Naunyn-Schmiedeberg's Arch Pharmacol (1987) 336:5–10

Naunyn-Schmiedeberg's
Archives of Pharmacology
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Novel anxiolytics discriminate between postsynaptic serotonin receptors mediating different physiological responses on single neurons of the rat hippocampus

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Summary. The effects of buspirone on hippocampal pyramidal cells of the CA1 region were examined by means of intracellular recordings in in vitro hippocampal brain slices. Bath administration of buspirone elicited a long lasting hyperpolarization which was mediated by an increase in potassium conductance and resembled the hyperpolarizing component of the response to 5-HT (5-hydroxytryptamine). Buspirone, however, failed to mimic the depolarizing action of 5-HT or to reduce the calcium-activated afterhyperpolarization. Quantitative comparisons of the hyperpolarizing responses of 5-HT and buspirone revealed that the maximal hyperpolarization induced by buspirone was significantly smaller than that induced by 5-HT. Since the buspirone induced hyperpolarization was also accompanied by a surmountable antagonism of 5-HT responses, these results indicate that buspirone behaves as a partial agonist at a subpopulation of 5-HT receptors in the CA1 region of the hippocampus. Administration of the buspirone congeners gepirone and isapirone also elicited a hyperpolarization and reduced 5-HT responses, although they lack antidopaminergic activity, indicating that the effects observed with buspirone are unlikely to be mediated through dopamine receptors. These results indicated that novel anxiolytics can discriminate between functional 5-HT receptors. In conjunction with previous biochemical and electrophysiological studies, the present results suggest that their administration might alter the balance of serotonergic actions on postsynaptic neurons.

Key words: Buspirone – 5-HT – 5-HT receptors – Anxiolytics – Hippocampus

Introduction

Buspirone is the prototypical compound of a novel class of non-benzodiazepine anxiolytics reported to be devoid of sedative and anticonvulsant side effects (Goldberg and Finnerty 1979; Taylor et al. 1984; Traber et al. 1984). While its mechanism of action is as yet unclear, buspirone exhibits little affinity for the benzodiazepine binding site and therefore is thought not to act by directly altering GABAergic transmission (Riblet et al. 1982). Buspirone and its analoges gepirone and isapirone do, however, exhibit high affinity for 5-HT_{1A} binding sites in rat and calf brain (Glaser and Traber 1983, 1985; Peroutka 1985) and it is possible that these binding sites might be relevant to their anxiolytic action. Therefore we have used intracellular recording in in vitro rat hippocampal slices to examine the possible actions of buspirone on 5-HT receptors in the CA1 region of the rat hippocampus, an area enriched in 5-HT_{1A} binding sites (Deshmukh et al. 1983; Pazos and Palacios 1985) and where we have recently described two actions of 5-HT mediated through pharmacologically distinct mechanisms (Andrade and Nicoll 1987). Some of these results have been previously presented in preliminary form (Andrade and Nicoll 1985).

Methods

Male albino rats (100–250 g) were used in these experiments. Hippocampal slices were prepared using a manual tissue chopper and incubated for at least 1 h in an interface chamber as described previously (Nicoll and Alger 1981). Single slices were transferred to a recording chamber where they were held submerged between two nylon nets and were continuously perfused with oxygenated medium of the following composition (in mmol/l): NaCl 119, KCl 2.5, NaH_2PO_4 1.0, $MgSO_4 \cdot 7H_2O$ 1.3, $CaCl_2$ 2.5, $NaHCO_3$ 26.2, and glucose 11. Temperature in the bath was continuously monitored and maintained between 29°C and 31°C.

