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Original Article

Modulatory effect of ventromedial hypothalamic D2 receptors on leptin and glucose concentration

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Abstract

Introduction: A specific role of dopamine D2 receptor signaling of midbrain and hypothalamic dopaminergic systems has not been yet identified in energy homeostasis. Here, we investigated effects of intra-ventromedial hypothalamus (VMH) administration of the D2 receptor agonist (quinpirole) and antagonist (sulpiride) on plasma leptin and glucose levels in fasted rats.

Methods: A guide cannula was stereotaxically implanted in the VMH of male Wistar rats (n=6/group). In experiment day, the fasted rats (20-24h) received a recommended dose of D2 receptor agonist (quinpilroe: 0.5µg), antagonist (sulpiride: 0.005µg) and saline (0.5µl) injected into the VMH. Blood samples were collected at 0, 30 and 60 min after injection, and plasma leptin and glucose were measured by Eliza kit and glucose oxidase method, respectively.

Results: Plasma leptin significantly increased in a time dependent manner in quinpirole group compared to control (P<0.01), while sulpiride markedly suppressed it (P<0.001). Increase in glucose levels was time dependently robust in quinpirole group (P<0.00). A significant reduction was observed in glucose levels in sulpiride compared to control group (P<0.05). There was also a negative correlation between glucose and leptin plasma levels in drug-treated rats.

Conclusion: These data suggest that altered the VMH D2-mediated neurotransmission might contribute to an alteration in the metabolic phenotype (leptin secretion and plasma glucose level) of rats.

Keywords:
Dopamine;
D2 receptor;
Glucose;
leptin;
Ventromedial nucleus

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Introduction

Substantial experiences indicate that energy balance is tightly regulated by well-coordinated interactions between the brain and peripheral metabolic organs. Hypothalamus is one of the structures responsible for the regulation of energy homeostasis that senses the nutrient status of the organism and integrates signals from peripheral hormones including leptin, ghrelin, insulin as well as from plasma glucose to maintain the energy balance at a desired level that its disruption may cause obesity (Roh et al., 2016; Timper and Brüning, 2017; Yu and Kim, 2012).

Dopamine (DA) is known to play an essential role in the control of feeding behavior (Meguid et al., 2000; Volkow et al., 2011). DA-deficient mice exhibit behaviors associated with seeking and ingesting

food, but they cannot consume food enough to survive (Zhou and Palmiter, 1995), suggesting an important role of DA signaling in physiological function of appetite centers. The importance of the DA signaling in the energy homeostasis is also confirmed by studies that indicating DA receptors are co-localized with the leptin receptors, where dopamine inhibits leptin signaling in the hypothalamus (Billes et al., 2012; Kim et al., 2010; Nogueiras and Seeley, 2012). Furthermore, D2R knock-out mice have an increased hypothalamic leptin sensitivity (Kim et al., 2010). Results obtained from previous studies suggest that leptin release is controlled by the dopaminergic neurons and that dopamine executes its physiological role on energy balance in partly via regulation of plasma level of leptin or other peripheral homeostatic signals (Doknic et al., 2002; Dunn et al., 2017; Kim et al., 2010; Kok et al., 2006b; Mastronardi et al., 2001). For example, D2R knock-out mice show a 75% reduction in the plasma leptin concentration compared to wild type mice (Kim et al., 2010). Conversely, previous observations provide the inhibitory effect of dopaminergic neurotransmission (systemic administration) on leptin secretion. In particular, it has been reported that treatment with bromocriptine, a dopamine D2 receptor agonist, significantly lowers the plasma leptin concentration in a single blood sample of humans with prolactinoma, even without affecting body weight (Doknic M et al., 2002). Furthermore, a single intravenous bolus injection of bromocriptine significantly reduced both basal and lipopolysaccharide-induced leptin release in rats, and short-term treatment with bromocriptine lowered circulating leptin levels in obese women, which suggests that dopaminergic neurotransmission is involved in the control of leptin release in human and animals (Dunn et al., 2017; Kok et al., 2006b; Mastronardi et al., 2001). Nevertheless, these studies have not identified a specific role for midbrain or appetite DA systems in the control of leptin release. In this regard, the role of hypothalamic dopaminergic neurotransmission on homeostasis system is unknown. Since D2R expression is relatively abundant in ventromedial hypothalamus, VMH (Bina and Cincotta, 2000; Clifton et al., 1991; Cooper and Al-Naser, 2006; Kuo, 2002; Meguid et al., 1997; Meguid et al., 2000; Volkow et al., 2011), hence, we investigated the role of local VMH D2R activation on regulation of plasma leptin concentration in rats.

Furthermore, a significant correlation has been shown between plasma glucose levels and cerebrospinal fluid concentrations of the dopamine (Blum et al., 2014; Dunn et al., 2012; Umhau et al., 2003), raising the possibility that leptin may affect plasma glucose levels. Therefore, we also evaluated correlation between plasma glucose and leptin concentrations.

Materials and methods

Animals

Male Wistar rats (220–250 g, Pasteur Institute of Iran, Tehran) were housed under controlled conditions (23±2 °C, 30-40% humidity and light on 07:00–19:00) with free access to standard rat chow and drinking water. Animals were fasted for 24 h, but they had free access to water. All procedures were conducted in according to the European Community Council Directive for Care and Use of Laboratory Animals.

Drugs

Quinpirole hydrochloride (dopamine D2 receptors agonist) and sulpiride (dopamine D2 receptors antagonist) were supplied from Sigma (St Louis, MO, USA).

