The Effect of Sympathetic Antagonists on the Antidepressant Action of Alprazolam

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Abstract: Alprazolam is an anti-anxiety drug shown to be effective in the treatment of depression. In this study, the effect of sympathetic receptor antagonists on alprazolam–induced antidepressant action was studied using a mouse model of forced swimming behavioral despair. The interaction of three sympathetic receptor antagonists with benzodiazepines, which may impact the clinical use of alprazolam, was also studied. Behavioral despair was examined in six groups of albino mice. Drugs were administered intraperitoneally. The control group received only a single dose of 1% Tween 80. The second group received a single dose of alprazolam, and the third group received an antagonist followed by alprazolam. The fourth group was treated with imipramine, and the fifth group received an antagonist followed by imipramine. The sixth group was treated with a single dose of an antagonist alone (atenolol, a β1-selective adrenoceptor antagonist; propranolol, a non selective β-adrenoceptor antagonist; and prazocin, an α1-adrenoceptor antagonist). Results confirmed the antidepressant action of alprazolam and imipramine. Prazocin treatment alone produced depression, but it significantly potentiated the antidepressant actions of imipramine and alprazolam. Atenolol alone produced an antidepressant effect and potentiated the antidepressant action of alprazolam. Propranolol treatment alone produced depression, and antagonized the effects of alprazolam and imipramine, even producing depression in combined treatments.In conclusion, our results reveal that alprazolam may produce antidepressant effects through the release of noradrenaline, which stimulates β2 receptors to produce an antidepressant action. Imipramine may act by activating β2 receptors by blocking or down-regulating β1 receptors.

Key words: Alprazolam; imipramine; swimming maze; atenolol; prazocin; propranolol.

Introduction

Alprazolam has antidepressant activity and has been shown to be similar in efficacy to imipramine in the treatment of unipolar depression in humans. Thus, alprazolam may be particularly useful in patients with mixed anxiety / depression [1]. However, its general acceptance as an antidepressant awaits further study. Deficiency of serotonin, noradrenaline and dopamine is implicated as a causal factor in depression [2,3]. However, since the 1960s there has been a strong emphasis on the role of norepinephrine in both the pathogenesis of effective disorders and the mechanism of action of antidepressant medications [2,4-6]. Theories of depression also acknowledge that other factors may be involved; the antidepressants may act on other neurotransmitters, such as acetylcholine and gamma-aminobutyric acid (GABA). The monoamines, serotonin and norepinephrine, also influence and are influenced by other processes in the brain. The neurochemical basis of depression is now considered more complex and not the result of any one specific deficit [6]. For example, the function of the hypothalamic pituitary axis and the involvement of stress-related hormones are increasingly believed to play a role in the development of depression [7].

It has been suggested that depression may result from down-regulation of the noradrenergic neuronal system, and antidepressants act to return the system to a state of equilibrium [8] by increasing neurotransmitter availability by a process that involves blocking reuptake in the presynaptic neuron. Consequently, the concentration of neurotransmitters in the synaptic cleft is increased [9].

Depression may also be due to a change in receptor function, not neurotransmitter concentration. As a result of preclinical investigation of antidepressant mechanisms of action, the monoamine hypothesis of depression was refined to include alterations in noradrenergic receptor function [10-12]. It has been suggested that the centrally active β1 and β2 adrenergic agonists produce antidepressant-like effects in several behavioral tests, suggesting that these receptors may be involved in the mediation of the effects of antidepressant drugs [13]. Down-regulation of β-receptors was proposed as the neuronal target for the effects of some antidepressants [14]. Duncan et al., [15] reported that imipramine, a common antidepressant drug, induces down-regulation of beta adrenergic receptors. Also, several studies revealed that α-adrenergic receptors may play an early role in the mechanism of depression and in the mechanism of action of antidepressants [16-18]. Thus, α-adrenoceptor dysfunction provides another hypothesis for pathogenesis of depression [19].

