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Serotonin does not mediate anxiolytic effects of buspirone in the fear-potentiated startle paradigm: comparison with 8-OH-DPAT and ipsapirone

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Abstract. The present study evaluated the role of various neurotransmitter systems in mediating buspirone's blockade of the fear-potentiated startle effect, where acoustic startle amplitude is normally increased in the presence of a light previously paired with a shock. Large lesions of the dorsal and median raphe nuclei or IP injections of the serotonin antagonists cinanserin (10 mg/kg) or cyproheptadine (5 mg/kg) did not alter fear-potentiated startle, nor did these treatments prevent buspirone (5 or 10 mg/kg SC) from blocking fear-potentiated startle. The 5-HT_{1A} agonist 8-OH-DPAT (2.5–10.0) did not block fear-potentiated startle even at doses that produced a marked "5-HT syndrome". Another 5-HT_{1A} agonist, ipsapirone (10–20 mg/kg), blocked potentiated startle only at a very high dose (40 mg/kg). *p*-Chlorophenylalanine and *p*-chloroamphetamine did not alter fear-potentiated startle. Finally, pretreatment with the benzodiazepine receptor antagonist RO-15-1788 (1 mg/kg); the opiate antagonist naloxone (2 mg/kg) or the α_2-adrenergic antagonist yohimbine (5 mg/kg) did not reduce fear-potentiated startle, nor did they prevent buspirone from blocking fear-potentiated startle. Taken together, the data do not support the hypothesis that buspirone's anxiolytic effects are mediated by actions at 5-HT_{1A} receptors and more generally indicate that serotonergic neurons do not play an important role in fear-potentiated startle.

Key words: Buspirone – 8-OH-DPAT – Ipsapirone – Anxiety – Fear – Serotonin – Raphe

The non-benzodiazepine anxiolytic compounds buspirone and gepirone block the expression of conditioned fear as measured with the fear-potentiated startle paradigm (Kehne et al. 1987). The purpose of the present study was to investigate some pharmacological mechanisms by which buspirone blocks fear-potentiated startle.

At the present time, the neurochemical mechanisms underlying buspirone's actions are not understood. One hypothesis is that buspirone's anxiolytic effect is attributable to an interaction with dopaminergic receptors (see Taylor et al. 1982, for review). Contrary to this explanation, gepirone (MJ-13805), an analogue of buspirone with an anxiolytic profile (Temple et al. 1982), and almost as potent as buspirone in blocking fear-potentiated startle, appears to lack activity at dopaminergic receptors (Temple et al. 1982).

Recent electrophysiological and biochemical studies have argued for an involvement of 5-HT receptors in the actions of buspirone, although the precise nature of this involvement is not clear. Buspirone produces an agonist-like reduction in serotonin turnover in various areas of the rodent brain (Hjorth and Carlsson 1982) and it binds with high affinity to 5-HT_1 receptors (Glasser and Traber 1983), probably of the 5-HT_{1A} subtype (Peroutka 1985). Buspirone depresses the firing rates of dorsal raphe neurons following intravenous (de Montigny et al. 1984; Vandermaelen et al. 1986) or iontophoretic (Vandermaelen et al. 1986) administration, consistent with a proposed action as a presynaptic 5-HT_{1A} agonist. In fact, Eison et al. (1986) reported that 5,7-dihydroxytryptamine lesions of 5-HT neurons blocked the anticonflict effects of buspirone and gepirone.

Other evidence supports a possible action at postsynaptic 5-HT_{1A} sites. Binding studies have indicated that the hippocampus has high densities of 5-HT_{1A} binding sites (Pazos and Palacios 1985). Buspirone hyperpolarizes cells in the hippocampus (Andrade and Nicoll 1985), and, along with other 5-HT_{1A} agonists, decreases the amplitude of the population spike elicited by stimulation of afferents to the hippocampus (Mauk et al. 1985). Furthermore, buspirone and other 5-HT_{1A} agonists block the excitation of hippocampal cells by iontophoretically-administered glutamate (Aghajanian et al. 1987). On the other hand, buspirone has been reported to be ineffective (Eison et al. 1986) or only weakly effective (Hjorth and Carlsson 1982) at producing the "5-HT syndrome" characteristic of 5-HT_{1A} receptor activation (Jacobs 1976). In fact, buspirone has sometimes been reported to act like a 5-HT antagonist, since it can attenuate the "5-HT syndrome" produced by 5-methoxy-N,N-dimethyltryptamine (Skolnick et al. 1985; Lucki and Ward 1986) or by 8-OH-DPAT (Reynolds et al. 1986).

