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5-Hydroxytryptamine$_{1A}$ Receptor-Mediated Effects of Buspirone, Gepirone and Ipsapirone

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KOENIG, J. I., H. Y. MELTZER AND G. A. GUDELSKY. *5-Hydroxytryptamine$_{1A}$ receptor-mediated effects of buspirone, gepirone and ipsapirone.* PHARMACOL BIOCHEM BEHAV **29**(4) 711–715, 1988.—The effects of the non-benzodiazepine anxiolytic agents, buspirone, gepirone and ipsapirone on body temperature and corticosterone secretion were studied in the rat. The administration of buspirone, gepirone and ipsapirone resulted in dose-related decreases in body temperature and increases in the plasma concentration of corticosterone. Spiperone produced a dose-related inhibition of the hypothermic and corticosterone responses to gepirone. Spiperone also inhibited ipsapirone-induced changes in body temperature and hormone secretion. Although spiperone also blocked the buspirone-induced stimulation of corticosterone, it did not attenuate the hypothermic response to buspirone at the dose tested. (−)-Pindolol, a potent 5-HT$_{1A}$ antagonist, prevented gepirone- and ipsapirone-induced hypothermia and corticosterone secretion. (−)-Pindolol also blocked the hypothermic but not the corticosterone response to buspirone. Ketanserin, a 5-HT$_2$ antagonist, did not inhibit the hypothermic or corticosterone responses produced by these novel anxiolytic agents. It is concluded that buspirone, gepirone and ipsapirone produce hypothermia and increase plasma concentrations of corticosterone by activating 5-HT$_{1A}$ receptor mechanisms.

Buspirone Gepirone Ipsapirone Anxiolytics 5-HT$_{1A}$ receptors Hormones Body temperature

THE administration of serotonergic agents has been shown to produce differential effects on body temperature in the rat [8, 15, 25]. It has been proposed that activation of receptors of the 5-HT$_{1A}$ subtype results in a hypothermic response, whereas activation of 5-HT$_2$ receptors produces a hyperthermic response [13–15, 18, 26].

Treatment of rats with serotonergic agents also has been shown to produce increased serum concentrations of corticosterone [10, 11, 20]. Recent data are suggestive that activation of either 5-HT$_2$ or 5-HT$_{1A}$ receptors results in the stimulation of corticosterone secretion [11,20].

The non-benzodiazepine anxiolytics buspirone, gepirone and ipsapirone have been shown to have high affinity for the 5-HT$_{1A}$ binding site under *in vitro* conditions [3, 12, 28, 31]. Smith and Peroutka [31] and Lucki and Ward [19] have concluded that buspirone and ipsapirone act *in vivo* as mixed 5-HT$_{1A}$ agonists/antagonists in view of the ability of these agents to partially antagonize the 5-HT behavioral syndrome elicited by 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) or 5-methoxy-N,N-dimethyltryptamine. The purpose of the present study was to determine the actions of buspirone, gepirone and ipsapirone *in vivo* at 5-HT$_{1A}$ receptor mechanisms that mediate hypothermia and corticosterone secretion.

METHOD

Animals

Adult male Sprague-Dawley rats (Zivic-Miller, Allison Park, PA) weighing 200–225 g were used in all experiments. The animals were housed in a temperature controlled room on a fixed light-dark cycle (lights on 0630–1830 hr). The animals had free access to food and water at all times.

Measurements of Body Temperature

The animals were transferred to an observation room (23–25°C) and a period of approximately 2 hr was allowed for accommodation of the animals to this environment. Temperature measurements were recorded 30 min, 15 min and immediately prior to the SC administration of buspirone, gepirone or ipsapirone. Changes in body temperature produced by these drugs were determined from measurements made 0 and 60 min after drug administration. Spiperone (0.1–1.0 mg/kg, IP), ketanserin (1 mg/kg, IP) or the vehicle was injected 60 min prior to the administration of buspirone, gepirone or ipsapirone. Some rats received (−)-pindolol 30 min prior to the administration of one of the anxiolytics. The doses of antagonists used were chosen on