The forced swimming test (FST) is a behavioral paradigm predicative of antidepressant activity in rodents. The immobility exhibited by rodents when they are placed in an inescapable cylinder of water reflects the cessation of persistent escape-directed behavior [20]. Exposure to the forced swimming test is also known to produce changes in the release of dopamine, norepinephrine, and serotonin in a variety of brain regions, and these effects interact with antidepressant drug treatments [21,22].

Experimental work on the antidepressant effect of alprazolam on animal behavior is scanty. To further understand the significance of alprazolam in treating depression, it is essential to characterize the mechanisms underlying its action, as they may relate to the proposed mechanisms of depression. Norepinephrine is a candidate in both the pathogenesis of affective disorders and the mechanism of action of antidepressants [23,24]. Therefore, the present study was conducted to investigate the effect of sympathetic antagonists on the proposed

antidepressant action of alprazolam in mice subjected to the behavior despair method.

Material and methods

Albino mice weighing between 20 and 40 g were used. Groups of 7 mice each were kept in separate cages at 20–25°C with 12 hours dark/light cycles. The drugs were suspended in 1% Tween 80 in water [25] because alprazolam is not freely soluble in saline; they were administered by the intraperitoneal route. Imipramine was used as the antidepressant [26], and the dose of 10 mg/kg was selected on the basis of a pilot test. Alprazolam was given at 5 mg/kg, also after pilot testing. Sympathetic antagonists' doses were based on previous studies [27, 30-33].

An experiment was conducted for each antagonist: 5 mg/kg of prazocin [27-30], 5 mg/kg of atenolol [31,32], and 1 mg/kg of propranolol [27,30,31,33]. In each experiment, the mice were divided into six groups (n=7). Group 1 (control) received only a single dose of 5 ml/kg of 1% Tween 80 (T80). Group 2 received a single dose of 5 mg/kg alprazolam and group 3 received a single dose of the antagonist followed by the same dose of alprazolam (5 mg/kg). Group 4 was treated with a single dose of imipramine (10 mg/kg) alone and group 5 received a single dose of the antagonist followed by the same dose of imipramine (10 mg/kg); Group 6 received a single dose of the antagonist alone.

A modified behavioral model of immobility, known as behavioral despair [34-37], was used. In this model, mice are forced to swim in a restricted space from which there is no escape. Following an initial period of vigorous activity, the mice adopt a characteristic immobile posture and no longer attempt to escape. Mice were subjected to the test 60 minutes after administration of the drugs. They were forced to swim for six minutes in a vertical glass cylinder (height: 27 cm; diameter: 16.5 cm) containing fresh tap water at 27 °C and a depth of 15 cm [38]. The onset of immobility was recorded during the last four minutes of the six-minute testing period; mice were judged immobile when they floated in an upright position and made only small movements to keep their head above water. [37].

The data were analyzed by SPSS8 software. The Kolmogrov Simonov maximum deviation test for goodness of fit was used to determine if the data were normally distributed. Treatments were compared by one-way ANOVA if the parameters were parametric and by the Mann–Whitney two samples (non–matched) test if they were not. The differences were considered significant at $p \leq 0.05$.

Results

Administration of prazocin alone resulted in significantly faster onset of immobility as compared to the control group. By contrast, imipramine alone or alprazolam alone produced significant delay of the onset compared to the control group. Prazocin combined with alprazolam significantly delayed the onset of immobility compared to alprazolam treatment. Treatment with prazocin together with imipramine delayed the onset of immobility compared to imipramine treatment alone (Table 1).

Table 1: Effect of prazocin on the onset of immobility

Treatment (n = 7)	Immobility onset (mean± SE, sec)
T80 (1 ml/kg)	38.2 ± 0.58
Alprazolam (5 mg/kg)	50.0± 0.71 *, a
Alprazolam+ Prazocin	56.4 ± 0.68*
Imipramine (10 mg/kg)	60.0 ± 0.71*, b
Imipramine + Prazocin	72.0 ± 1.82*
Prazocin (5 mg\kg)	1.4 ± 6.06*, a, b

* Significantly different from the control T80-treated group at $p \leq 0.05$. a = significantly different from Alpr+Prz treated group at $p \leq 0.05$; b = significantly different from Impr+Prz treated group at $p \leq 0.05$.

