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Buspirone-induced Prolactin Secretion in Man is Not 5-HT_{1A} Receptor Mediated: Effect of Pindolol Pretreatment

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ABSTRACT

The effect of the nonbenzodiazepine anxiolytic, buspirone (Buspar®), a serotonin (5-$HT)_{1A}$ partial agonist, which also has dopamine $(DA)_2$ receptor antagonist properties, on prolactin and cortisol secretion was examined in eight normal male volunteers. The oral administration of buspirone (30 mg) significantly increased plasma prolactin concentrations but did not singnificantly increase plasma cortisol concentrations in this study. The oral administration of pindolol (30 mg), a beta adrenoceptor antagonist which is also a 5-HT_{1A} receptor antagonist, had no significant effect on basal prolactin or cortisol levels. Moreover, pretreatment with pindolol did not significantly inhibit the buspirone-induced increase in prolactin secretion. These preliminary data are suggestive that buspirone-induced prolactin secretion is not mediated via 5-HT_{1A} receptor activation.

Key Words: Buspirone, Pindolol, Prolactin, Cortisol, Dopamine, 5-HT_{1A} receptors

INTRODUCTION

Buspirone hydrochloride (Buspar®), has been shown to be a clinically effective anxiolytic with a different pharmacologic and clinical profile than that of the benzodiazepines (Goa and Ward 1986). Initially, the pharmacological effects of buspirone were attributed to its mixed dopamine $(DA)_2$ antagonist and partial agonist properties in rodents (McMillen *et al.*, 1983). However, subsequent radioligand binding studies demonstrated that buspirone has a much higher affinity for the 5-HT_{1A} binding site than DA_2 binding sites (Peroutka 1985). Moreover, behavioral, biochemical and electrophysiological studies are also consistent with a 5-HT_{1A} partial agonist action of buspirone (Hjorth and Carlsson 1982; De Vivo and Maayani 1986; Cunningham *et al.*, 1987.) Thus, it has been suggested that the primary pharmacological effects of buspirone are mediated via its interaction with 5-HT_{1A} receptors (Taylor *et al.*, 1988).

We have previously reported that buspirone stimulates prolactin (PRL) and growth hormone secretion in man (Meltzer *et al.*, 1983) and PRL secretion in rodents (Meltzer *et al.*, 1982). We initially suggested that the effect of buspirone on PRL secretion was due to its DA_2 antagonist properties. However, the recent studies of Neuhauser *et al.* (1988), Gregory *et al.* (1990) and Coccaro *et al.* (1990), to be reviewed subsequently, are suggestive that buspirone-induced PRL secretion is mediated via 5-HT_{1A} receptor mechanisms. Definitive evidence is lacking, however, as to the importance of the serotonergic mechanisms in buspirone-induced PRL secretion in man.

The current study was undertaken to determine whether the effect of buspirone on plasma PRL and cortisol secretion is inhibited by pindolol. Pindolol is a beta adrenoceptor blocker which is also a potent 5-HT_{1A} antagonist (Nahorski and

Willcocks 1983; Trickleblank *et al.*, 1985; Hjorth and Carlsson 1986). Inhibition by pindolol of the buspirone-induced increase in hormone secretion would be consistent with the hypothesis that this response is mediated via a 5-HT_{1A} receptor mechanism.

SUBJECTS AND METHODS

Subjects

Eight normal male volunteers, age 21~34 years (mean±S.D., 26.1±4.0), participated in these studies. All subjects had normal medical and psychiatric evaluations, as well as basic laboratory examinations such as CBC, urinalysis, liver function tests, blood chemistries, thyroid function tests, and electrocardiograms. Those with past psychiatric history or psychiatric history in first-degree relatives were excluded. Subjects were free of psychotropic medications. No subject had received any medication for one week prior to the study. There were no significant differences in age or body weight between subjects.

Procedures

All volunteers gave written informed consent before participating in these studies. Each subject was tested on four occasions separated by a minimum of seven days. The neuroendocrine studies were performed in a manner similar to that previously described (Meltzer *et al.*, 1983). Briefly, after an overnight fast, volunteers arrived at the University Hospital research ward at approximately 8:30 AM on each study day. The subjects were restricted to bedrest during the 4 hour study and not allowed to sleep or eat. An indwelling intravenous catheter was placed in a forearm vein for repeated blood sampling (3 ml/sample). Either pindolol 30 mg (3 capsules) or placebo (3 capsules) was given immediately after catheter placement. The first baseline blood sample was obtained 30 min after catheter placement, and two more baseline samples were collected at 15 min intervals. Buspirone, 30 mg, or placebo was administered, immediately following the last baseline sampling. The test drugs were administered orally in random order on a single blind basis.