Intracellular recordings were obtained from pyramidal cells of the CA1 region using standard electrophysiological techniques. Briefly, electrodes were pulled on a Narashigi vertical puller to give resistances of 50 MΩ to 200 MΩ when filled with 2 mol/l potassium methylsulphate or 3 mol/l potassium chloride. Electrodes were lowered into the slice with the aid of a motorized hydraulic microdrive (David Kopf) and cells were impaled by briefly increasing the capacity compensation to cause the headstage to oscillate. Subsequent to impalement, cells were hyperpolarized with 1 s long current pulses delivered at 0.5 Hz, a procedure that appeared to help in the recovery and "sealing" of the cell. Electrical signals were amplified with a M-707 amplifier (WPI Instruments) and recorded on a Gould paper chart recorder. Fast transient signals which could not be captured by this recorder were digitalized and disk stored with the aid of a Nicollet 4094 digital oscilloscope. Calcium-dependent afterhyperpolarizations were elicited by triggering calcium

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spikes in the presence of 0.3 μmol/l tetrodotoxin (TTX) and 5 mmol/l tetraethylammonium chloride.

Drugs were administered at known concentrations in the bath or delivered locally to the proximity of the recorded neuron by microiontophoresis. 5-HT solutions to be bath administered were prepared immediately prior to application and administered at a flow rate of approximately 2–3 ml/min. Under these conditions responses to bath administered 5-HT usually exhibited a latency of 20–60 s and equilibrated within 2–3 min. Wash out of the 5-HT was usually accomplished within 2 min. Buspirone and its analogs were also bath administered but, as the time needed for equilibration of these compounds was somewhat longer, 5 min or more were allowed for full equilibration to take place.

5-HT microiontophoresis was accomplished by placing a blunt micropipette filled with 40 mmol/l 5-HT creatinine sulphate (pH 4.0) immediately above the pyramidal cell layer and the amplitude of the 5-HT response was controlled by altering the amplitude or the duration of the current pulse (usually 3–10 s at 40–80 nA). When dose responses were constructed using 5-HT iontophoresis, pulses of logarithmically increasing duration were used, as it is known that the amount of a compound ejected by iontophoresis is linearly related to the ejection time (Bloom 1975). With the iontophoretic micropipette positioned over the slice no retaining current was usually necessary, thus avoiding "warm up" artifacts. Dose response curves obtained in this manner were used to calculate apparent pA2 values from equieffective pulse durations in the presence and absence of buspirone (Kenakin and Black 1978). In two cells tested with two concentrations of buspirone each, the slopes of the Schild regressions obtained with this method were very close to unity. In iontophoretic experiments where a constant 5-HT response was used, ejection pulses were adjusted to give 5–10 mV hyperpolarizations.

Reversal potentials (E_{revs}) for 5-HT and buspirone were determined by comparing steady state current voltage (IV) relations in the presence of TTX (0.3 μmol/l) before and after drug administration. In this procedure the E_{rev} corresponds to the voltage at which the IV lines cross and the accuracy of this determination was improved by fitting a least square linear regression to the non-rectifying portion of the IV curve (approximately −70 mV to −110 mV). Comparing IV relations to determine E_{revs} was chosen over the more conventional method of pulsing the drug while holding the membrane potential at varying levels because of the small amplitude and slow time course of the buspirone response. 5-HT creatinine sulfate and tetraethylammonium chloride were purchased from Sigma and TTX from Calbiochem. Buspirone HCl and gepirone HCl were gifts from Brystol Myers Corp. (Evansville, IN, USA), isapirone HCl (TVX Q 7821) from Troponwerke (Cologne, FRG), and spiperone from Janssen (Beerse, Belgium).

Results

Administration of buspirone (1–100 μmol/l) to hippocampal pyramidal cells of the CA1 elicited a hyperpolarization, which was accompanied by a decrease in input resistance (n = 30 cells, Fig. 1a). This hyperpolarization was small and variable averaging 3 mV ± 1.9 mV at 10 μmol/l (n = 13 cells) and 4 mV ± 0.7 mV at 30 μmol/l (n = 5 cells), a concentration that appeared to be near maximal. The buspirone induced hyperpolarizations could be obtained in normal medium or medium containing TTX (0.3 μmol/l), a concentration which blocks fast sodium channels in this preparation and therefore any action potential dependent release of transmitter.