Administration of atenolol alone significantly delayed the onset of immobility compared to the control group. Administration of alprazolam alone caused a substantial delay (30-48%) in the onset of immobility compared to the control group (vehicle alone). However, the difference was statistically significant in only two of the three experiments. The effect of alprazolam was significantly potentiated when administered with atenolol. Imipramine administration produced significant delay in the onset of immobility compared to the control group. Administration of atenolol combined with imipramine did not significantly change the effect of imipramine (Table 2).

Propranolol alone resulted in a significantly earlier onset of immobility compared to the control group. Alprazolam produced a significant delay in the onset of immobility compared to the control group. Imipramine significantly delayed the onset of immobility compared to the control group. The combination of propranolol and alprazolam produced significantly faster onset of immobility than observed in either the alprazolam or the control group. Propranolol significantly shortened the time to onset of immobility compared to the imipramine treated group or the control group (Table 3).

Table 2: Effect of atenolol on the onset of immobility

Treatment (n = 7)	Immobility onset (mean±SE, sec)
T80 (1 ml/kg)	39.6 ± 0.69
Alprazolam (5 mg/kg)	58.7 ± 10.34 a
Alprazolam+ Atenolol	89.9 ± 0.77*
Imipramine (10 mg/kg)	96.3 ± 3.09*
Imipramine +Atenolol	98.4 ± 0.78*
Atenolol (5 mg\kg)	88.7 ± 3.59*, b

* Significantly different from the control T80-treated group at $p \leq 0.05$. a = significantly different from Alpr+Aten treated group at $p \leq 0.05$; b = significantly different from Impr+Aten treated group at $p \leq 0.05$.

Discussion

The antidepressant effect of alprazolam was investigated using the forced swimming test as an acute stress model. Although the forced swimming test does not induce in mice symptoms similar to human depression, it was used because it is simple and reliable across

laboratories. In addition, the majority of antidepressants have been shown to prolong the time to onset of the immobility, and their effectiveness correlates significantly with clinical potency [39] Alprazolam gave a uniform effect as an antidepressant in this animal model of depression. Mice treated with alprazolam showed a delay in the onset of immobility compared to the control group. The putative antidepressant effect of alprazolam may be mediated by a GABA-ergic mechanism that is independent of the benzodiazepine receptor. In a previous communication [40], it was reported that flumazenil (an antagonist at the benzodiazepine receptor), did not alter the antidepressant effect of alprazolam (or imipramine), whereas these effects were blocked by picrotoxin. Unlike diazepam, alprazolam may enhance the release of serotonin (5-HT) in the hippocampus, and this may at least partly explain its antidepressant activity [41]. Several observations indicate that alprazolam and standard antidepressants have some similar actions, such as the down-regulation of the beta-adrenergic receptor and their anti-anxiety effect [42].

Table 3: Effect of propranolol on the onset of immobility

Treatment (n = 7)	**Immobility onset (mean±SE, sec)**
T80 (1 ml/kg)	53.6 ± 0.37
Alprazolam (5 mg/kg)	61.0 ± 1.23*, a
Alprazolam + Propranolol	26.4 ± 0.57*
Imipramine (10 mg/kg)	83.6 ± 0.99*, b
Imipramine + Propranolol	37.4 ± 1.10*
Propranolol (1 mg\kg)	36.6 ± 0.69*, a

*Significantly different from the control T80-treated group at p≤ 0.05. a = significantly different from Alpr+Prop treated group at p≤0.05; b = significantly different from Impr+Prop treated group at p≤0.05.