The purpose of the present study was to investigate possible serotonergic mechanisms underlying buspirone's anxiolytic action in the fear-potentiated startle paradigm. Various manipulations that alter serotonin function (electrolytic lesions of the serotonin-containing neurons in the dorsal and median raphe nuclei or various serotonergic antagonists) were tested for their ability to alter buspirone's blockade of potentiated startle. Other 5-HT agonists were tested to determine if they mimicked the ability of buspirone to block potentiated startle. These included ipsapirone, 8-OH-

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DPAT, and the 5-HT releaser *p*-chloroamphetamine. In addition, since previous research has shown that stimulation of benzodiazepine, opiate, or α_2-adrenergic receptors blocks fear-potentiated startle (Davis 1979a, b; Davis et al. 1979), specific antagonists for these receptors were tested for their ability to prevent buspirone's blockade of potentiated startle.

Materials and methods

Animals

A total of 144 rats were used. They were all male, albino, Sprague-Dawley (Charles River Co.) weighing between 300 and 400 g. They were housed in group cages of five rats each and maintained on a 12 h:12 h light/dark schedule. Food and water were continuously available. All animals were drug-naive at the start of the experiment.

Apparatus

Potentiated startle training. Five identical boxes (30 × 25 cm × 25 cm high) were used for potentiated startle training. The sides and top of each box were constructed of aluminum, while Plexiglas composed the front and back walls. Each floor consisted of 4.8-mm stainless steel bars spaced 19 mm apart. The boxes were located on two shelves within a 1 × 1 m × 2 m high ventilated, sound-attenuating chamber. The conditioned stimulus (CS) was produced by an 8 W fluorescent light bulb (100 μs rise-time) located on the outside of the back wall of each training box. The unconditioned stimulus (US) was shock generated by five Lehigh Valley constant-current shockers (SGS-004) located outside the chamber. Shock intensity was measured with a 1 Kohm resistor across a differential channel of an oscilloscope in series with a 100 Kohm resistor connected between adjacent floor bars in each training box. Current was defined as the RMS voltage across the 1 Kohm resistor where mA = 0.707 × 0.5 × peak-to-peak voltage. According to this method the shock current was 0.6 mA.

Potentiated startle testing. The apparatus used to measure startle has been described previously (Cassella and Davis 1986). Briefly, five separate stabilimeters were used to record the amplitude of the startle response. Each stabilimeter consisted of an 8 × 15 cm × 15 cm high Plexiglas and wire mesh cage suspended between compression springs within a steel frame. An 8 W fluorescent bulb identical to that used for training was attached to the back of each cage. Cage movement resulted in displacement of an accelerometer where the resultant voltage was proportional to the velocity of displacement. Startle amplitude was defined as the maximum accelerometer voltage that occurred during the first 200 ms after the startle stimulus was delivered and was measured with a specially designed sample-and-hold circuit interfaced to a PDP-11 computer. The stabilimeters were housed in a dimly-lighted, ventilated, sound attenuating chamber. Each cage was located 10 cm from a high frequency speaker (Radio Shack Supertweeter). The startle stimulus was a 50 ms burst of white noise having a rise-decay time of 5 ms. Background white noise, provided by a white noise generator, was 55 db. Sound level measurements were made within the cages using a General Radio Model 1551-C sound level meter (A-scale).

Procedure

Prior to fear conditioning the rats were placed in the startle cages and given a brief test period in order to assign each rat into matched groups having equivalent startle levels. Naive rats were placed in the startle test cages and after 5 min presented with 30 startle stimuli, ten at each of three different intensities (95, 105, and 115 db). The various stimulus intensities were presented in a balanced, irregular order across this test session. The rats subsequently were divided into groups of five rats each with each group having a similar mean startle amplitude based on these 30 stimuli.