A hyperpolarization such as that elicited by buspirone could result from an increase in either potassium or chloride conductance. Previous studies in this preparation (Alger and Nicoll 1980) have shown that spontaneous chloride-dependent GABAergic IPSPs reverse polarity when intracellular chloride is increased by using KCl containing electrodes. Therefore, we examined whether the buspirone induced hyperpolarizations would also reverse under these conditions, as would be expected if they were mediated by an increase in chloride conductance. In three cells tested with KCl containing electrodes and at a time when spontaneous IPSPs could be seen to have "reversed", buspirone administration (100 μmol/l) was still found to elicit a hyperpolarization. As these results suggested that the buspirone induced hyperpolarization was mediated by an increase in potassium conductance, this possibility was further tested by examining the E_{rev} for the hyperpolarization. In three experiments conducted in the presence of an extracellular potassium concentration of 2.5 mmol/l, the E_{rev} for the buspirone induce hyperpolarization was found to be −105 mV ± 9.5 mV (mean ± SD, n = 3 cells). This E_{rev} was not significantly different from that obtained in the same cells for the 5-HT induced hyperpolarization (−110 mV ± 10.1 mV, mean ± SD, n = 3 cells), which has previously been shown to be mediated by a pure increase in a potassium conductance (Andrade and Nicoll 1987).

In view of the reported affinity of buspirone for the 5-HT_{1A} binding site, we compared its actions with those of 5-HT. In these cells, 5-HT administration elicits a hyperpolarization through 5-HT_{1A} receptors, which is often followed by a slower, longer lasting depolarization (Fig. 1a), which is associated with a conductance decrease and a reduction in the calcium-activated afterhyperpolarization. This response is mediated by a different 5-HT receptor, which does not conform to any of the known 5-HT binding sites (Fig. 1b and Andrade and Nicoll 1987). While it is clear from these results that buspirone qualitatively mimics the hyperpolarizing action of 5-HT, its ability to mimic the depolarizing component and the decrease in the calcium-activating afterhyperpolarization was difficult to assess in view of the long duration of the response to buspirone. Therefore we attempted to block the hyperpolarizing action of buspirone with spiperone (3 μmol/l), a concentration which has previously been shown to abolish selectively the 5-HT induced hyperpolarizing component (Andrade and Nicoll 1987). As shown in Fig. 1b, under these conditions, the hyperpolarizing action of 5-HT is completely blocked and the depolarizing component and the reduction in the calcium-activated afterhyperpolarization appear in isolation. Similarly, spiperone also completely antagonizes the hyperpolarizing response to buspirone, although this compound, unlike 5-HT, fails to elicit any depolarization or to reduce the calcium-activated afterhyperpolarization.

Although these results suggested that buspirone functions as a selective agonist at the 5-HT receptors mediating the hyperpolarizing response in the rat hippocampus, it was noticed that the buspirone induced hyperpolarizations were substantially smaller than those routinely