Blood samples were obtained every 30 minutes over a three hour time period. All blood smples were collected from the intravenous cannula into plastic tubes containing EDTA and the protease inhivitor, aprotinin. The blood was spun in plastic tubes and plasma was stored at −20°C until the time of assay for cortisol and PRL concentrations.

Body temperature was monitored with a calibrated electronic thermometer, sublingually, at each time point of blood collection. Side effects were assessed by observation and inquiry by a trained observer throughout the study.

Hormone assay procedures

Plasma PRL and cortisol concentrations were measured by standard double-antibody radioimmunoassay with reagents provided by the National Institute of Diabetes, Digestive and Kidney Diseases and the National Hormone and Pituitary Program (University of Maryland) and using procedures previously described in our laboratory (Meltzer *et al.*, 1983; 1984). The kit used to measure plasma cortisol was purchased from Diagnostic Products (Los Angeles, CA). The intra- and interassay coefficients of variation for PRL and cortisol were less than 7% and 5%, respectively.

Statistical analysis

Baseline concentrations ($Time_0$) of plasma PRL and cortisol across the four challenge tests were compared using a two-way (protocol: placebo vs buspirone and drug: placebo vs. pindolol) repeated measures analysis of variance (ANOVA). To test the effects of buspirone and pindolol on overall hormone secretion, a two-way repeated measures analysis of covariance (ANCOVA) of the area under the curve (AUC) was conducted with $Time_0$ as the covariate. The AUC was computed using Simpson's rule. The same analyses were repeated with peak-baseline PRL and cortisol (delta PRL and cortisol). Finally, a three-way repeated measures ANOVA (time[0, 30, 60, 90, 120, 150, 180], drug, protocol) was carried out. Statistical analysis was conducted utilizing PROC GLM SAS (SAS Institute, Inc. 1988).

RESULTS

Plasma PRL and cortisol

The effect of pretreatment with pindolol (30 mg) or placebo on plasma PRL and cortisol levels fol-

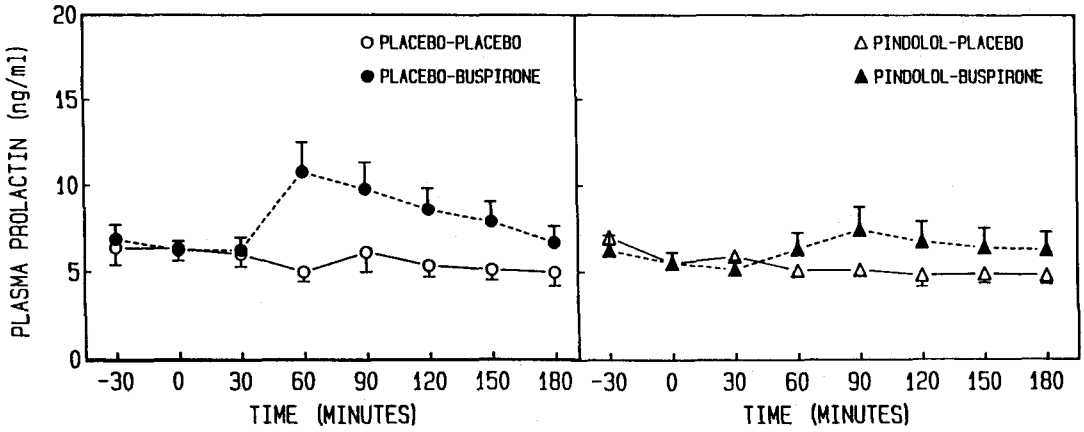

Fig. 1. Effect of pindolol on buspirone-induced plasma prolactin concentration in 8 healty male volunteers. Pindolol (30 mg) or placebo was administered 60 min before buspirone or placebo which was given at time 0. Value indicates mean±SEM

