

## ORIGINAL INVESTIGATION

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## Effects of alprazolam on the acoustic startle response in humans

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**Abstract** In the present study, we assessed the effects of the potent benzodiazepine alprazolam on the human acoustic startle response in healthy volunteers. Eight undergraduate students received single oral doses of placebo and alprazolam 2 mg on 2 separate days, according to a double-blind balanced crossover design. Electromyographic activity of the orbicularis oculi muscle was recorded 5, 7 and 11 h after drug administration. At each recording time, subjects received 21 acoustic stimuli (1 KHz, 116 dB, 50 ms duration) separated by variable intervals (8–30 s, mean 16.5 s). Consistent with previous results obtained for diazepam in humans, alprazolam significantly reduced the amplitude of the startle reflex. A patent increase in onset latency was also observed, this being a novel effect not previously described for benzodiazepines in human studies. Both effects were maximum at 5 h after dosing, the startle response experiencing a recovery as the drug disappeared from systemic circulation. These results indicate a potent inhibitory effect of alprazolam on baseline startle at the dose used, with a robust time-dependent recovery of initial values effectively counteracting between-session habituation.

**Key words** Acoustic startle response · Alprazolam · Placebo · Human

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### Introduction

The startle reflex is a short latency whole-body muscular response caused by sudden intense stimuli. It is first detected in the facial and neck muscles, increasing in latency as it reaches the lower limbs (Landis and Hunt 1939). This robust phenomenon, which is present in all mammals (Davis 1984), is thought to be a primitive preservative behavior directed at protecting the individual from external threats. The startle response can be elicited in humans by visual and tactile stimuli, although it is most effectively triggered by loud sounds (Landis and Hunt 1939). Classically, the structures involved in the firing of this reflex have been located in the brainstem (Davis et al. 1982). A recent article has proposed a simplified three-synapse neurophysiological circuit, involving neurons in the cochlear root, the nucleus reticularis pontis caudalis and motoneurons in the facial motor nucleus and spinal cord (Davis 1996). Interestingly, this basic startle reflex circuit is effectively modulated by descending neural pathways, which confer on it a high degree of plasticity, seen as habituation and prepulse facilitation or inhibition of the original response (Hoffman and Ison 1980).

The various pathways implicated in the modulation of the startle reflex and the large number of neurotransmitters involved (Davis 1984) render this reflex especially attractive for behavioral and pharmacological manipulation. The fact that in rats the startle reflex is enhanced by fear, and that this emotional response can be triggered by conditioned stimuli previously paired with shock, has provided a useful animal model for studying fear and anxiety. This “fear-potentiated startle” paradigm has been used to evaluate the effects of both anxiogenic and anti-anxiety drugs. Thus, research on rats has shown that anxiety-provoking drugs such as yohimbine and piperoxane increase fear-potentiated startle, whereas drugs that reduce fear or anxiety in humans, such as benzodiazepines, clonidine,

buspirone and morphine, can effectively decrease it (for review, see Davis 1986).

Data related to startle modification after administration of anxiolytic drugs in humans are scarce. Recently, the  $\alpha_2$ -adrenoceptor agonist clonidine (Kumari et al. 1996; Abduljawad et al. 1997) and diazepam (Abduljawad et al. 1997) have been found to reduce startle amplitude in humans. Results for diazepam in the latter study seemed to contradict those observed in a previous work (Patrick et al. 1996) in which authors found that diazepam failed to reduce baseline startle amplitude significantly, although it did block startle amplitude potentiation occasioned by images with a negative emotional valence, a condition in which volunteers were administered the startling stimuli paired with the viewing of unpleasant slides. In neither study did the authors find variations in onset latency of the electromyographic response after dosing with diazepam.

In the present experiment, we examined the effects of a single oral dose of alprazolam on the acoustic component of the startle response in healthy volunteers. The aim of the study was to assess the effects of this potent benzodiazepine, used in the treatment of anxiety and panic disorder, on both amplitude and onset latency of the reflex. The time course of alprazolam's effects on startle was also studied. Consequently, unlike in previous studies, electromyographic activity of the orbicularis oculi muscle was recorded at various time points after the drug's peak plasma concentrations (+5 h, +7 h, +11 h after drug intake). We postulated that a potential alprazolam-induced blocking of startle would be followed by a time-dependent recovery, easily observable by measuring the time course of the eyeblink reflex as the drug was gradually being eliminated from the body.