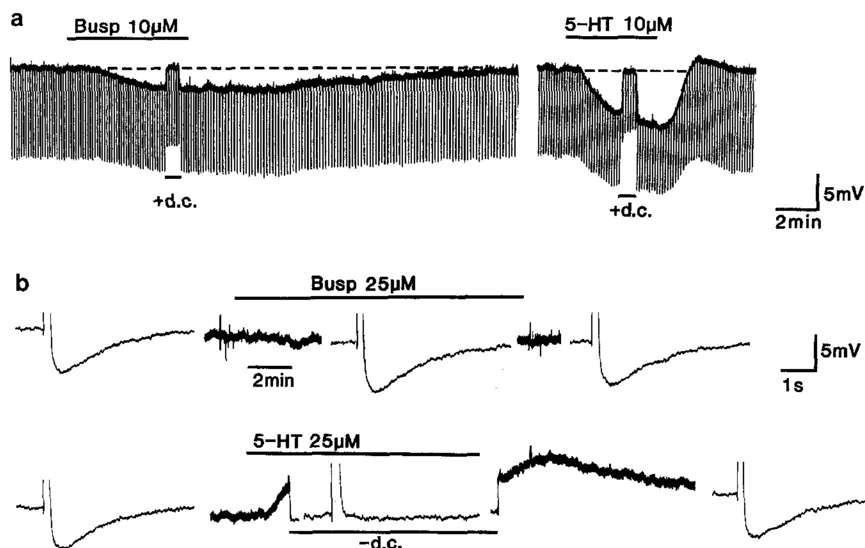

Fig. 1a, b. Effects of buspirone and 5-HT on hippocampal pyramidal cells. **a** Buspirone administration (10 μmol/l) elicits a hyperpolarization which recovers slowly following the end of the buspirone administration. Vertical deflections correspond to the membrane potential changes elicited by hyperpolarizing constant current pulses (70 ms duration). Notice that the amplitude of these deflections is reduced in the presence of buspirone indicating that the buspirone induced hyperpolarization is accompanied by an increase in membrane conductance. This last effect is seen most clearly when the membrane potential is restored to its initial level by injection of constant current through the electrode (*+dc*). Administration of 5-HT at the same concentration to the same cell also elicits a hyperpolarization which is accompanied by a decrease in input resistance and is followed by a transient small depolarization. **b** In another cell recorded in the presence of spiperone (3 μmol/l), the hyperpolarizing actions of buspirone and 5-HT are blocked. While buspirone is now without any effect on the membrane potential or the calcium-activated afterhyperpolarization, 5-HT elicits a slow and long lasting depolarization which is associated with a reduction of the calcium-activated afterhyperpolarization. Top calibration bar applies to both figures except during the recovery from buspirone when the chart recorder speed was halved to illustrate a complete recovery

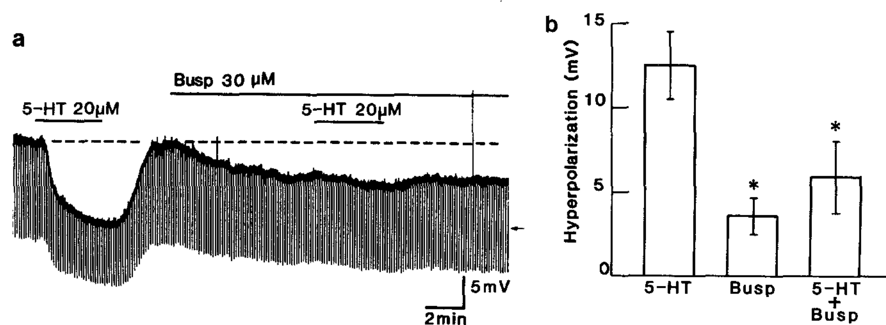

Fig. 2a, b. Comparison of the effects of buspirone and 5-HT on hippocampal pyramidal cells. **a** Administration of a near maximal concentration of 5-HT hyperpolarizes this cell by 13 mV while administration of a near maximal concentration of buspirone hyperpolarizes this cell by only 5 mV. This observation suggests that buspirone possesses a lower intrinsic activity than 5-HT. When the effect of 5-HT was tested in the presence of buspirone, the response to 5-HT was markedly reduced (compare to arrow at the end of record). **b** Comparison of the hyperpolarizations induced by 5-HT (20 μmol/l), buspirone (30 μmol/l) and by their coadministration in six pyramidal cells. The hyperpolarization induced by buspirone and by 5-HT plus buspirone coadministered were both found to be significantly smaller ($p < 0.05$) than that induced by 5-HT administered alone