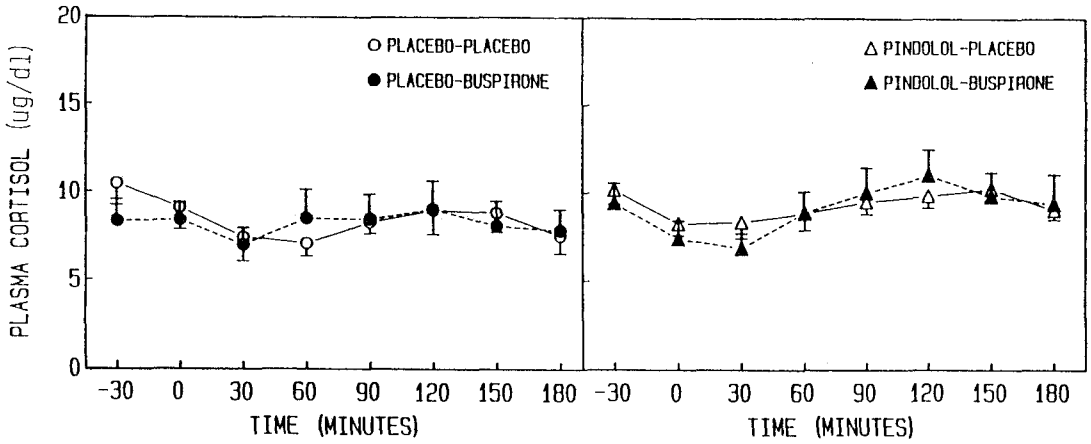

Fig. 2. Effect of pindolol on buspiorne-induced plasma cortisol concentration in 8 healthy male volunteers. Pindolol (30 mg) or placebo was administered 60 min before buspirone (30 mg) or placebo which was given at time O. Value indicates mean±SEM

lowing buspirone (30 mg) or placebo challenge are illustrated in Figures 1 and 2, respectively. Baseline PRL, PRL AUC and delta PRL levels are given in Table 1. Baseline plasma PRL levels were lower in the pindolol conditions (5.5±1.4 ng/ml) vs the placebo condition (6.3±1.75 ng/ml; p=0.03). There was no significant difference in baseline plasma cortisol levels between the pindolol studies (7.8±μg/dl) and the placebo studies (8.7±3.1 μg/dl).

A repeated measures ANCOVA for AUC of plasma PRL concentration revealed a significant main effect for protocol (placebo vs buspirone; F=20.75, df=1, 7, p=0.003), but no drug effect (placebo vs pindolol) or interaction between protocol and drung (F=1.22, df=1, 7, p=0.31; F=1.55, df=1, 6, p=0.26, respectively). Thus, buspirone significantly increased PRL secretion in these subjects.

Table 1. Effect of pindolol and buspirone on prolactin secretion in normal volunteers

pretreatment (drug)	Treatment (protocol)	Basal PRL (ng/ml)	AUC (ng/ml×180 min)	Delta PRL (ng/ml)
placebo	placebo	6.4±2.0	39.0±12.4	0.1±3.5
placebo	buspirone	6.3±1.5	56.2±18.8	5.4±4.5
pindolol	placebo	5.0±0.9	36.2± 6.3	0.3±2.0
pindolol	buspirone	5.5±1.8	43.8±16.6	2.6±3.5

Each value is the mean±S.D. of normal male volunteers

However, pretreatment with pindolol had no significant effect on buspirone-induced PRL secretion (Table 1). Identical results were obtained with the two-way ANCOVA of delta PRL: only a significant protocol effect was noted ($p=0.001$). The three-way ANOVA also showed only a significant protocol effect ($p=0.007$) and time x protocol interaction ($p=0.0001$). The correlation between the PRL response to buspirone and body weight was not significant ($rho=0.28$, $p=0.51$).

There was no significant drug, protocol, time, or any interactions for analyses of the cortisol response data (data not presented). There was also no significant effect of pindolol on basal plasma cortisol levels ($p=0.26$). Thus, it can be concluded that buspirone did not significantly increase cortisol levels nor did pindolol affect basal cortisol levels.

Side effect profile

There were no significant side effects in any of the challenge studies. One subject pretreated with pindolol complained on headache and dizziness 30 minutes following buspirone administration. No significant change in vital signs was noted in any of the subjects. We noted no change in body temperature with buspirone (data not presented).