## Materials and methods

### Subjects

Eight undergraduate students (five males and three females; mean age 21.8 years, range: 20–23) were included, after having given their written informed consent. Subjects were paid for their voluntary participation. None of them had a history of psychiatric or neurological disorders. They had not taken medication in the 2 weeks preceding this study and they abstained from alcohol, tobacco and caffeinated drinks 48 h prior to each experimental day. The study was conducted in accordance with the Declarations of Helsinki and Tokyo concerning experimentation on humans and was approved by the hospital's Ethics Committee. Prior to their inclusion in the study, subjects answered two personality questionnaires: the Eysenck Personality Inventory (Eysenk and Eysenk 1963) (EPI), and the trait-anxiety scale from the State-Trait Anxiety Inventory (Spielberger et al. 1970) (STAI-T). The purpose of personality screening was to assess for possible extreme scores on relevant emotion-related trait dimensions (Cook et al. 1991). Mean trait-anxiety value (STAI) was 14.62 (range 8–21), 8.88 (5–14) for the Neuroticism subscale and 12.5 (9–17) for the Extraversion subscale. Subjects were told that the purpose of the experiment was to assess

individual reactivity to intense auditory stimuli under different drug conditions.

### Stimulus

The acoustic startle stimulus was a 1-kHz pure tone of 116 dB [A], with a 50-ms duration and an instantaneous rise/fall time, presented binaurally through air headphones.

### Procedure

The experiment was carried out according to a double-blind randomized crossover placebo-controlled design. Subjects received a single oral dose of either alprazolam 2 mg or placebo in a balanced order. Experimental days were 1 week apart. In order to study a hypothetical inhibition of the startle response and its recovery with time, the recording sessions were undertaken at time points corresponding to the descending portion of the concentration-time curve (i.e. elimination phase). Accordingly, the first recording time was set at 5 h after drug administration, which is between two and three times the  $t_{max}$  value reported in the literature for a 2 mg immediate release alprazolam formulation (Mumford et al. 1994).

Subjects attended the research unit on 2 separate experimental days. On both occasions, they received alprazolam or placebo and participated in three recording sessions held 5, 7 and 11 h after drug/placebo administration. Upon arrival in the laboratory, they received instructions from the experimenter, a cannula was placed for drawing blood samples in the cubital vein and medication was given. During each recording session they were seated in a comfortable reclining chair in a dimly lit sound-attenuated and electrically shielded chamber, and were asked to remain alert throughout the experiment. They were visually monitored for alertness during the recording. Blood was drawn immediately prior to each session and at various additional time points in order to establish the drug's pharmacokinetic profile. Drug plasma concentrations were assessed through a previously published HPLC method (Rieck and Platt 1992).

Each recording session consisted of an initial startle trial followed by four blocks of five trials. The inter-trial interval varied randomly from 8 to 30 s, with a mean value of 16.5 s. Different inter-trial interval sequences were used in each recording session within the same experimental day, the only constraint being that mean values for inter-trial intervals remained equal for each session. The same three sequences were administered in the placebo and alprazolam conditions. Immediately after each recording session, participants were asked to rate their level of drowsiness and the perceived intensity of the sound probe by means of visual analog scales (VAS), consisting of two 100-mm horizontal lines (none, extreme).

### Psychophysiological recording

Surface orbicularis oculi electromyographic activity (EMG) was bipolarly recorded with two 0.5 cm disk electrodes (Ag/AgCl), placed 1 cm below and 1 cm medial from the external canthus of the left eye, following the guidelines set by Fridlund and Cacioppo (1986). Spontaneous and voluntary blinking was also controlled by means of two electrodes placed above and below the right eye and the ground electrode was placed on the forehead. Impedance level was maintained below 5 k $\Omega$ . Special care was taken to ensure the accurate positioning of the electrodes in order to avoid measurement errors between the two treatment conditions. Raw EMG was AC amplified with a Grass 8 plus amplifier, using a 10- to 500-Hz bandpass analog filter. The EMG signal was digitized at a 1000 Hz rate.

