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Bromocriptine-induced dissociation of hyperglycemia and prolactin response to restraint

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Abstract

The present study investigated the effects of immobilization (restraint stress) on rat chronically treated with a D_2 receptor agonist (bromocriptine, 0.4 mg/100 g body weight, injected daily intraperitoneally (ip) for 2 weeks) on plasma glucose, prolactin, and insulin levels. During restraint, the plasma prolactin of vehicle-treated (VEH) rats increased rapidly, reaching a peak at 10 min (57.9 ± 8.1 ng/ml, $P < .01$). In contrast, restraint failed to induce any significant change in the plasma prolactin levels of bromocriptine-treated (BR) rats. The hyperglycemic response to immobilization was 97% higher ($P < .05$) in BR rats than in VEH rats. Our data demonstrate that prolactin secretion and hyperglycemia in response to restraint can be dissociated by chronic treatment with BR, which also increased the hyperglycemic response to immobilization probably due to central D_2 dopaminergic activity. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Prolactin; Hyperglycemia; Insulin; Bromocriptine; Restraint-stress

The sympatho-adrenal and pituitary–adrenal cortex axes are the most sensitive and specific indicators of stress in animals. Increased plasma levels of catecholamines and glucocorticoides are generally considered as the classical response to stress (Herman and Cullinan, 1997; Kvetnansky et al., 1992; Pacak et al., 1998). However, prolactin release from the pituitary gland and hyperglycemia are also highly sensitive markers of both physical and psychological stress in mammals (Demarest et al., 1985a,b; Gala, 1990; Minamitani et al., 1987; Reis et al., 1994, 1996a,b, 1998). We have recently shown that pituitary release of prolactin (reflecting an acute neuroendocrine response) is more intense in a psychological model of stress (restraint). On the other hand, hyperglycemia (an early metabolic response) is closely related to physical damage but not to the degree of anxiety (Reis et al., 1996a, 1998). Increases in prolactin concentrations stimulate tuberoberoinfundibular neurons, with consequent increased rates of synthesis, turnover, and release of dopamine in the median eminence (Demarest et al., 1985a,b; Minamitani et al., 1987). Hyperprolactinemia also induces a higher hyperglycemic response to immobilization stress (Reis et al., 1996a). There are many studies showing that stimulation of D_2 dopaminergic receptors in brain may have some influence on blood glucose regulation by mechanism, which is dependent upon catecholamine release from adrenal medulla (Arneric et al., 1984a,b; Quik and Sourkes, 1977; Saller and Kreamer 1991). Stimulatory role for endogenous dopamine in the regulation of hypothalamo-pituitary–adrenal activity during basal and stress situation has also been demonstrated (Borowsky and Kuhn, 1992, 1993; Casolini et al., 1993). Furthermore, high dopamine reactivity has been linked to a reduced PRL and an increased ACTH response after stress (Rots et al., 1996). These results support the hypothesis of a dopaminergic influence on the control of glucose and insulin secretion response to stress situation. However, little attention has been paid to the participation of dopaminergic tonus in this control despite the wide clinical use of dopaminergic agents, such as bromocriptine (BR). Dopamine agonists are the

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preferred treatment for both symptomatic microprolactinomas and macroprolactinomas; these drugs result in normalization of hormones levels and tumor shrinkage in most treated patients (Shimon and Melmed, 1998). Bromocriptine is D_2 dopaminergic agonist clinically utilized as a chronic therapeutic agent that inhibits prolactin secretion in males and females of all mammalian species tested so far. Chronic treatment with BR also reduces body fat stores and improves glucose tolerance in obese subjects (Cincotta and Meier, 1996; Cincotta et al., 1991). When acutely administered in fasting rats, BR increases hepatic gluconeogenesis and plasma glucose (Schmidt et al., 1983), but does not influence plasma glucose levels, insulin secretion (Uvnäs-Moberg et al., 1996), or ACTH response to stress (Kiss, 1988) in fed rats. On the other hand, prolactin has been shown to increase β-cell proliferation (Sorenson and Brelje, 1997), glucose-stimulated insulin secretion (Reis et al., 1997; Sorenson and Brelje, 1997), stimulate tyrosine phosphorylation of insulin receptor substrate-1, -2 and -3 (Berlanga et al., 1997; Yamauchi et al., 1998), and increase the release of corticosterone by adrenal cortex cells (Chang et al., 1999). These studies suggest that chronic treatment with BR that produces an increase of D_2 dopaminergic tonus and decrease prolactin secretion would induce an inadequate metabolic response to stress. Therefore, the glucose and insulin response to restraint in animals chronically treated with a dopaminergic agonist is of great physiological interest. The experiment described in the present report was designed to determine the effect of the increased dopaminergic tonus brought about by chronic treatment with BR on the hyperglycemic and insulin and prolactin secretion response to restraint stress.