DISCUSSION

The results obtained in the present study are consistent with previous findings in which the oral administration of buspirone significantly increased plasma PRL concentrations in normal male volunteers as compared to placebo (Meltzer *et al.*, 1983; Gregory *et al.*, 1990). The 30 mg dose of buspirone had no significant effect on plasma cortisol concentrations in this small sample. Pretreatment with pindolol, a 5-HT_{1A} antagonist, did not significantly inhibit the buspirone-induced plasma PRL secretion. These data suggest that buspirone-induced PRL secretion is not mediated via 5-HT_{1A} receptor activation.

It has been reported that pretreatment with pindolol, 30 mg, the same dose used in this study, inhibited the cortisol response to ipsapirone, another 5-HT_{1A} partial agonist (Dompert *et al.*, 1985) in normal volunteers (Lesch *et al.*, 1989) consistent with our previous report that in rodents, ipsapirone has an inhibitory effect on PRL secretion, probalbly because of its weak DA_2 agonist properties (Nash and Meltzer 1989). Similarly, gepirone, another 5-HT_{1A} partial agonist (Hamon *et al.*, 1986) stimulates cortisol but not PRL secretion in man (Anderson *et al.*, 1990; Rausch *et al.*, 1990) and had DA agnonist properties in rodents (Nash and Meltzer 1989). Furthermore, pretreatment with pindolol blocked the corticosterone response to ipsapirone and gepirone but not buspirone in rodents (Koenig *et al.*, 1988). These results suggest that the cortisol and corticosterone responses following ipsapirone and gepirone adminstration are 5-HT_{1A} mediated, whereas the corticosterone response to buspirone is less clearly 5-HT_{1A}-mediated.

The failure of pindolol to inhibit the PRL response to buspirone in this study suggests that at this dose, the PRL response to buspirone is not 5-HT_{1A} mediated. Studies in our laboratory have found that the dose of pindolol employed in this study entirely inhibits the 5-hydroxytryptophan-induced increase in PRL secretion in normal volunteers (Meltzer *et al.* in preparation). This is further evidence for a 5-HT_{1A} mediated influence on PRL secretion in man. Furthermore, the failure of buspirone to increase cortisol secretion at 30 mg is

further evidence that at this dose, at least, buspirone provides a much weaker stimulus of the hypothalamic-pituitary-adrenal axis than does a comparable dose of ipsapirone (Lesch *et al.*, 1989). The fact that buspirone did not affect body temperature whereas ipsapirone decreases body temperature in normal volunteers (Lesch *et al.*, 1990) is another indication that buspirone is a weaker 5-HT_{1A} agonist. Buspirone produces an erratic increas in cortisol secretion at doses of 60 or 90 mg p.o. (Meltzer, unpublished results). This effect could be 5-HT_{1A} mediated, but further study is needed to test that possibility.

Two previous studies have suggested buspirone increases PRL secretion in man by a 5-HT_{1A} mechanism. Gregory *et al.* (1990) found that buspirone (15 mg, p.o.) administration increased PRL secretion in six male and three female normal volunteers, and that pretreatment with the putative 5-HT antagonist, metergoline (4 mg), significantly inhibited the buspirone-induced PRL secretion in these subjects. However, this study did not include a metergoline-placebo control group. Metergoline is a weak DA agonist which could inhibit PRL secretion by this mechanism (Krulich *et al.*, 1981). In fact, the authors acknowledge this point and do not rule out the possibility that buspirone increases PRL secretion via DA receptor antagonism. In another report, Coccaro *et al.* (1990) found that metergoline or pindolol pretreatment inhibited the buspirone-induced increase in PRL secretion in two male volunteers and suggested that buspirone-induced PRL secretion may be a useful measure of 5-HT_1-like receptor activation in man. This study is flawed by the small sample size and the absence of a placebo control.

The absence of a cortisol response to buspirone at a dose of 30 mg p.o. is noteworthy. As previously mentioned, ipsapirone increases cortisol secretion in man at doses of 0.2～0.3 mg/kg. Gepirone, another 5-HT_{1A} agonist, also produces a dose-related increase in cortisol secretion in normal volunteers (Anderson *et al.*, 1990). These results indicate that buspirone must be a weaker 5-HT_{1A} partial agonist than either gepirone or ipsapirone.