observed with 5-HT. Indeed, when maximal or near maximal responses to 5-HT (20 μmol/l) and buspirone (30 μmol/l) were elicited sequentially in the same neuron, the buspirone response was found to be consistently smaller than the 5-HT response with the maximal hyperpolarization elicited by buspirone being only 32% ± 9% (mean ± SD) of that elicited by 5-HT (Fig. 2a, b, $n = 6$ cells). This observation suggested that buspirone might be acting as a partial agonist at 5-HT receptors. Since a partial agonist would be expected to effectively antagonize the effect of 5-HT, we examined whether 5-HT responses could be reduced by buspirone administration. As illustrated in Fig. 2a and Fig. 3, buspirone administration (1–50 μmol/l) simultaneously hyperpolarized these cells and reduced the response to 5-HT ($n = 23$ cells). This effect was independent of the hyperpolarization induced by buspirone as the reduction in the 5-HT response persisted even when the membrane potential was restored to its pre-drug level by current injection (Fig. 3a). Moreover, the 5-HT responses elicited in the presence of buspirone (20–30 μmol/l) failed to hyperpolarize the cells to the same degree as under control conditions, even though the response started from a more hyperpolarized membrane potential (Fig. 2a). Thus, the combined hyperpolarization (buspirone plus 5-HT) was less than that elicited by 5-HT in the absence of buspirone (Fig. 2b). As illustrated in Fig. 3b, the buspirone induced reduction of the response to

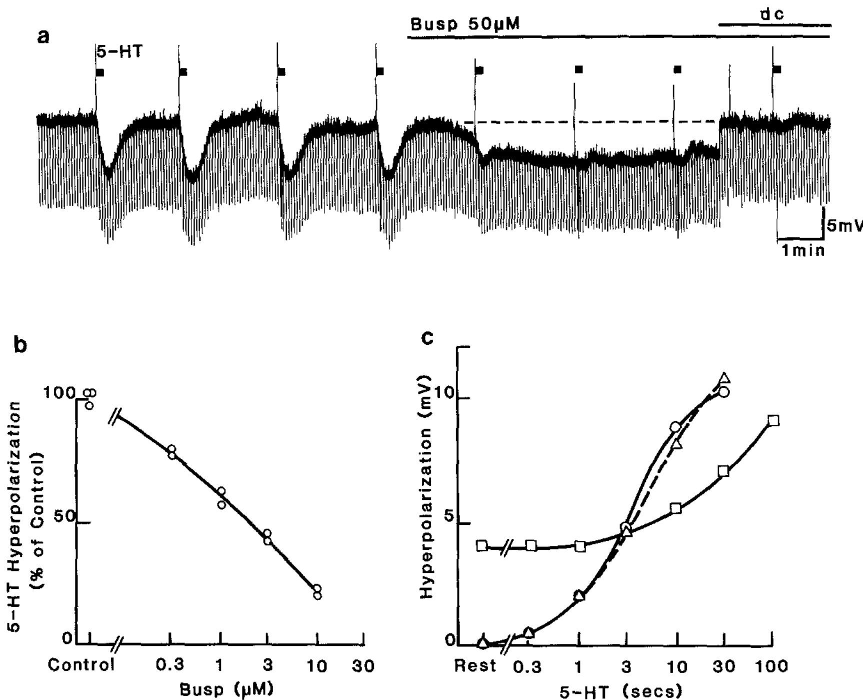

Fig. 3a–c. Buspirone reduces 5-HT responses in a dose dependent and surmountable manner. **a** Administration of buspirone elicits a hyperpolarization and a reduction in the hyperpolarizations induced by 5-HT. This reduction in the response to 5-HT does not result simply from a decrease in the driving force for the 5-HT response since repolarization of the membrane potential by constant current injection does not restore the responses to 5-HT. *b* The buspirone induced reduction of 5-HT responses is dose dependent and exhibits an IC_{50} of 1–3 μmol/l. **c** 5-HT iontophoresis with pulses of increasing duration results in dose dependent hyperpolarizations. Buspirone administration (10 μmol/l) elicits a 4 mV hyperpolarization and completely blocks the effects of short pulses of 5-HT. Administration of longer pulses of 5-HT, however, can surmount this blockade. Because of membrane potential drift during the buspirone wash, the membrane potential was restored to control level by constant current injection to obtain the wash curve. ○ Control, □ buspirone, △ wash