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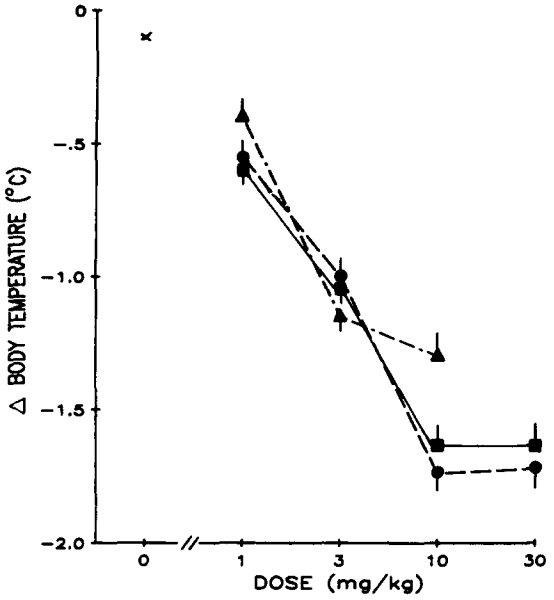

FIG. 1. Hypothermic response to buspirone, gepirone and ipsapirone. Changes in body temperature were measured between 0 and 60 min after the SC administration of buspirone, gepirone, ipsapirone or the vehicle. Symbols represent the mean±S.E. of 6 rats. ×: vehicle; ●: buspirone; ■: gepirone; ▲: ipsapirone.

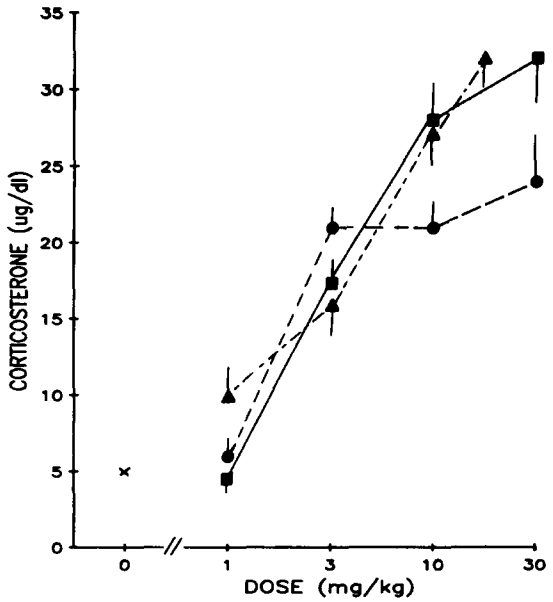

FIG. 2. Effects of buspirone, gepirone or ipsapirone on plasma corticosterone concentrations. Rats were killed by decapitation 60 min after the SC injection of buspirone, gepirone, ipsapirone or the solvent vehicle. Symbols represent the mean±S.E. of 6 rats. Symbols as in Fig. 1.

the basis of the results of a previous study [15]. Body temperatures were determined using a telethermometer and a thermistor probe that was inserted approximately 5 cm into the rectum.

Determination of Serum Corticosterone Concentrations

Rats were killed by decapitation 60 min after the SC administration of 1–10 mg/kg of buspirone, gepirone, ipsapirone or the solvent vehicle. Spiperone (0.1–3 mg/kg), ketanserin (1 mg/kg, IP) or the vehicle was injected 60 min prior to one of the anxiolytic agents. Some rats were treated with (−)-pindolol (0.3 mg/kg, SC) 30 min prior to the administration of buspirone, gepirone or ipsapirone. The doses of antagonists used were chosen on the basis of the results of a previous study [20].

Blood was collected into chilled polypropylene tubes containing 400 μl of a 10% EDTA solution. Plasma was collected and stored at −80°C until assayed for corticosterone content.

Assays

Plasma concentrations of corticosterone were determined by radioimmunoassay employing an antibody from Radioassay Systems Laboratories, Inc. (Carson, CA). Unlabeled corticosterone used in preparing assay standards was purchased from Steraloids, Inc. (Wilton, NH). Tritiated corticosterone was purchased from New England Nuclear (Boston, MA). The assay sensitivity was 20 pg/ml. The interassay coefficient of variation was 7% and the intraassay coefficient of variation was 4%.