## Data analysis

The EMG raw signal was subsequently full-wave rectified off-line and smoothed using a 5-point moving average filter. Startle latency onset was defined as the first increment of EMG level two standard deviations above the average baseline, not followed by a return to baseline within the next 15 ms. Baseline EMG was computed as the mean EMG in the 30 points preceding stimulus onset. Trials in which the apparent response had an onset latency of less than 20 ms after stimulus administration and/or a rise time greater than 95 ms were discarded. In those trials in which no response was detected, amplitude and latency were scored as a missing value and were excluded from further calculations. The mean percentage of rejected trials was 7.6%. No significant differences between the different treatment conditions and sessions were found. Peak eyeblink amplitude was defined as the highest point in the EMG response within a time window of 120 ms after stimulus administration.

Besides the above-mentioned parameters, level of reactivity and short-term habituation were also assessed (Braff et al. 1992). Reactivity was defined as the value of blink amplitude for each subject in the first startle trial. The short-term habituation effect was tested by introducing a within-subject factor (block) in the statistical analysis. Blink amplitude and latency were averaged for each block of stimuli within each recording session, and these data were subjected to a  $4 \times 2 \times 3$  (block, treatment and session) analysis of variance (ANOVA) with repeated measures. Greenhouse-Geisser epsilon was used to correct possible violations of the sphericity assumption and to reduce type I errors (Jennings 1987). The exact  $P$  values after correction are shown.

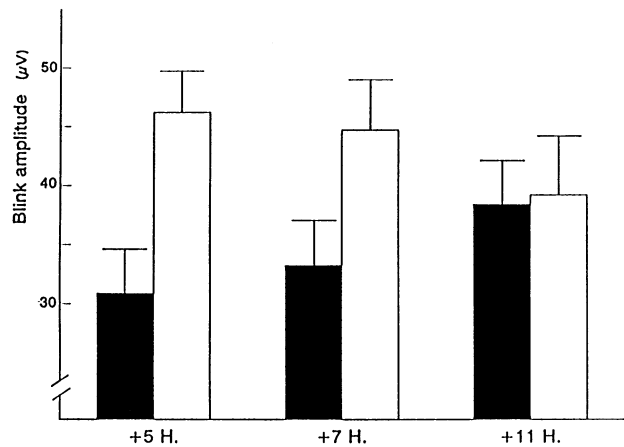
## Results

### Reactivity and habituation

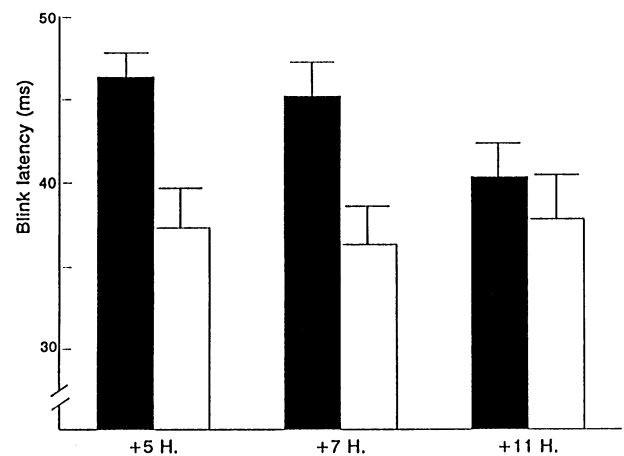
There were no significant main effects of treatment, session or their interaction for amplitude of the first eyeblink reflex. Regarding habituation within each session (short-term habituation), a main effect of block was found [ $F(3,21) = 22.71$ ,  $P = 0.001$ ,  $\epsilon = 0.4652$ ] for eyeblink amplitude in the ANOVA. The mean amplitude of the eyeblink reflex showed linear [ $F(1,7) = 27.1$ ,  $P = 0.001$ ] and quadratic [ $F(1,7) = 13.9$ ,  $P = 0.007$ ] reduction tendencies across blocks [mean amplitude for the first block was  $43.6 \mu\text{V} \pm 2.5$  (SEM); 2nd block,  $37.8 \mu\text{V} \pm 3.4$ ; 3rd block,  $36.5 \mu\text{V} \pm 3.8$  and 4th block  $34.3 \mu\text{V} \pm 4.0$ ]. As no significant interaction was found between block and the other factors (treatment, session or their interaction), block factor will be omitted in the following paragraphs in order to simplify the exposition of results.

