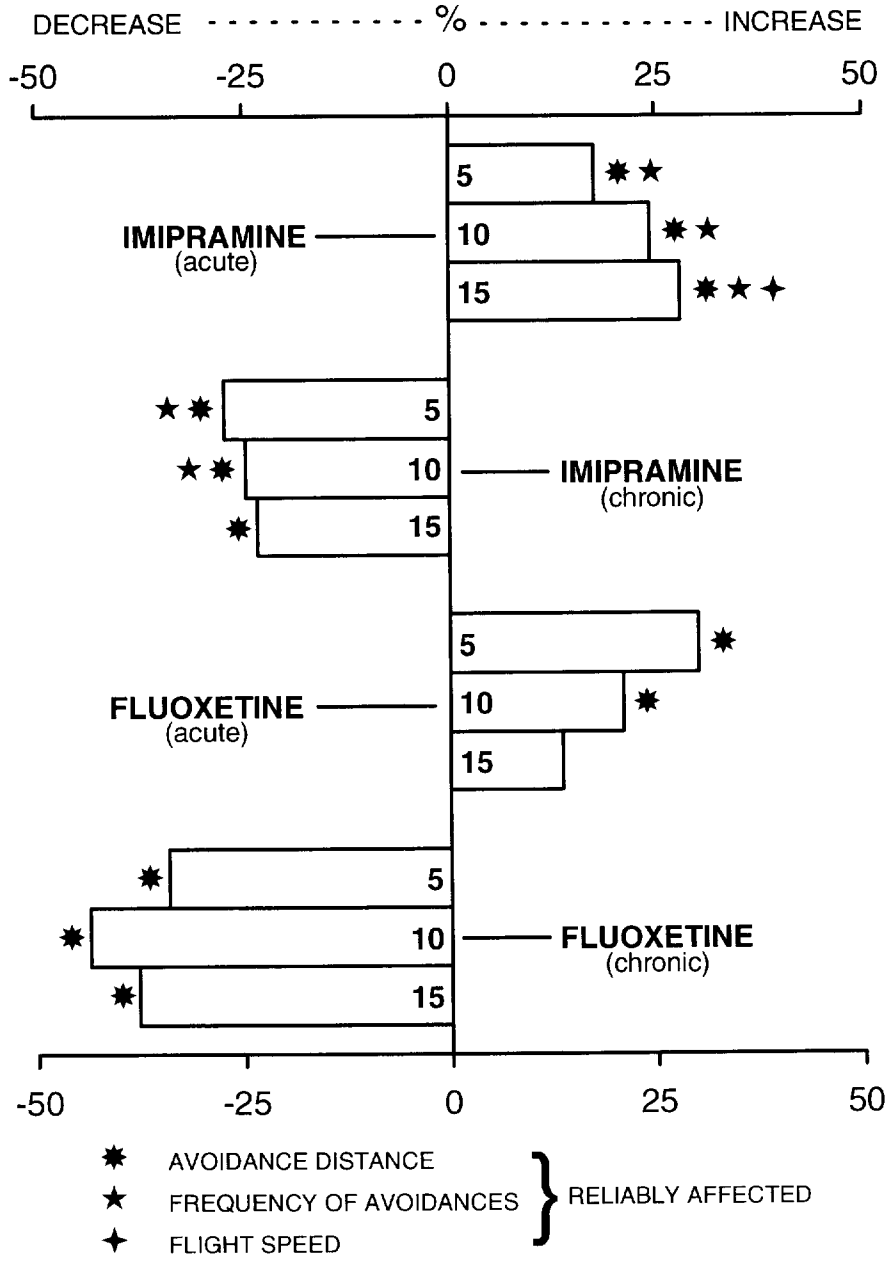

Fig 4. Effects of two 5-HT reuptake inhibitors on three flight measures in the Mouse Defense Test Battery.

Table 1

Effects of Various Psychoactive Drugs on the Flight/Avoidance Responses in the Mouse Defense Test Battery. Comparison with their Effect on Panic Attacks.

		PANIC	FLIGHT
CHLORDIAZEPOXIDE	*BZPR full agonist*	(↓)	(↓)
ALPRAZOLAM (ACUTE)	*BZPR full agonist*	(↓)	(↓)
ALPRAZOLAM (CHRONIC)		↓	↓
FLUMAZENIL	*BZPR antagonist*	↑	↑
GEPIRONE	*5-HT$_{1A}$ partial agonist*	↓/o	o
IMIPRAMINE (ACUTE)	*NA/5-HT reuptake inhibitor*	↑	↑
IMIPRAMINE (CHRONIC)		↓	↓
FLUOXETINE (ACUTE)	*5-HT reuptake inhibitor*	↑	↑
FLUOXETINE (CHRONIC)		↓	↓
YOHIMBINE	*α_2 antagonist*	↑	↑

↑ indicates an increase in the response; ↓ indicates a decrease in the response; (↓) indicates a decrease at motor-imparing doses only; o ineffective; BZPR: Benzodiazepine Receptor.

Table 2

Effects of Various Psychoactive Drugs not yet Tested Against Panic Attacks that Affected Flight/Avoidance Responses in the Mouse Defense Test Battery: Potential Panic-Modulating Drugs.

		FLIGHT	PANIC?
RO 19-8022	*BZPR partial agonist*	↓	↓
RO 19-4603	*BZPR inverse agonist*	↑	↑
S 21187	*5-HT$_{1A}$ antagonist*	↓	↓
PIRENPERONE	*5-HT$_{2A}$ antagonist*	↓	↓

↑ indicates an increase in the response; ↓ indicates a decrease in the response.

may have face validity as model of PA. Indeed, this view is supported by clinical observations indicating that PD patients often report intense desire to flee or escape from the place where the PA is occurring (DSM-IV, 1994). The extensive pharmacological evaluation of the MDTB has demonstrated that panic-modulating agents specifically affect animals' flight responses with

panicogenic treatment increasing flight and panicolytic drug challenge decreasing it (Table 1). Notably, avoidance distance and, to a lesser extent, number of avoidance measures appear to be particularly sensitive to panic-modulating drug treatment. In addition, anti-GAD agents such as chlordiazepoxide or gepirone failed to affect this response in a selective manner (i.e. at non sedative doses). Overall, these findings strongly support the predictive validity of the MDTB. Also, in view of the effects on flight of several compounds whose action on PA is not known yet, we can anticipate potential efficacy of Ro 19-8022 and S 21187 in the clinical management of PD (Table 2), creating predictions which can be confirmed or disproved by clinical trials involving these compounds. Evaluation of the construct validity of the MDTB as of any other model of psychopathology, is a complex issue, involving the extent to which neurobehavioral defense systems are conservative and represented in much the same form across mammals. The animal work in this area is expanding rapidly, however, and at present attempts to evaluate this criterion are perhaps more compromised by the lack of understanding of human behavior, than that of animals.

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