Drugs

Buspirone and gepirone were obtained from Bristol Myers Pharmaceuticals, Inc. (Evansville, IN). Ipsapirone was obtained from Troponwerke, Köln, FRG. Ketanserin was obtained from Janssen Pharmaceuticals (Beerse, Belgium). Spiperone was purchased from Research Biochemicals, Inc. (Wayland, MA). (−)-Pindolol was obtained from Sandoz Pharmaceuticals (Basel, Switzerland). Buspirone, gepirone, ipsapirone and ketanserin were dissoved in distilled water. Spiperone was dissoved in 0.1 M tartaric acid. (−)-Pindolol was dissolved in 100 μl of 1 N hydrochloric acid and diluted to volume with 0.15 M NaCl.

Statistical Analysis

The data were analyzed by analysis-of-variance in combination with Student-Newman-Keuls test for multiple comparisons of means. Statistically significant p values were considered to be those less than 0.05.

RESULTS

Treatment of the rats with buspirone, gepirone or ipsapirone produced a dose-related decrease in body temperature (Fig. 1). A decrease in body temperature of 1.2–1.7°C was observed following the SC administration of 10 mg/kg of each of these drugs. Significant ($p<0.05$) hypothermic responses were produced by as little as 1 mg/kg of any one of the drugs. Buspirone, gepirone and ipsapirone were essentially equipotent in the production of hypothermic responses.

Buspirone, gepirone and ipsapirone also produced dose-related increases in plasma corticosterone concentrations (Fig. 2). The doses required to increase corticosterone concentrations were similar to those required to elicit hypothermic responses, although a dose of 3 mg/kg of any one of the drugs was necessary to produce a significant ($p<0.05$) corticosterone response (Figs. 1 and 2). The

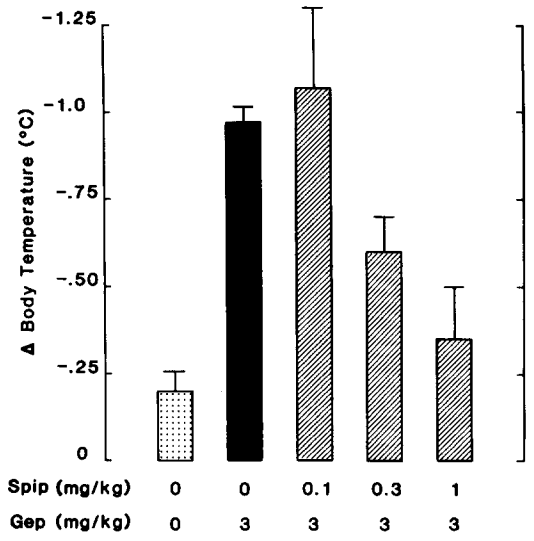

FIG. 3. Antagonism by spiperone of gepirone-induced hypothermia. Rats received spiperone (0.1–1.0 mg/kg, IP) or the vehicle 60 min prior to an injection of gepirone (3 mg/kg, SC) or its vehicle. Changes in body temperature were determined from measurements made prior to and 60 min after the administration of gepirone. Column heights and vertical lines represent the means±S.E.s, respectively, of 6 rats.

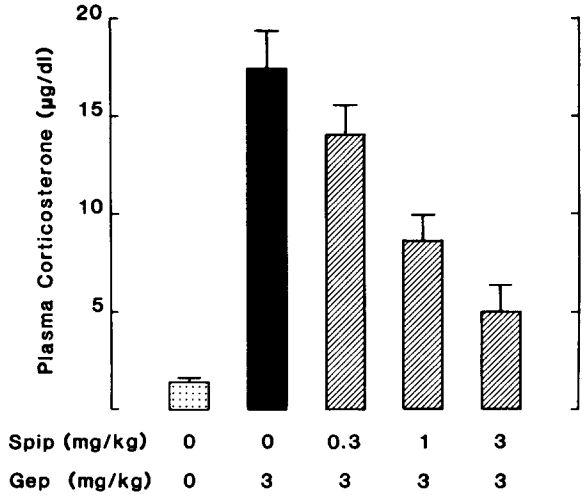

FIG. 4. Antagonism by spiperone of the gepirone-induced elevation of plasma corticosterone concentrations. Rats were injected with spiperone (0.3–3 mg/kg, IP) or the vehicle 60 min prior to the administration of gepirone (3 mg/kg, SC) or its vehicle. Rats were killed by decapitation 60 min after the administration of gepirone, and trunk blood was collected for the determination of corticosterone. Column heights and vertical lines represent the means±S.E.s of 6 rats.