### Onset latency and amplitude of eyeblink reflex

Figure 1 presents the main results for mean eyeblink amplitude. As expected, startle magnitude was affected by alprazolam, with a significant amplitude reduction in this treatment condition compared to placebo [ $F(1,7) = 8.87$ ,  $P = 0.021$ ; alprazolam:  $34.1 \mu\text{V} \pm 3.1$ ; placebo:  $43.3 \mu\text{V} \pm 4.1$ ]. Although session effect was not significant [ $F(2,14) = 0.02$ ], the interaction between



**Fig. 1** Mean startle amplitudes (in  $\mu\text{V}$ ) in the alprazolam and placebo conditions in the three recording sessions after 5, 7 and 11 h of drug administration. Error bars denote 1 SEM. ■ Alprazolam, □ placebo



**Fig. 2** Mean onset latencies (in ms) in the alprazolam and placebo conditions in the three recording sessions after 5, 7 and 11 h of drug administration. Error bars denote 1 SEM. ■ Alprazolam, □ placebo

treatment  $\times$  session was found to be significant [ $F(2,14) = 7.87$ ,  $P = 0.021$ ,  $\epsilon = 0.5621$ ]. This interaction reflected a different pattern of startle amplitude variation throughout sessions in each experimental condition. A progressive increase was observed after alprazolam, while a gradual decrease was obtained after placebo.

As shown in Fig. 2, alprazolam increased the onset latency of the eyeblink reflex [ $F(1,7) = 23.73$ ,  $P = 0.002$ ; alprazolam  $43.9 \text{ ms} \pm 1.5$ ; placebo:  $37.1 \text{ ms} \pm 2.3$ ]. Moreover, onset latency tended to decrease within each treatment condition. This resulted in a significant session main effect [ $F(1,7) = 4.83$ ,  $P = 0.034$ ,  $\epsilon = 0.8458$ ]. However, the latency reduction experienced by the eyeblink reflex between sessions under alprazolam treatment was more intense than in the placebo condition. This effect was reflected by a significant treatment  $\times$  session interaction [ $F(2,14) = 5.23$ ,  $P = 0.025$ ,  $\epsilon = 0.9024$ ].

**Table 1** Visual analog scale ratings in millimetres and plasma levels of alprazolam in ng/ml [mean (SEM)] in the alprazolam and placebo conditions, in the three recording sessions after 5, 7 and 11 h of drug administration

	Alprazolam 2 mg			Placebo		
	+5 h	+7 h	+11 h	+5 h	+7 h	+11 h
Drowsiness	50.3 (5.4)	42.3 (7.8)	29.2 (4.8)	16.6 (4.7)	22.5 (5.4)	21.0 (6.4)
Sound intensity	58.3 (5.4)	64.2 (3.7)	68.1 (4.2)	69.1 (3.1)	65.0 (6.7)	63.7 (9.0)
Plasma levels	25.6 (1.2)	21.8 (1.2)	16.0 (1.3)	–	–	–

### Subjective effects (VAS scales), anxiety and plasma levels

A significant treatment effect was observed for drowsiness [ $F(1,7) = 10.26$ ,  $P = 0.015$ ; alprazolam:  $40.6 \text{ mm} \pm 5.4$ ; placebo:  $20.04 \text{ mm} \pm 4.7$ ]. Additionally, the interaction between treatment  $\times$  session was found to be significant [ $F(2,14) = 5.32$ ,  $P = 0.032$ ,  $\epsilon = 0.7566$ ]. No significant effects were observed for perceived sound intensity, although subjective intensity tended to increase linearly from the first to the third session in the alprazolam condition as can be seen in Table 1. There were no significant Pearson correlations between anxiety scores (STAI or Neuroticism subscale) and startle amplitude or latency measures. Alprazolam's  $C_{\text{max}}$  and  $T_{\text{max}}$  values were  $34.48 \pm 4.99 \text{ ng/ml}$  (mean  $\pm$  SD) and 135, 45–180 min (median, range), respectively. Mean plasma levels immediately before the three recording sessions are shown in Table 1.