1. Methods

1.1. Animals

Adult male Wistar rats (12 weeks) were used in these experiments. Animals had free access to Purina rat chow and water and were housed in temperature controlled quarters with 14 h of light (5–19 h) per day. At the age of 9 weeks, they started to be treated with CB-154 (Bromocriptine, Sandoz, Basel, Switzerland), a dopamine agonist, or its diluent. Bromocriptine was dissolved in sterilized water and injected daily intraperitoneally (ip) at a dose of 0.4 mg/100 g body weight for 2 weeks. Atrial cannulation was performed through the jugular vein under ether anesthesia 1 or 2 days before the experiments. The catheter was kept patent by instillation of 1 ml of heparinized saline (Liquemine, Roche, 25 IU/ml).

1.2. Restraint stress

On the day of the experiment, the rats had their venous catheter rinsed and connected to a polyethylene tube (PE 50) filled with heparinized saline (10 IU/ml). The animals were then returned to their homecages 1 h before immobilization. The rats were freely moving and were not handled from this time until the start of the restraint stress. The rats were stressed for 60 min by being introduced into plastic tubes (21 cm length, 4.5 cm diameter) where they could not move. Blood samples (0.3 ml) were collected at −2, 5, 10, 15, 30, and 60 min while the animals were inside the restraint stressor, through a polyethylene tube adapted to the venous catheter.

1.3. Chemical analysis

Blood was centrifuged at 4°C and plasma was stored at −20°C until the assay for glucose, insulin, and prolactin concentrations. Glucose was assayed in duplicate by the glucose-oxidase method (GOD-ANA, Lab Test, Brazil). Insulin was measured by radioimmunoassay (Novo Nordisk, Bagvaerd, Denmark) using rat insulin as standard, human ^{125}I-labeled insulin as a tracer, and ethanol separation of the bound and free fractions. The average intra- and interassay coefficients of variation were 3.0% and 11.4%, respectively. Plasma prolactin was measured in duplicate by radioimmunoassay using materials supplied by the NIDDK (Bethesda, MD, USA). The samples were run in the same assay with a sensitivity of 2 ng/ml plasma and intraassay coefficient of variation of 8%.

1.4. Statistical analysis

Differences between groups (area under the curve) were checked by ANOVA followed by the Newman–Keuls test. Values from samples taken before and after the beginning of restraint stress were compared to basal values using a repeated-measures ANOVA and checked by the paired t test.

2. Results

As illustrated in Fig. 1, the basal prolactin levels of the groups treated with BR were not significantly different from those of the control group treated with vehicle (VEH). Restraint stress induced a marked increase in the plasma prolactin levels of VEH rats at 5 min (11.6 ± 3.6 ng/ml, basal vs. 55.7 ± 6.1 ng/ml, at 5 min), which reached a peak at 10 min (57.9 ± 8.1 ng/ml, $P < .01$) and remained elevated up to 60 min (30.1 ± 6.6 ng/ml, $P < .01$). On the other hand, restraint failed to induce any significant change in plasma prolactin levels in the BR group.

During restraint, there was a strong increase in blood glucose levels in both the BR and VEH groups (Fig. 2A). At 5 min, they were already significantly higher than the basal levels (7.79 ± 0.57 mM for VEH and 8.07 ± 0.43 mM for BR; $P < .01$ vs. basal levels of 6.04 ± 0.30 mM for VEH and

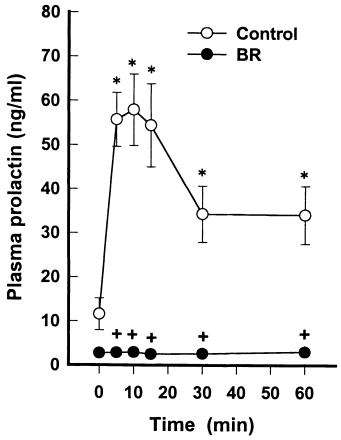

Fig. 1. Effect of restraint stress on plasma prolactin secretion in rats chronically treated with bromocriptine (BR, 10 rats) or with vehicle (Control, nine rats). Data are plotted as means ± S.E.M. * $P < .01$ vs. basal values; + $P < .01$ vs. the VEH group.