On the day following this matching procedure, the rats were trained for potentiated startle. On each of 2 consecutive days, the animals were placed in the training boxes and after 5 min received the first of ten light-shock pairings. The shock was delivered during the last 500 ms of the 3700 ms duration light at an average inter-trial interval of 4 min (range 3–5 min).

Three to four days following the second training session the animals were tested for potentiated startle. After the appropriate drug injections, the rats were placed in the startle cages and after 5 min presented with ten noise bursts (95 dB) in the dark. After these initial ten stimuli each animal received 20 noise bursts at each of three different stimulus intensities (90, 95, 105 dB) with half of the stimuli at each of these intensities presented in darkness (Noise-Alone trial type) while the other half of the stimuli were presented 3200 ms after the onset of the 3700 ms duration light (Light-Noise trial type). All startle stimuli were presented at a 30-s interstimulus interval. The ten occurrences of each of the six different trial types (e.g., Light-Noise at 95 dB) were presented in a balanced, irregular order across the test session.

Effects of raphe lesions on buspirone's blockade of potentiated startle. Nine rats were matched and trained for potentiated startle over the next 2 days, as described above. Two days later each rat was anesthetized with chloral hydrate and placed into a stereotaxic instrument fitted with blunt ear bars. The skull was exposed and holes were drilled in the skull on the midline at two A–P placements, 7.3 and 8.3 mm posterior to bregma. A Kopf NE-300 electrode (0.25 mm in diameter) insulated to within 0.5 mm of its tip was lowered to a depth of 6.2 and 8.5 mm below the top of the skull through the anterior hole and 6.6 and 8.5 through the posterior hole. A 0.1 mA anodal current was then passed for 60 s at each depth. Thus, four lesions were placed in each of four rats. Sham animals were treated identically except that no current was passed in these rats.

Two weeks after surgery, the sham-operated and raphe-lesioned rats were tested for potentiated startle as described above. Immediately prior to testing, half of the raphe-lesioned rats and half of the sham-operated rats were injected subcutaneously (SC) in the flank with 10 mg/kg buspirone-HCl. The other rats were injected with saline. On the next test day, the rats previously injected with saline were now treated with buspirone and vice versa.

Effects of p-chlorophenylalanine (PCPA) on potentiated startle. Two groups of five rats each were matched and trained for potentiated startle on each of the next 2 days. At 3 and 4 days after training, one group was injected IP with 300 mg/kg (free base weight) PCPA. The other

group was injected with saline on each of 2 days. Two days later all rats were tested for potentiated startle as described above.

Effects of 5-HT and non-5-HT antagonists on buspirone's blockade of potentiated startle. Twelve groups of five rats each were matched, trained and tested for potentiated startle. Separate groups of five rats were pretreated with either saline, cinanserin-HCl (10 mg/kg, salt weight), cyproheptadine (5 mg/kg), naloxone (2.0 mg/kg), Ro 15-1788 (1.0 mg/kg), or yohimbine (5.0 mg/kg) and then treated SC 15 min later with either saline or buspirone (5.0 mg/kg). The rats were immediately placed into the startle cages and testing was begun. The doses and pretreatment times were chosen on the basis of previous studies (Davis 1979a, b; Davis et al. 1979).

Effects of p-chloroamphetamine (PCA), ipsapirone, and 8-OH-DPAT on potentiated startle. Thirteen groups of rats were matched, trained, and tested to generate separate dose-response curves for IP administration of 8-OH DPAT (saline, 2.5, 5.0, and 10 mg/kg, $n=5$ in each group), or ipsapirone (saline, 10.0, 20.0, and 40.0 mg/kg, $n=10$ in each group) on potentiated startle. Injections were made immediately prior to testing. In addition, the effect of *p*-chloroamphetamine (5.0 mg/kg, IP) was assessed in a separate group of rats ($n=5$) 15 min after injection.