anxiolytic agents were nearly equipotent in the production of elevated plasma concentrations of corticosterone.

The administration of gepirone (3 mg/kg) produced a significant ($p<0.05$) 1°C decrease in body temperature that was inhibited, dose-dependently, by spiperone (Fig. 3). Gepirone-induced hypothermia was inhibited ($p<0.05$) approximately 50% by 0.3 mg/kg of spiperone, and a dose of 1 mg/kg of spiperone completely abolished this response to gepirone. The gepirone-induced increase in plasma corticosterone concentrations also was dose-dependently antagonized by spiperone (Fig. 4). Doses of spiperone (1 and 3 mg/kg) that were required to significantly ($p<0.05$) attenuate the corticosterone response to gepirone were slightly greater than those (0.3 and 1 mg/kg) necessary to significantly ($p<0.05$) inhibit the hypothermic response to gepirone.

Shown in Fig. 5 are the effects of several 5-HT antagonists on anxiolytic-induced hypothermia. Ketanserin (1 mg/kg) did not significantly alter the decreases in body temperature induced by gepirone, buspirone or ipsapirone. In contrast, both spiperone (1 mg/kg) and (−)-pindolol (0.3 mg/kg) significantly ($p<0.05$) attenuated these hypothermic responses, although the hypothermic effect of buspirone was unaffected by this dose of spiperone.

The administration of pindolol (0.3 mg/kg) alone had no significant effect on body temperature. The injection of ketanserin (1 mg/kg) or spiperone (0.3 mg/kg) produced decreases in body temperature of 0.8 and 1.0°C, respectively, which were significantly ($p<0.05$) greater than that (−0.3°C) produced by the solvent vehicle (data not shown). There was no correlation between the effect of the antagonists alone on body temperature and the extent to which they antagonized the anxiolytic-induced hypothermia.

The effects of these 5-HT antagonists on buspirone-, gepirone- and ipsapirone-induced increases in plasma corticosterone concentrations are presented in Fig. 6. Ketanserin

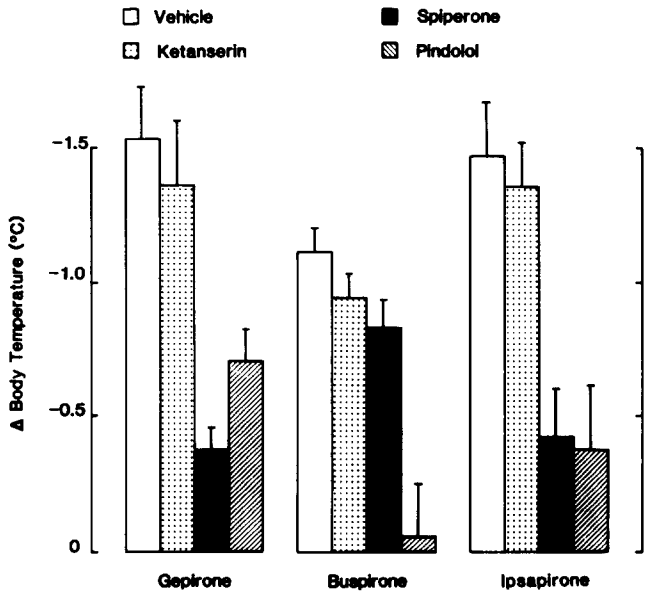

FIG. 5. Effect of 5-HT antagonists on the hypothermic responses to novel anxiolytic agents. Rats were injected with ketanserin (1 mg/kg, IP), spiperone (1.0 mg/kg, IP) or the vehicle 60 min prior to an injection of gepirone (3 mg/kg, SC), buspirone (3 mg/kg, SC) or ipsapirone (10 mg/kg, SC). (−)-Pindolol (0.3 mg/kg, SC) was administered 30 min prior to one of the anxiolytics. Changes in body temperature were measured between 0 and 60 min after the administration of the anxiolytics. Column heights and vertical lines represent the means and S.E.s, respectively, of 6 rats.