The circulating level of corticotropin-releasing factor (CRF) is elevated in major depression and other psychiatric disorders [43,44]. In the forced swimming test, there is a dose-dependent increase of endogenous CRF, which may play a role in the behavioral response in this model [45]. CRF serves as a neurotransmitter in locus coeruleus, the largest aggregate of noradrenaline-containing cells in the mammalian brain. It is thought to be hypersecreted in depression and upon initiation of the stress response [46-48]. The inhibition of 5HT reuptake (by sertraline) may serve as a functional antagonist of CRF in depression [49]. Pharmacologically distinct antidepressants can interfere with CRF function in the locus coeruleus. This may be an important common mechanism for antidepressant activity [49]. Alprazolam may produce its antidepressant effect by decreasing the release of CRF in locus coeruleus, amygdala and several cortical regions [43]; it may also enhance the release of 5HT in hippocampus [41], which would serve as a functional antagonist of CRF [49].

Imipramine, a typical antidepressant, produced a significant delay in the onset of immobility compared to the control group. Imipramine inhibits presynaptic reuptake of the biogenic amines, serotonin and noradrenaline to produce antidepressant action [50-52]. Imipramine may produce its antidepressant action through GABA-ergic mechanisms, causing the release of catecholamine [40,53-56]. Imipramine may also increase calcium release from intracellular stores [57].

Prazocin (α1-adrenoceptor antagonist) alone produced depression, possibly by antagonizing endogenous noradrenaline. Prazocin produces CNS sympathetic inhibition indirectly through α2-adrenoceptor mechanisms. Reduction of α1 noradrenergic neurotransmission increases depressive behavior, coupled with the fact that this change can result from elevated corticosteroid secretion [58]. Prazocin significantly increased the antidepressant effects of imipramine. Prazocin may decrease the plasma level of interleukin-1 (stress marker) [59,60], which may lead to the potentiation of imipramine action. Imipramine may produce antidepressant effects through postsynaptic α2-agonist (clonidine), which will activate a sub-threshold dose of imipramine [37]. In an earlier study, small doses of clonidine potentiated the effects of antidepressants in the mouse in a similar forced swimming test [61]. Prazocin treatment with alprazolam has significant synergistic effects on alprazolam antidepressant action, which may occur by decreasing the level of interleukin–1 [59]. Also alprazolam, but not diazepam, activates brain α2-adrenoceptors. This may contribute to the effectiveness of alprazolam in the treatment of anxiety disorders [62]. Also, whereas alprazolam increases hippocampal 5-HT release, diazepam decreases it. In the CA1 region of the hippocampus, the α2-adrenergic agonist clonidine increased 5-HT release [41]. The neurochemical profile of alprazolam was similar to that of the α2-adrenergic agonist, clonidine. Enhanced 5-HT release in the hippocampus, exhibited by the atypical benzodiazepine, alprazolam but not by the typical benzodiazepine, diazepam, may be an underlying mechanism for the antidepressant activity of alprazolam [41]. Therefore, blocking α1 by prazocin may potentiate alprazolam action through the activation of α2 receptors.

Atenolol is a selective β1 adrenoceptor antagonist, and by itself it produced significant antidepressant action. This effect may be through blocking β1 receptors [63]. At least in some instances, the antidepressant effect of atenolol may be mediated by the down-regulation of β1-adrenoceptor [64,65]. In general, receptor down-regulation is a long-term effect of chronic drug administration and does not occur acutely following the administration of a single dose. Also, atenolol is a hydrophilic molecule that does not easily penetrate the blood-brain barrier [63]. Therefore, it is safe to rule out β1-adrenoceptor down-regulation as the mechanism for the atenolol effect observed in our study.

Several possibilities may explain the antidepressant effect of atenolol. The dose used in this study was sufficient to partially penetrate the CNS and produce the observed effect. Atenolol may act peripherally to initiate an unknown mechanism that affects the noradrenergic system centrally. It is also possible that the atenolol observations may constitute a false positive result of a β-blocker. Blocking a steady-state agonist response to measure the potency of an antagonist might in some cases yield erroneous results and the response should be interpreted cautiously [66].