Results

Table 1 shows the mean amplitude startle response on the Noise-Alone and Light-Noise trials after injection of either buspirone or saline in the sham-operated rats, raphe-lesioned rats, and in rats treated 48 h earlier with either saline or PCPA. An overall analysis of variance (ANOVA) on the raphe lesion data used trial type (Light-Noise versus Noise-Alone) and drug (buspirone versus saline) as within-subjects factors, and surgery (Raphe versus Sham lesion) as a between-subjects factor. In this and subsequent experiments, the data were collapsed across stimulus intensity unless the statistical analysis indicated an effect of, or interaction with, intensity. The presence of potentiated startle was indicated by an effect of trial type [$F(1,7)=12.30$, $P<0.01$] and the blockade of potentiated startle by buspirone was indicated by a significant trial type by drug interaction [$F(1,7)=12.09$, $P<0.01$]. There were no main effects of surgery and no interactions involving the surgery factor, indicating that raphe lesions did not alter potentiated startle or the ability of buspirone to block potentiated startle. Figure 1 shows histological reconstructions demonstrating the largest (cross hatched) and smallest (solid) lesions of the dorsal and median raphe nuclei. All rats had substantial damage to both nuclei. Analysis of the PCPA data revealed a significant effect of trial type [$F(1,8)=43.95$, $P<0.001$], but no drug by trial type interaction ($F<1$).

Table 1. Mean amplitude startle on Noise-Alone and Light-Noise trial types following SC administration of saline or buspirone in rats that had been previously received electrolytic or sham lesions of the raphe nuclei, or in rats that had been pretreated with IP saline or PCPA. Data are collapsed across the three stimulus intensities used to elicit startle

Treatment	Test trial		
	Noise-Alone	Light-Noise	Potentiated startle
Sham lesion			
Saline	81.7	113.6	+31.9
Buspirone	79.2	78.5	− 0.7
Raphe lesion			
Saline	89.4	127.6	+38.2
Buspirone	102.4	90.9	−11.5
Saline	59.2	89.4	+30.2
PCPA	66.3	112.7	+46.4

Figure 2 shows the effects of IP administration of various doses of ipsapirone (left panel) or 8-OH DPAT (right panel) on potentiated startle, collapsed across the three stimulus intensities. The right panel of Fig. 2 shows that 8-OH DPAT failed to block potentiated startle. The drug doses used did produce a marked behavioral effect in the form of a "5-HT syndrome". ANOVA revealed a significant effect of fear [$F(1,16)=146.04$, $P<0.001$], but no dose by fear interaction [$F(3,16)=1.30$, not statistically significant), supporting the conclusion that 8-OH DPAT did not block potentiated startle. The left panel of Fig. 2 shows that ipsapirone blocked potentiated startle only at the highest dose administered (40 mg/kg). Analysis of the ipsapirone data revealed a significant effect of fear [$F(1,36)=55.27$, $P<0.001$], a significant effect of dose [$F(3,36)=5.74$, $P<0.002$], and a significant dose by fear interaction [$F(3,36)=4.78$, $P<0.01$]. Subsequent individual *t*-tests revealed that potentiated startle was present in the saline-treated rats [$t(9)=4.22$, $P<0.005$], and in rats treated with 10 mg/kg [$t(9)=6.09$, $P<0.001$] or 20 mg/kg doses [$t(9)=3.01$, $P<0.05$], whereas it was blocked at the 40 mg/kg dose [$t(9)=1.62$, n.s.]. The Noise-Alone trials for the rats receiving 40 mg/kg ipsapirone were significantly depressed relative to the Noise-Alone trials for rats receiving saline [$t(18)=3.27$, $P<0.005$], indicating that the blockade of potentiated startle by ipsapirone occurred only at a dose which by itself significantly depressed startle amplitude. In addition, potentiated startle was demonstrated in a separate group of rats treated with 5 mg/kg PCA [data not shown; Noise-Alone: 74.2; Light-Noise: 119.0; $t=4.21$, $P<0.02$].