6.02 ± 0.32 mM for BR). The glucose levels of both groups remained significantly above the basal levels throughout the experimental period, with higher levels at 60 min (8.24 ± 0.44 mM for VEH vs. 10.40 ± 0.92 mM for BR). Although both groups showed significant hyperglycemic responses to restraint stress, the BR group showed higher hyperglycemic increments when compared to the VEH group. This effect can be more accurately observed at 10 and 15 min (Fig. 2A). Analysis of the 60-min integrated area under the glucose curve also showed that this area was much larger for the BR group than for the VEH group (Fig. 3A, $P < .01$).

As illustrated in Figs. 2B and 3B, during the 60 min of restraint, there was no significant change in insulin levels in either group despite the presence of hyperglycemia.

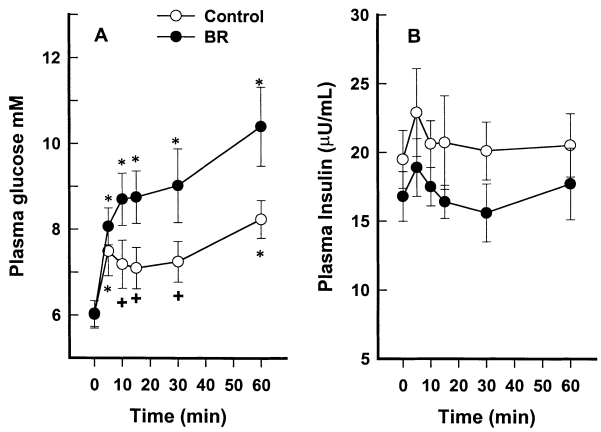

Fig. 2. Effect of restraint stress on plasma glucose levels (A) and insulin secretion (B) in rats chronically treated with BR (10 rats) or with vehicle (nine rats). Data are plotted as means ± S.E.M. * $P < .05$ vs. basal values; + $P < .05$ vs. basal values.

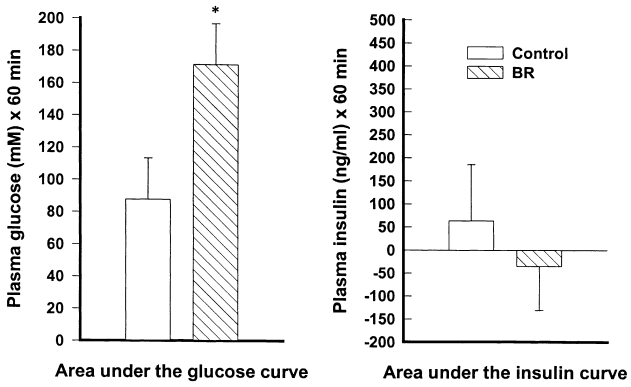

Fig. 3. Integrated areas under the glucose (A) and insulin (B) curves (shown in Fig. 2A and B) of rats chronically treated with BR or with vehicle. Data are plotted as means ± S.E.M. * $P < .05$ vs. VEH group.

3. Discussion

The present data demonstrate that the concomitant increase of prolactin secretion and hyperglycemia in response to restraint stress can be dissociated by chronic treatment with BR, a D_2 dopaminergic agonist. Bromocriptine treatment increased the hyperglycemic response to immobilization with no significant change in plasma prolactin levels. Our data suggest that, besides the increased central dopaminergic tonus indicated by the lower basal levels and the complete blockade of restraint-induced prolactin secretion, BR-treated rats also showed an increased sympathetic response to stress. This increased sympathetic activation is indicated by the higher blood glucose levels observed during immobilization in BR-treated rats. In support of these results is the evidence that stimulation of D_2 dopaminergic receptors in the brain can activate the sympathoadrenal system, which ultimately modifies the glucoregulatory responses (Arneric et al., 1984a,b; Furthermore, catecholamine from the adrenal medulla has been shown to be released by the action of D_2 dopaminergic agonist into the central nervous system (Arneric et al., 1984a,b; Quik and Sourkes, 1977; Saller and Kreamer 1991).

Immobilization is a simple, effective stressor that produces large increases in plasma levels of noradrenaline and adrenaline, consistent with activation of the sympathetic and adrenomedullary systems (Kvetnansky et al., 1992; Pacak et al., 1998). During immobilization, the increase in plasma levels of catecholamine levels is extremely rapid, typically reaching peak levels within 1 min of immobilization (Kvetnansky et al., 1992). In fact, stress increases the sympathetic tone, which accounts for the major effect of plasma hyperglycemia and the inhibition of insulin secretion (Kvetnansky et al., 1992; Yamada et al., 1993). Therefore, the increased stimulation of D_2 receptors by BR in our experiment may have facilitated the sympathoadrenal activity during restraint. We should like to emphasize that inhibition of insulin secretion by stress occurs via the hypothalamus and is mediated by the release of adrenal catecholamines (Havel

and Taborsky, 1989; Frohman et al., 1973; Smith et al., 1973; Smythe et al., 1989; Storlien et al., 1985).