### Discussion

Alprazolam 2 mg significantly reduced startle amplitude compared to placebo, in agreement with results obtained by Abduljawad et al. (1997), after administration of a 10 mg dose of the benzodiazepine diazepam. This robust effect would suggest that benzodiazepines as a group can effectively modulate the intensity of the reflex, and thus provide further evidence supporting a common inhibitory activity of anxiolytic drugs on human startle response, as previous work done with the  $\alpha_2$ -adrenoceptor agonist clonidine (Kumari et al. 1996) has found an analogous dampening effect, despite their different binding sites in the CNS. Additionally, alprazolam produced a marked increase in latency onset. This phenomenon has not received much attention in the literature, although data regarding noradrenergic modulation of this parameter are available. Thus, both latency increases and reductions have been described by Kumari et al. (1996) and Morgan et al. (1993), after administration of clonidine and yohimbine, respectively. In addition, alcohol has also been found to increase startle onset latency (Stritzke et al. 1995), whereas previous experiments with benzodiazepines have failed to detect this effect (Patrick et al. 1996; Abduljawad et al. 1997).

The design of the study, with recordings at different time points after alprazolam administration, allowed

us to study the time course of drug effects on startle. The response underwent a time-dependent recovery throughout sessions, which was made apparent as a tendency of amplitude and latency towards values observed after placebo. Thus, after dosing with alprazolam, amplitude values were lowest at the first recording point, 5 h after ingestion, gradually increasing at 7 h and reaching a maximum at 11 h. Conversely, a clear between-session habituation process was observed after administration of placebo. Therefore, it can be inferred that startle amplitude tended to increase as the drug was being eliminated from the system, opposing the habituation process seen in the absence of the drug. Onset latency displayed the opposite evolution, being maximum at 5 h and declining with time. As previously mentioned, both parameters tended towards values seen in the placebo condition although they did not reach them, which suggests that although masked by the potent effects of alprazolam, between-session habituation was still present. Interestingly, a similar within-session habituation pattern was observed for both treatments, with responses in the initial blocks of each session being greater than in the later blocks. Similar to the results obtained by Kumari et al. (1996), alprazolam had no effect on the rate of habituation.

At first glance, startle amplitude values after alprazolam would seem to be consistent with previous animal work (Davis 1986), which indicates that drugs belonging to different structural groups, but having a common anxiety relieving activity in humans, effectively reduce startle in rats when the fear-potentiated startle paradigm, a proposed fear and anxiety animal model, is used. This has been demonstrated for the barbiturate sodium amyltal (Chi 1965), the benzodiazepines diazepam and flurazepam (Davis 1979a; Berg and Davis 1984), morphine (Davis 1979b), alcohol (Williams 1960, in Davis 1986) and the serotonergic anxiolytics buspirone and gepirone (Davis et al. 1985). The implication of noradrenergic pathways modulating fear-potentiated startle has also been described, as the  $\alpha_2$ -adrenoceptor agonist clonidine also causes an effective blockade of the response (Davis et al. 1979). Conversely, drugs that cause anxiety in humans by increasing noradrenergic transmission, such as piperoxane and yohimbine, increase fear-potentiated startle in rats (Davis et al. 1979). Additionally, the suppression of fear-potentiated startle caused by diazepam in rats has been effectively reversed by the benzodiazepine antagonist R015-1788 (Berg and Davis 1984). All the above-mentioned anxiolytics have been reported to

reduce the potentiated startle in rats without decreasing baseline startle, thus displaying a selective action on the enhanced response.