Figure 3 shows the effects of various IP pretreatments with saline, 5 mg/kg cyproheptadine, 10 mg/kg cinanserin, 5 mg/kg yohimbine, 1.0 mg/kg Ro 15-1788, and 2.0 mg/kg naloxone on potentiated startle in rats that were subsequently treated SC with either water or 2.5 mg/kg buspirone. Each bar represents data collapsed across the two lowest eliciting stimulus intensities (95, 105 dB). The highest intensity was not included, since buspirone, in combination with the antagonists, generally appeared to depress the Noise-Alone trials at this intensity. This intensity-dependent depression was indicated in a 3-factor ANOVA of the Noise-Alone trials, which revealed a significant treatment by intensity by pretreatment interaction [$F(2,96)=23.38$, $P<0.001$]. Analysis of the data from the two lower intensities revealed significant effects of fear [95 dB: $F(1,48)=27.57$, $P<0.001$; 105 db: $F(1,48)=68.18$, $P<0.001$] and significant treatment by fear interactions [95 dB: $F(1,48)=24.96$, $P<0.001$; 105 dB: $F(1,48)=31.84$, $P<0.001$], indicating that buspirone blocked potentiated startle. More importantly, there was no treatment by fear by pretreatment interaction ($F<1$ at both intensities), indicating that buspirone's blockade of potentiated startle was

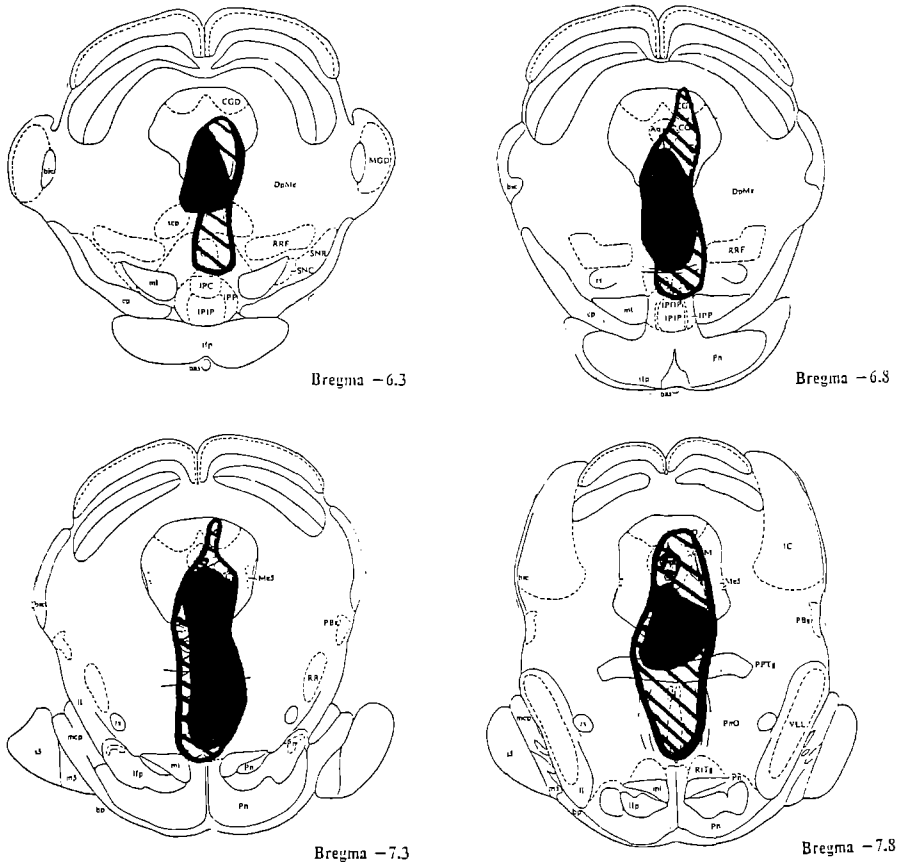

Fig. 1. Histological reconstruction demonstrating the largest *(cross-hatched)* and smallest *(solid)* lesions of the dorsal and median raphe nuclei. All rats had substantial damage to both nuclei