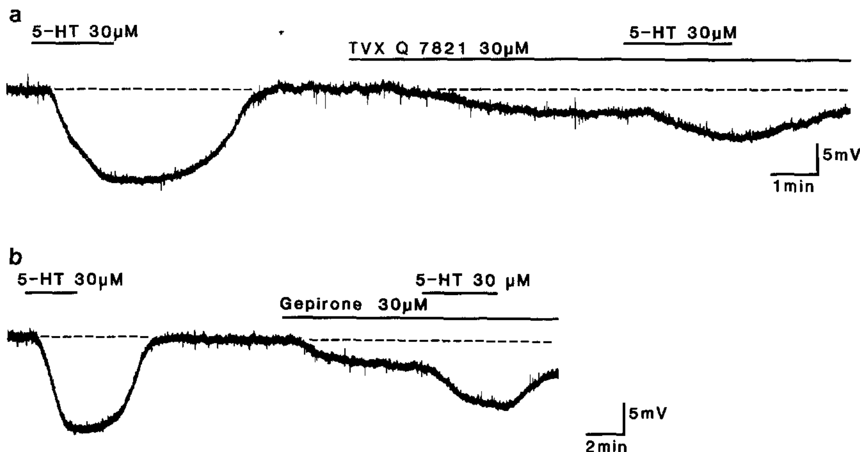

Fig. 4a, b
Effect of gepirone and isapirone on membrane potential and 5-HT responses. Administration of the buspirone analogs, gepirone (**a**) and isapirone (**b**), hyperpolarize these cells and antagonize the 5-HT induced hyperpolarization. Notice that in the presence of these compounds the maximal hyperpolarization induced by 5-HT is reduced although it was elicited from a more hyperpolarized membrane potential

5-HT was concentration dependent, exhibiting a IC_{50} of about 2–3 μmol/l (n = 4 cells), and this antagonism was at least partially surmountable at low concentrations of buspirone (Fig. 3c, n = 5). In order to obtain an estimate of the affinity of buspirone for the 5-HT receptor, apparent pA2 values were calculated using the duration ratios of equieffective iontophoretic pulses of 5-HT in the presence of 1–5 μmol/l buspirone. The pA2 values calculated in this way averaged 6.22, which corresponded to approximately 600 nmol/l (n = 5 cells).

In addition to its serotonergic actions, buspirone can also act on dopaminergic receptors (Riblet et al. 1982) and antagonizes presynaptic dopaminergic responses (McMillen and Mattiace 1983). Since spiperone antagonizes dopamine as well as $5\text{-}HT_{1A}$ receptors, it was possible that buspirone's effects might have been mediated by dopamine receptors. Therefore the effects of buspirone were compared to those of gepirone and isapirone, analogues which lack dopaminergic activity but exhibit similar affinity for 5-HT binding sites and similar activity in the Vogel conflict test, an animal model for anxiolytic activity (Vogel et al. 1971; Riblet et al. 1982). Administration of gepirone (1–50 μmol/l) to hippocampal slices, like buspirone, elicited a small hyperpolarization and antagonized the hyperpolarizing action of 5-HT

(Fig. 4, n = 14 cells). The mean hyperpolarization induced by 15 µmol/l of gepirone was 3 mV ± 1.1 mV (n = 6). Similar effects were obtained with isapirone (Fig. 4).