(1 mg/kg) did not alter the corticosterone responses to any of these anxiolytic agents. In contrast, spiperone (3 mg/kg) significantly ($p<0.05$) attenuated the gepirone-, buspirone- and ipsapirone-induced elevations of plasma corticosterone

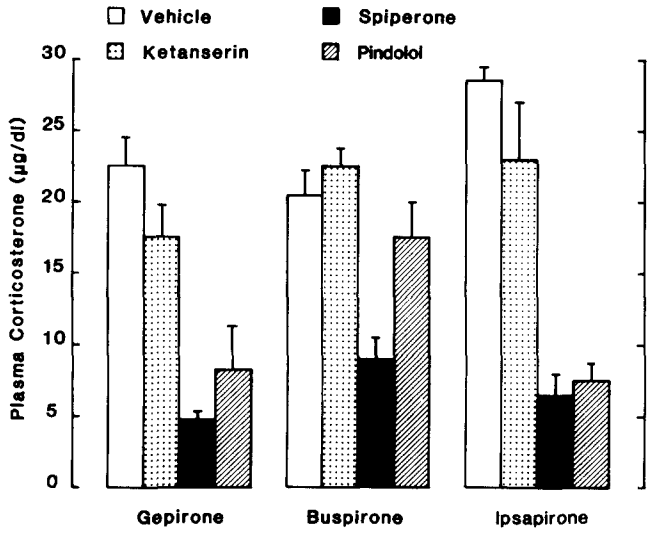

FIG. 6. Effects of 5-HT antagonists on the corticosterone response to novel anxiolytic agents. Rats were injected with ketanserin (1 mg/kg, IP), spiperone (3 mg/kg, IP) or the vehicle 60 min prior to the administration of gepirone (3 mg/kg, SC), buspirone (3 mg/kg, SC) or ipsapirone (10 mg/kg, SC). (−)-Pindolol (0.3 mg/kg, SC) was injected 30 min prior to one of the anxiolytics. The animals were killed 60 min after the injection of the anxiolytics, and trunk blood was collected for the determination of corticosterone. The plasma corticosterone concentrations in rats that received only vehicle injections were 2±1 μg/dl (mean±S.E.). Column heights and vertical lines represent the means±S.E.s, respectively, of 6 rats.

concentrations. (−)-Pindolol (0.3 mg/kg) also significantly ($p<0.05$) inhibited the corticosterone responses to gepirone and ipsapirone, but the corticosterone response to buspirone was unaffected.

The administration of any of the 5-HT antagonists alone did not significantly alter plasma corticosterone concentrations (data not shown).

DISCUSSION

Activation of the 5-HT_{1A} receptors by 8-OH-DPAT has been shown to decrease body temperature in the rat [13–15, 18]. The hypothermia induced by 8-OH-DPAT can be attenuated by spiperone and (−)-pindolol [15], both known to possess high affinity for the 5-HT_{1A} receptor [6, 19, 22]. Ketanserin, a selective 5-HT_2 antagonist, has been shown to be without effect on 8-OH-DPAT-induced hypothermia [15].

In the present study, we have found that the novel anxiolytic agents, buspirone, gepirone and ipsapirone, also decrease the body temperature of rats in a dose-related manner. In addition, (−)-pindolol inhibited the hypothermic responses of buspirone, gepirone and ipsapirone. Spiperone also antagonized these hypothermic responses with the exception of that elicited by buspirone. In contrast, ketanserin, a 5-HT_2 antagonist, did not antagonize the hypothermia produced by these agents. The similarity of the interactions of these 5-HT antagonists with buspirone, gepirone and ipsapirone and with 8-OH-DPAT [15], a selective 5-HT_{1A} agonist, is supportive of the conclusion that the hypothermic responses induced by buspirone, gepirone and ipsapirone are mediated by activation of 5-HT_{1A} receptors.