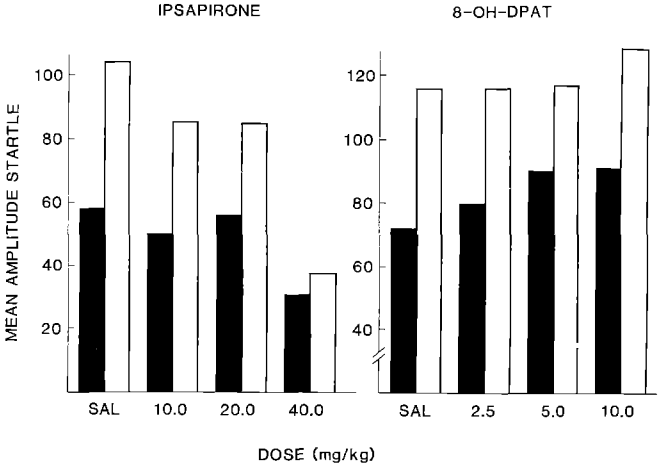

Fig. 2. Mean amplitude startle on Noise-Alone trials *(dark bars)* and Light-Noise trials *(open bars)* in rats treated SC with saline or ipsapirone (10.0, 20.0, or 40.0 mg/kg; *left panel*) or in rats treated IP with saline or 8-OH-DPAT (2.5, 5.0 or 10.0 mg/kg; *right panel*). Data are collapsed across the three stimulus intensities used to elicit startle

not significantly attenuated by the antagonists of these different receptor types.

Discussion

The primary goal of this study was to use a variety of manipulations to evaluate the possible role of serotonin neurons or receptors in mediating the ability of buspirone to block conditioned fear measured with the potentiated startle response. Buspirone is known to depress markedly the firing rate of neurons in the dorsal raphe nucleus after intraveneous or iontophoretic application (Vandermaelen et al. 1986), indicating a pre-synaptic locus of action. However, buspirone's blockade of potentiated startle was not attenuated by electrolytic lesions of the dorsal and median raphe nuclei. Buspirone is also known to have actions at post-synaptic receptors in areas such as the hippocampus (Andrade and Nicoll 1985). However, its actions on fear-potentiated startle were not blocked by pretreatment with the serotonergic antagonists cinanserin or cyproheptadine. Moreover, exploratory studies showed that pindolol (10 mg/kg), another 5-HT_1 antagonist (Tricklebank et al. 1984), also did not prevent buspirone's anxiolytic effect. While this may simply reflect an inability of these antagonists to block buspirone at a 5-HT-1A receptor, buspirone's anxiolytic action was not mimicked by PCA, at a dose and test-time in which the drug would be expected to increase 5-HT release. Moreover, ipsapirone did not block fear-potentiated startle except at a very high dose. Since in vitro studies have previously demonstrated that ipsapirone is slightly more potent than buspirone in binding to 5-HT_{1A} sites labeled with ^{3}H-8-OH-DPAT (Peroutka 1985), the marked difference in potency between buspirone and ipsapirone in the present study probably indicates that these compounds do not block potentiated startle by actions at 5-HT_{1A} binding sites. This conclusion is supported by the fact that the highly selective 5-HT_{1A} agonist, 8-OH-DPAT, did not block potentiated startle despite a clear indication of receptor activation evidenced by a pronounced "5-HT syndrome" observed during fear-potentiated startle testing.