Contrary to our data, several human studies showed depressive symptoms after atenolol. Most of the authors suggested that atenolol lowers melatonin release via specific inhibition of β1-adrenoreceptors. The decrease in melatonin may contribute to the disturbance in sleep and mood associated with atenolol use [19,67-70]. In our study atenolol did not change the effect of imipramine significantly, possibly because the maximal capacity of imipramine to down regulate the β-receptor was reached. Therefore, atenolol acting by the same mechanism did not change imipramine antidepressant effects significantly. Atenolol produced a significant synergistic effect on alprazolam antidepressant action. This effect can be explained by the pronounced β2 receptor activity due to the blocking of β1 receptor. This explanation may be accepted if the dose used in this study was enough for atenolol to partially penetrate the CNS, or atenolol could be acting through a peripheral mechanism to induce this effect. Alprazolam induces release of noradrenaline through a GABA-ergic mechanism [40,52-55], which stimulates the sensitive β2-receptor, and as a result atenolol significantly potentiates the antidepressant action of alprazolam. Alprazolam did not change the effect of atenolol; this is observed by comparing the group treated with atenolol alone to the combined treatment with atenolol and alprazolam. This may be due to the maximum effect produced by both drugs on β1 (inhibition) and β2 (stimulation).

Propranolol alone showed a significant depression. This may be due to blocking β2 and β1 receptors. Blocking β1 -receptors produces antidepressant action as observed by the atenolol effect, while blocking both β1 and β2 receptors produced depression. This indicates that β2 stimulation produces antidepressant effect. Reduced central β-receptor activation may contribute to depressive symptoms associated with β-adrenergic blocking drugs [71]. In the forced swimming test, it was found that isoprenaline increases the duration of immobility, while salbutamol decreases it [72]. The central β1and β2 receptors may be acting in opposite direction to modify the duration of immobility which means that activation of β1 leads to enhanced behavioral despair while β2 activation reverses this effect [72]. In animals, the psychopharmacological profile of β2 stimulant (salbutamol) is, to a certain extent, very similar to tricyclic antidepressant drugs such as imipramine [73,74]. In endogenous depressive patients, the antidepressant effect of salbutamol is both clear and rapid [73,75]. It was speculated that the antidepressant effect of imipramine is related to the stimulation of central β2 adrenergic receptors [73]. Both salbutamol and imipramine prevent or reverse reserpine induced hypothermia while these effects were antagonized by propranolol, suggesting that the stimulation of β-adrenergic receptors could be a common mechanism underlying their effects [76]. Stimulation of the central β2 adrenergic receptor, particularly those located in the hippocampus, produces antidepressant-like effects on behavior [77]. Also, β2 agonist (salbutamol) facilitates 5HT transmission in the rat brain probably via stimulation of central β receptors [78]. The reduction in Ca2+i that is caused by inhibiting Ca2+ influx through voltage-gated channels and by enhancing Ca2+ efflux may contribute in part to the antidepressant-like activity shown by salbutamol, as verapamil and nifedipine possessed antidepressant-like properties [79,80].

Imipramine may cause down regulation or blockade of β1 receptors, thus the balance between β1 and β2 receptors is disturbed leading to the predominance of β2–receptor activity which produces an antidepressant effect. Blocking β1 or stimulation of β2 receptors may mediate the mechanism of imipramine antidepressant action. Administration of propranolol with imipramine produced significant antagonism of imipramine antidepressant effect, and even produced significant depression. This observation may be explained by the blockade of β2–adrenoreceptors.

Propranolol, a non-selective β-blocker, combined with alprazolam abolished alprazolam antidepressant effects and even produced significant depression. Alprazolam induces the release of mono-amine transmitters through GABA-ergic system [53-56]. Stimulation of the β2–adrenoreceptors by the released noradrenaline leads to antidepressant action. Our observation of the depressant effect of propranolol agrees with previous studies which associate β blockers with induction of symptoms of depression as mentioned above.

In conclusion, this study demonstrates that alprazolam has a significant antidepressant effect in the rodent forced swimming behavioral model. Our data also indicate that this effect may be mediated by the release of noradrenaline, which stimulates β2-adrenoeceptors. Imipramine may produce its antidepressant action through the activation of β2 receptors by down regulating or blocking the β1-receptor.

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