In view of this selective activity, Patrick et al. (1996) have postulated that anxiolytic drugs would modulate the reflex by acting upon a putative secondary neural circuit (Hitchcock and Davis 1991) responsible for the fear potentiation of the basic response. According to data from histological and electrical stimulation studies, the amygdala would play a major role in this circuit. In fact, the nucleus reticularis pontis caudalis receives direct projections from the central nucleus of the amygdala (Rosen et al. 1991) and electrical stimulation of the latter elicits a behavioural state that can be readily assimilated with fear (Davis 1996). Conversely, lesions in this pathway have been shown to prevent fear-potentiated startle (Hitchcock and Davis 1991). Thus, the effects of anxiolytics on the fear-potentiated startle would be due to a specific effect on this secondary modulatory pathway, and the observed amplitude reductions would not obey a direct drug action on the basic neural arc or a decrease in general activation.

Nevertheless, results derived from human research using anxiogenic and anxiolytic drugs are more controversial than data obtained in animal studies. Regarding anxiety-provoking drugs, the  $\alpha_2$ -adrenoceptor antagonist yohimbine has been found to increase startle baseline amplitude and reduce startle baseline latency in both healthy subjects (Morgan et al. 1993; Krystal et al. 1997) and detoxified alcoholics (Krystal et al. 1997). In another study, however, Morgan et al. (1995) observed amplitude increases after dosing with yohimbine in combat veterans with post-traumatic stress disorder, but not in combat controls. The unspecific CNS stimulant caffeine has also been found to increase baseline startle magnitude in habitual caffeine users (Andrews et al. 1998).

Contradictory results regarding startle modulation are also to be found in the few human studies carried out to date with benzodiazepines. On one hand, in the present study and in that by Abduljawad et al. (1997), benzodiazepines have been shown to reduce baseline startle. In both cases, startle probes were used, without the simultaneous administration of conditioned or emotional cues. On the other hand, Patrick et al. (1996) concluded that diazepam effectively blocked fear-potentiated startle in humans, without showing any measurable effects on baseline startle levels. They studied the effects of 10 and 15 mg doses of diazepam on the startle response in a setting in which subjects were presented with neutral or aversive slides. It appears that they observed a selective blocking effect of the higher dose on startle potentiation induced by slides with a negative emotional load, with no effects for either dose on overall startle magnitude. It is difficult to find a valid explanation for these contradictory results, given that Abduljawad had already found baseline startle reduc-

tions at the 10 mg dose level. In view of the potent effects shown by alprazolam on startle amplitude in the present study, and considering human data for other CNS depressors such as alcohol (Stritzke et al. 1995) and clonidine (Kumari et al. 1996; Abduljawad et al. 1997), we are inclined to believe that all these drugs are capable of eliciting an unspecific effect on general activation, since variation in the parameters evaluated in the present study ran parallel to subjective drowsiness scores. Besides their anxiolytic activity, benzodiazepines also display a sedative action, an effect usually regarded as undesirable. Consequently, a reduction in general activation levels may also have contributed, together with anxiolytic activity, to the marked inhibition of the startle response caused by alprazolam. Nevertheless, we cannot disregard the large corpus of data derived from animal studies, suggesting a selective action of anxiolytics on structures involved in the genesis of the fear and anxiety responses. It could be argued that the reductions of baseline startle seen in the present study may have been due to the large alprazolam dose used. In this regard, although within the habitual therapeutic dose ranges, the dose administered was in fact higher than the diazepam doses used by Abduljawad et al. and Patrick et al. in their studies, being roughly equivalent to 20 mg diazepam (Baldessarini 1996). This probably translated into a greater sedative activity, which may have accounted for the reductions in baseline startle. Were it so, this explanation for the present results would still not help clarify why Patrick et al. observed only a selective effect of diazepam on the fear-potentiated startle after administering 15 mg diazepam, whereas Abduljawad saw reductions in baseline startle using a 10 mg dose. Obviously, further human studies using wider dose ranges of anxiolytic/sedative drugs are needed, implementing both the basic and the fear-potentiated startle paradigms, in order to ascertain the viability of a possible human psychophysiological model that could discriminate between sedation and anxiolytic activity and could therefore serve for the screening of novel drugs with putative selective anxiolytic properties.

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