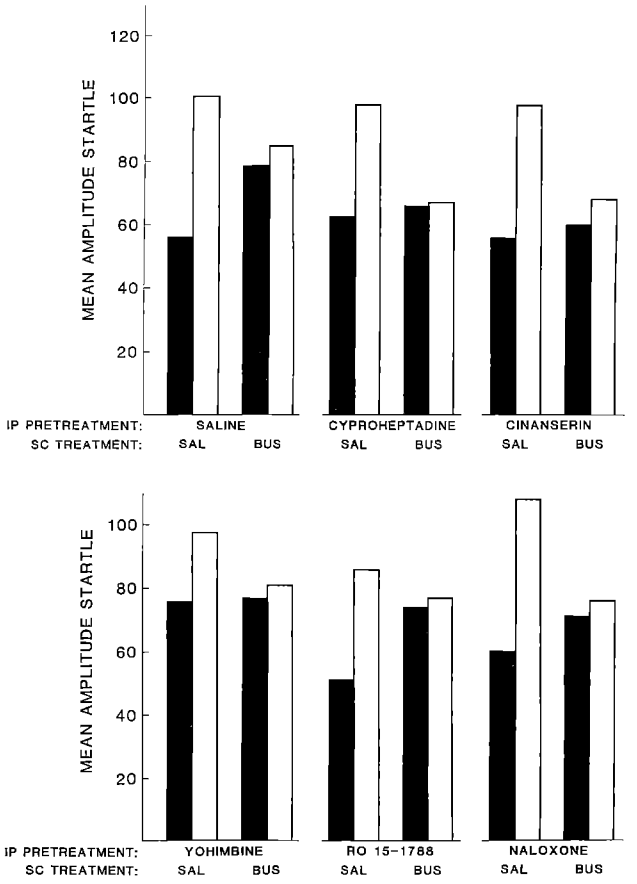

Fig. 3. Mean amplitude startle on Noise-Alone trials *(dark bars)* or Light-Noise trials *(open bars)* in rats pretreated IP with saline, 5.0 mg/kg cyproheptadine, 10.0 mg/kg cinanserin, 5.0 mg/kg yohimbine, 1.0 mg/kg Ro-15 1788, or 2.0 mg/kg naloxone and treated SC with either saline or 5.0 mg/kg buspirone. Data are collapsed across the two lowest stimulus intensities used to elicit startle

Thus, despite buspirone's well documented actions on serotonergic neurons (see Introduction), the present study suggests that these actions are not involved in buspirone's blockade of fear-potentiated startle.

It should be emphasized that in addition to having no effect on buspirone's anxiolytic action, the various manipulations of serotonergic systems used in the present study failed, by themselves, to alter potentiated startle performance. Thus raphe lesions, *p*-chlorophenylalanine, *p*-chloroamphetamine, cinanserin or cyproheptadine did not cause measurable changes in fear-potentiated startle. This lack of involvement of serotonin in potentiated startle can be contrasted to results obtained using other animal models of anxiety. Thus, a large number of studies have shown that treatments that deplete 5-HT are associated with anticonflict effects (cf Soubrie 1986) although notable exceptions can be found (Commissaris and Rech 1982; Kilts et al. 1982). In addition, serotonin plays a role in the acquisition and performance of conditioned fear as measured with avoidance paradigms (Archer 1982; Ogren 1982a, b, 1985; Ogren and Johansson 1985). Thus, the serotonin releaser *p*-chloroamphetamine disrupted passive avoidance performance when injected prior to testing (Archer 1982) whereas, in the present study, it did not alter the performance of potentiated startle. The reason for the apparent lack of involvement of serotonin in potentiated startle relative to these other paradigms is currently not known. One plausible explanation has been provided by Soubrie (1986), who suggested that serotonin may not be involved specifically in anxiety, but more generally in the inhibition of inappropriate responses. Thus, in animal models where anxiety results in the animal's withholding responses to avoid punishment (i.e., not licking a water spout; not jumping off a platform onto an electrified grid), decreases in serotonergic function might generally diminish the ability of the animal to withhold that response. In the startle paradigm the potentiation of an elicited reflex response serves as the index of fear rather than the withholding of a response. An alternative explanation is that potentiated startle measures a different type of fear that may be insensitive to pharmacological manipulation of the serotonin system.

Given the contradictory evidence from preclinical models of anxiety implicating serotonin involvement in buspirone's anxiolytic action in particular and anxiety in general, it is of interest to note clinical studies that have used serotonergic drugs in the treatment of anxiety. Anxiolytic properties have been reported for the serotonin antagonist mianserin (Murphy 1978) and for the serotonin uptake blocker zimelidine (Evans and Moore 1981; Koczkas et al. 1981). On the other hand, PCPA has been reported to increase anxiety in depressed patients treated with tranylcypromine (Shopsin et al. 1976). Moreover, indirect evidence gathered from CSF metabolite studies suggests an inverse relationship between serotonin activity and anxiety (see Soubrie 1986). Thus, the clinical evidence for the involvement of serotonin in anxiety currently remains unclear.