In the rat, activation of 5-HT mechanisms by direct receptor stimulation or the administration of 5-HT precursors results in the stimulation of the secretion of corticosterone [9,11]. The stimulation of corticosterone secretion induced by quipazine or 6-chloro-2-(1-piperazinyl)pyrazine (MK-212) is antagonized by the 5-HT_2 antagonist ketanserin [11,20], whereas that produced by the selective 5-HT_{1A} agonist 8-OH-DPAT [17,24] is selectively antagonized by (−)-pindolol and spiperone [20]. Hence, it has been suggested that activation of either 5-HT_2 or 5-HT_{1A} receptors results in an elevation of plasma corticosterone concentrations [20].

In the present study, buspirone, gepirone and ipsapirone elevated plasma corticosterone concentrations. The ability of buspirone to stimulate corticosterone secretion has been demonstrated previously [23,25]. The corticosterone responses to buspirone, gepirone and ipsapirone were antagonized by (−)-pindolol and spiperone with the exception of the inability of (−)-pindolol to antagonize the response to buspirone. Moreover, ketanserin, at a dose which effectively antagonizes quipazine- or MK-212-induced corticosterone secretion [11,20], did not alter the stimulation of corticosterone secretion induced by these anxiolytics. These findings are supportive of the contention that the stimulation of corticosterone secretion produced by buspirone, gepirone and ipsapirone is mediated by activation of 5-HT_{1A} receptors.

The effect of buspirone on body temperature was not antagonized by spiperone, and its effect on corticosterone was unaffected by (−)-pindolol, whereas the effects of gepirone and ipsapirone on body temperature and corticosterone secretion were antagonized by both of these agents. Since only single doses of spiperone and (−)-pindolol were tested for antagonism of the responses to buspirone, it is possible that slight differences exist in the potency of spiperone and (−)-pindolol to antagonize some of the actions of buspirone compared to the antagonism of the responses of gepirone and ipsapirone. Alternatively, this difference may be due to the fact that buspirone [16,29], in contrast to gepirone and ipsapirone [12, 28, 30], can affect dopaminergic and noradrenergic mechanisms.

It has been shown that buspirone, gepirone and ipsapirone have nanomolar affinities for binding sites labelled by ^{3}H-5-HT or ^{3}H-8-OH-DPAT [12, 28, 31]. In addition, studies with ^{3}H-ipsapirone indicate that it labels receptors of the 5-HT_{1A} subtype *in vivo* [12]. Data from some behavioral and electrophysiological studies are supportive of the view that buspirone and ipsapirone are agonists at 5-HT_{1A} receptors. In studies of drug discrimination [1] and feeding behavior [4], ipsapirone and buspirone have been found to mimic the effects of 8-OH-DPAT. Furthermore, buspirone [36], gepirone and ipsapirone [32] mimic 8-OH-DPAT [2,7] in the inhibition of firing of serotonergic neurons in the dorsal raphé nucleus.

However, Skolnick *et al.* [30] reported that neither buspirone nor gepirone produce the "5-HT behavioral syndrome" which is thought to be mediated through activation of 5-HT_{1A} receptors [21, 33, 34]. Eison and colleagues [5] have found that only gepirone, at high doses, produces this behavioral syndrome. Indeed, Smith and Peroutka [31], and subsequently Lucki and Ward [22], have reported that buspirone and ipsapirone antagonize some of the motor responses of the 5-HT behavioral syndrome produced by 8-OH-DPAT. It has been concluded by these investigators that these novel anxiolytics may be mixed agonists/antagonists at the 5-HT_{1A} receptor that mediates the 5-HT behavioral syndrome [22,31].

The results of the present study in which buspirone, gepirone and ipsapirone produced changes in body tempera-

ture and corticosterone secretion similar to those produced by 8-OH-DPAT [15,20] are consistent with the view that these novel anxiolytics can elicit 5-HT$_{1A}$ receptor-mediated responses.

ACKNOWLEDGEMENTS

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