Discussion

The main conclusion of this study is that the novel, non-benzodiazepine, anxiolytic buspirone functions as a partial 5-HT agonist in the hippocampus, selectively activating a subclass of 5-HT receptors which increase potassium conductance and hyperpolarize these cells. Several lines of evidence support this conclusion. Administration of buspirone as well as its analogs gepirone and isapirone, like 5-HT, hyperpolarized pyramidal cells of the CA1 region. Since this hyperpolarization was associated with a conductance increase, was still present after reversing the chloride gradient and exhibited a E_{rev} expected for a pure increase in potassium conductance, these results suggest that buspirone, like 5-HT, hyperpolarizes these cells by opening potassium selective ion channels. Buspirone, however, mimicks only one of the responses to 5-HT observed in these cells, as it failed to elicit a slow depolarization or to reduce the calcium-activated afterhyperpolarization. These results, therefore, indicate that buspirone selectively activates a subclass of functional 5-HT receptors in the hippocampus. Since we have previously reported that the 5-HT receptors mediating the hyperpolarizing response exhibit many of the properties of the 5-HT_{1A} binding sites present in this region, this report supports the suggestion that these receptors correspond to the 5-HT_{1A} binding sites. The effects of buspirone on 5-HT_{1A} receptors in this region presumably explain its ability to selectively mimic the 5-HT induced reduction in the population spike in the CA1 region of the hippocampus (Rowan and Anwyl 1987).

While the buspirone induced hyperpolarization resembled qualitatively that induced by 5-HT, buspirone was found to be considerably less effective and the maximal hyperpolarization induced by buspirone was only about a third as large as that induced by 5-HT, even when both responses were determined in the same cell. Moreover, buspirone caused a dose dependent antagonism of 5-HT responses. Such behavior can most readily be explained by buspirone acting as a partial agonist in which it is unable to elicit a maximal response when fully occupying all the available receptors and therefore also behaves as an antagonist. In support of such a role for buspirone, the reduction in 5-HT responses elicited by this drug was found to be surmountable, at least at low buspirone concentrations. Also consistent with this possibility is the previous observation that buspirone functions as a partial agonist at 5-HT_{1A} receptors mediating inhibition of adenylate cyclase (Devivo and Maayani 1986).

Little is known at present regarding the mechanism by which buspirone elicits its behavioral effects. While buspirone does exhibit high affinity for 5-HT binding sites in the CNS, it also binds to dopamine receptors, albeit with less affinity (Riblet et al. 1982). Previous studies (Temple et al. 1982; McMillen and Mattiace 1983) have suggested that the actions of buspirone on dopamine receptors are unlikely to be responsible for its anxiolytic activity, since the putative anxiolytics gepirone and isapirone are inactive at these receptors. These compounds, however, share common actions at 5-HT_{1A} receptors in the hippocampus supporting the idea that it is their actions on 5-HT systems that contribute to their anxiolytic activity (Hjorth and Carlsson 1982). This possibility is strengthened by the observation that 8-OHDPAT, although structurally dissimilar, also exhibits partial agonist activity at the 5-HT_{1A} receptor (Andrade and Nicoll 1987) and anxiolytic activity in animal models (Engel et al. 1984).

The actions of these compounds on 5-HT systems are likely to involve both the serotonergic neurons themselves and their postsynaptic targets. Buspirone has been reported to reduce 5-HT metabolites in rat brain (Hjorth and Carlsson 1982) and the administration of buspirone (Vandermaelen et al. 1986), gepirone (Gelbach and Vandermaelen 1985) or isapirone (Sprouse and Aghajanian 1986) has been reported to inhibit spontaneous activity in the dorsal raphé. Such effects would be expected to decrease serotonergic synaptic transmission in many areas of the forebrain. In addition, we have shown in this report that these compounds can act postsynaptically as partial agonists at 5-HT_{1A} receptors while blocking responses to 5-HT. Such combined actions should produce, both by pre- and postsynaptic actions, a functional disconnection of 5-HT_{1A} receptors from the serotonergic neurons while selectively maintaining a low level of serotonergic tone at 5-HT_{1A} receptors. The behavioral consequences of these actions and their possible relevance to anxiety states remains to be explored.

Acknowledgements. This work was supported by NIH grants MH 09189, MH 38256, MH 0437 (RSDA), and NS 24205.

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Received February 26, 1986/Accepted February 23, 1987