If the PRL response to buspirone is not 5-HT_{1A} mediated, it is likely that it is DA_2-mediated as previously suggested (Meltzer *et al.*, 1982, 1983). At this dose, which is the clinically effective dose (Goa and Ward 1986), buspirone has occasionally been reported to produce akathesia and other extrapyramidal symptoms (Brody *et al.*, 1990), including one possible case of oral dyskinesia developing in an 85 y.o. woman after three days of buspirone treatment (Strauss 1988). The distribution of ^{3}H-buspirone binding sites is consistent with a DA_2-receptor blocking profile in rat and bovine brain (Bruning *et al.*, 1989). It remains to be determined if any of the clinical effects of buspirone, including its anxiolytic effect, is due to a weak DA_2 blocking effect. The 5-HT_{1A} partial agonists appear, in general, to have some agonist or antagonist effect at DA_2 receptors. Thus, buspirone has weak DA_2 antagonist and partial agonist properties (Meltzer 1982; McMillen *et al.*, 1983) while gepirone and ipsapirone have weak DA agonist properties (Nash and Meltzer 1989). 8-hydroxy-2-(di-n-propylamine) tetratin (8-OH-DPAT) has been shown to have DA_2 agonist (Simonovic *et al.*, 1984) as well as 5-HT_{1A} agonist properties (Middlemiss and Fozard 1983). 1-[2- (4-aminophenyl) ethyl]-4-(3-trifluoromethylphenyl) piperazine (LY 165163, PAPP) is buspirone-related compound which has both 5-HT_{1A} and DA_2 blocking properties within the same dose range (Donohoe *et al.*, 1987).

A role of 5-HT_{1A} receptors in the regulation of PRL secretion is also not supported by some preclinical studies using the currently available agonists or antagonists. For example, intra-peritoneal or subcutaneous administration of the prototypic 5-HT_{1A} agonist, 8-OH-DPAT, slightly increased or had no effect on PRL secretion in rats (Simonovic *et al.*, 1984; Di Renzo *et al.*, 1989; Van de Kar *et al.*, 1989). However, Willoughby *et al.* (1988) found that the direct injection of 8-OH-DPAT into the medial basal hypothalamus produced a dose dependent increase in PRL secretion in rats. In addition, the intravenous administration of 8-OH-DPAT has been reported to produce a rapid, short-lived increase in PRL secretion (Aulakh *et al.*, 1988). 8-OH-DPAT might be acting via a non-5-HT_{1A} mechanism.

Although buspirone dose not appear to have an effect on hypothalamic 5-HT_{1A} receptors which stimulate cortisol secretion at the dose used in this study, this does not rule out that it might stimulate 5-HT_{1A} receptors located in other brain regions. Since buspirone is a partial 5-HT_{1A} agonist (De Vivo and Maayani 1986), it might be expected to have a variable effect in different brain regions based on the availability of 5-HT and the number and sensitivity of 5-HT_{1A} receptors.

In conclusion, the results reported here demonstrate that pindolol pretreatment does not inhibit the buspirone-induced increase in plasma PRL. These results provide further indirect support for our previous suggestion (Meltzer *et al.*, 1983) that the effect of buspirone on PRL secretion in man may be primarily due to an antidopaminergic mechanism. These results suggest that buspirone is not a useful probe of the serotonergic system in man, pending definitive evidence that is stimulates PRL secretion via a 5-HT_{1A} mechanism. It remains to be determined if the weak DA_2 blocking properties of buspirone contribute to its anxiolytic profile, or to its side effects.

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Buspirone-induced Prolaction 분비와 5-HT$_{1A}$ 수용체: Pindolol 전처치 효과

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Nonbenzodiazepine계 항불안제인 buspirone을 이용하여 건강한 8명의 남자를 대상으로 prolactin과 cortisol분비를 측정하였다. Buspirone는 Dopamine$_2$ 수용체 antagonist 성질 뿐 아니라 5-HT$_{1A}$ partial agonist 효과가 있는 것으로 보고되고 있다.

Buspirone 30 mg 경구투여시 혈청 prolactin 농도는 유의한 증가를 보였으나 혈청 cortisol 농도의 변화는 차이가 없었다. beta adrenoreceptor antagonist이면서 5-HT$_{1A}$ 수용체 antagonist로 알려진 pindolol (30 mg)을 경구 투여한 결과 기초 혈청 prolactin이나 cortisol 농도는 유의한 차이가 없었다. Pinodlol을 전처치한 경우 buspirone-induced prolaction 분비의 유의한 억제효과는 없었다. 이상의 성적은 buspirone-induced prolactin 분비증가는 아마도 5-HT$_{1A}$ 수용체 활성과 관련되지 않음을 시사하는 것으로 사료된다.