Hypothalamic dopaminergic neurons are thought to be regulated, to a large extent, by the actions of prolactin. High concentrations of circulating prolactin stimulate dopaminergic neurons inducing an increased rate of synthesis, turnover, and release of dopamine in the median eminence (Demarest et al., 1985a,b). Our data showed that chronic treatment with the D_2 receptor agonist increased the hyperglycemic response to stress whose intensity was similar to that observed in previous studies with hyperprolactinemic (Reis et al., 1994, 1996a,b) rats, perhaps reflecting the high central dopaminergic activity of both situations. It is important to point out that D_2 receptor stimulation produces an increase in the blood glucose levels that is prevented by centrally acting D_2 antagonist but not by D_2 peripheral acting D_2 antagonist such as domperidone (Saller and Kreamer, 1991). The stimulatory effect of BR on the hypothalamo-pituitary-adrenal axis through the central D_2 receptor would increase the corticotropin release and plasma concentration of corticosterone, a well-known hyperglycemic hormone. However, after prolonged treatment with BR no change in adrenal weigh or plasma corticosterone level was found in rats (Cameron and Scarisbrick, 1973). On the other hand, inhibition of prolactin secretion by BR may have contributed to the increased hyperglycemic response since prolactin increases glucose-stimulated insulin secretion and improves peripheral glucose utilization (Reis et al., 1997; Sorenson and Brelje, 1997).

Besides its central effects, the peripheral action of BR directly in the liver may also have contributed to the higher hyperglycemic response induced by restraint stress in BR-treated rats. The presence of dopamine D_2 receptors has been shown in hepatocytes and intraperitoneal administration of the D_2 receptor agonist activates the gluconeogenesis and hepatic glucose production in fasting rats (Schmidt et al., 1983). Activation of hepatic gluconeogenic enzymes induced by chronic treatment with BR may have facilitated a higher glycemic response to stress, even though acute intraperitoneal injection of BR has been shown not to influence plasma glucose levels or insulin secretion in fed rats (Uvnäs-Moberg et al., 1996).

The group of rats treated with VEH showed the expected fast prolactin release in response to restraint stress, as also observed by others (Gala, 1990; Minamitani et al., 1987; Nonaka, 1999). In contrast, stress-induced prolactin secretion was completely blocked in BR-treated rats, indicating a strong inhibition by treatment with BR. These results provide further evidence that restraint stress is under the control of a D_2 dopaminergic mechanism. The response to stress-induced prolactin secretion is under the control of the paraventricular nucleus of the hypothalamus (PVN) (Minamitani et al., 1987), the site of origin of several putative prolactin-releasing factors (Gala, 1990; Kjaer et al., 1995). Electrolytic lesions of the PVN of male rats completely abolish prolactin secretion in response to restraint stress and ether anesthesia (Minamitani et al., 1987). Prolactin secretion is regulated by both prolactin-inhibiting factors, mainly dopamine, and prolactin-releasing factors. Dopamine secreted from terminal tuberoinfundibular (TIDA) neurons into the external layer of the median eminence enters the hypothalamic hypophyseal portal vascular system and is thereby transported to the adenohypophysis. Dopamine binds to stereospecific receptors in the adenohypophysis and inhibits prolactin secretion (Gala, 1990). Acute restraint stress has been reported to decrease dopamine synthesis and turnover in the median eminence (Demarest et al., 1985a,b; Gala, 1990). The stress-induced decrease in TIDA neuronal activity should facilitate the actions of putative prolactin-releasing factors (Demarest et al., 1985a,b; Minamitani et al., 1987). The action of restraint stress on TIDA neurons and prolactin secretion is mediated by both cholinergic and 5HT receptors. This is supported by the observation that muscarinic cholinergic receptor antagonists (Demarest et al., 1985b) and 5HT receptor antagonists (Nonaka, 1999) block these effects of restraint stress. Disinhibition of tonic dopamine release has been reported not to be a significant factor in causing acute prolactin secretion during stress, a secretory response mainly mediated by the PVN (Minamitani et al., 1987). However, in the present study, BR treatment completely abolished the prolactin responses to stress, suggesting that high levels of D_2 agonist are able to block the action of prolactin-releasing factors from the PVN.

Finally, we conclude that chronic treatment with the D_2 receptor agonist determines the dissociation of the control of concomitant increase in prolactin secretion and hyperglycemia in response to restraint stress. The increased D_2 dopaminergic tonus accounted for the higher hyperglycemic response and strong inhibition of prolactin secretion following restraint stress.

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