Because of the apparent lack of involvement of serotonin in buspirone's blockade of potentiated startle, other pharmacological mechanisms of action were investigated. Previous studies have shown that potentiated startle can be blocked by the α_2-agonist clonidine (Davis et al. 1979), by the opiate agonist morphine (Davis 1979b), or by the benzodiazepines diazepam or flurazepam (Davis 1979a; Berg and Davis 1984). Buspirone's blockade of potentiated startle is not attributable to an α_2-adrenergic agonist action based on the following data. First, the buspirone effect was not blocked by pretreatment with the α_2-adrenergic antagonist yohimbine (present study). Second, unlike clonidine, which depresses single unit firing of locus coeruleus neurons (Cedarbaum and Aghajanian 1978), buspirone actually increases locus coeruleus firing through a mechanism independent of α_2-adrenergic receptors (Sanghera and German 1983). Furthermore, both gepirone and the common metabolite 1-PP share buspirone's action of increasing locus coeruleus firing. The fact that 1-PP is ineffective in blocking potentiated startle (Kehne et al. 1987) further dissociates buspirone's effect on locus coeruleus activity from its anti-anxiety action on potentiated startle.

Other studies demonstrated that buspirone's blockade of fear-potentiated startle was not affected by naloxone or by RO 15-1788, indicating that buspirone's blockade of potentiated startle does not seem to result from an agonist action at either opiate or benzodiazepine receptors.

As indicated in the Introduction, buspirone has been reported to bind to dopamine receptors (Stanton et al. 1981; Peroutka 1985). Buspirone acts like a dopamine antagonist in that it markedly increases dopamine turnover (Hjorth and Carlson 1982; McMillen and McDonald 1983; McMillen and Mattiace 1983) and antagonizes apomorphine-induced stereotypies (Riblet et al. 1982). However,

buspirone does not seem to have a classic neuroleptic profile since it does not produce catalepsy nor does it block apomorphine-induced turning in rats given unilateral 6-OHDA lesions of the substantia nigra (McMillen et al. 1983). On the basis of electrophysiological studies, it has been suggested that buspirone's ability to increase dopamine turnover may result from antagonism of pre-synaptic dopamine autoreceptors (McMillen et al. 1983).

Several lines of evidence argue against a simple role for dopamine in mediating buspirone's blockade of potentiated startle. First, the analogue gepirone was only slightly less potent than buspirone in blocking potentiated startle (Kehne et al. 1987). Unlike buspirone, gepirone does not bind to dopamine receptors (Riblet et al. 1982), suggesting that a common dopamine antagonist action does not underlie the anxiolytic activity of these compounds. However, the possibility that buspirone might work through a different neurochemical mechanism than gepirone cannot be excluded. Second, severe depletion of dopamine in the caudate nucleus produced by 6-OHDA infusions into the substantia nigra does not block or attenuate potentiated startle (Hitchcock and Davis, unpublished observations). It is possible that buspirone's actions might be mediated through non-striatal dopaminergic pathways. Using other models of anxiety, both positive (Pich and Samanin 1986) and negative (Witkin and Barrett 1986) involvement of dopamine in the anxiolytic effects of buspirone have been reported. However, Louilot et al. (1986) have recently used in vivo voltammetric methods to show that buspirone elevated DOPAC levels in the striatum but not in the nucleus accumbens (a meso-limbic projection area).

In addition to actions on monoaminergic systems, buspirone has been proposed to have a picrotoxin-like antagonist effect on presynaptic GABA receptors (Eison and Eison 1984). These authors suggested that a buspirone action on presynaptic GABA receptors could enhance GABA transmission, thereby having a functional effect similar to that of the benzodiazepines. Further studies will evaluate the possible involvement of GABA and non-striatal dopaminergic receptors (e.g., in the central nucleus of the amygdala which is known to be critical for potentiated startle – Hitchcock and Davis 1986) in the expression of fear-potentiated startle and its blockade by buspirone.

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