Stereotaxic surgery

After one week of habituation to the housing conditions, for cannulation and verification of placement, rats were deeply anesthetized with chlorate hydrate (400 mg/kg; ip) and fitted with a 23-gauge stainless steel cannula placed just above the right VMH. Stereotaxic coordinates were determined from the rat brain atlas of Paxinos and Watson (2007): lateral: +0.7 mm from midline; dorsoventral: 8.5 mm from skull surface; anteroposterior: 2.4 mm from the bregma. The injector extended one mm beyond the end of the guide cannula. After surgery, the animals were allowed a 5-day recovery period before experimental trials. Injection of compound drugs or saline was performed under chlorate hydrate anesthesia using a hamilton one µl syringe through silastic tubing in a volume of 0.5µl over 30s. After the injection, the needle was left in place for an additional 30s. After completion of the experiments, rats were killed and cannula placements were verified histologically (Eliassi et al., 2009).

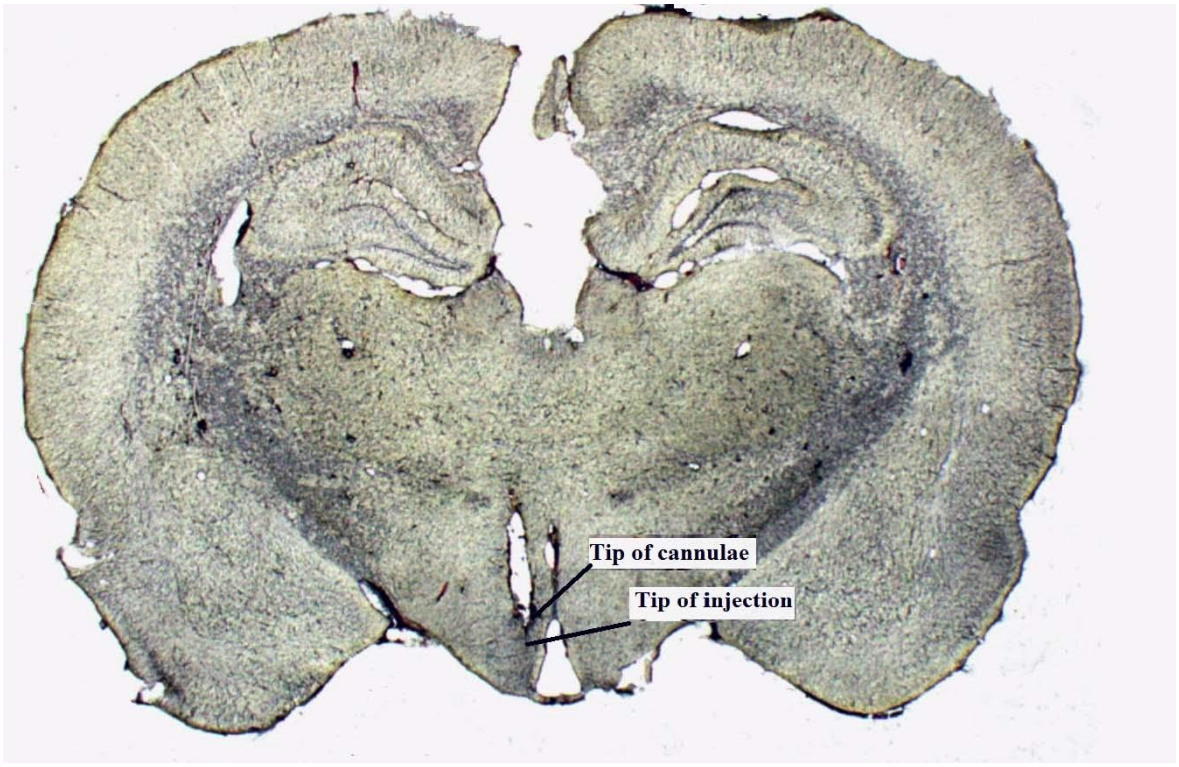

Fig.1. Representative photomicrograph of transverse section showing the intra-VMH injection. Representative position of the injection cannula is indicated by an arrowhead.

Treatments

In the experiment, rats in control and treatment groups, received a recommended dose of D2R agonist/antagonist (0.5µg and 0.005 µg) or saline (0.5µl) into the VMH, respectively, after a 20-h fasting period (Bakhshi, 2009). The recommended dose of D2 receptor agonist/antagonist was based on that used in other study in our lab (data not published). To investigate the time-course effect of the VMH injection of drugs, blood sampling was performed at 0, 30 and 60 min after drugs injection.

After blood sampling, plasma leptin and glucose levels were measured using leptin ELISA kit with intra-assay precision CV< 10% (Zellbio Company ELISA kit-Germany) and glucose oxidase method (Pars Azmoon, Iran). All experiments were performed at 9:30 am.

Statistical analysis

Statistical analysis was performed using SPSS version 16 statistical software. Results are shown as the mean±SEM. The differences between groups in the hormone study were checked by repeated measures design and one-way ANOVA followed by Tukey's HSD test (hormone analysis at one time). Correlation between changes in leptin level and glucose concentration was performed using Pearson correlation at the 5% error term. $P< 0.05$ was considered statistically significant.

Results

In the present study, we evaluated whether modulatory effect of hypothalamic D2R receptors on energy homeostasis could be through the regulation of leptin secretion and glucose metabolism.

Effect of D2R agonist and antagonist on the plasma concentration of leptin

The leptin secretion pattern over time (a period of 1 h) was evaluated following microinjection of quinpirole (0.5µg) into the VMH. Plasma leptin level significantly changed in different groups ($P<0.05$, Fig. 2A). Further analysis revealed a significant increase ($P<0.05$) in plasma leptin from the basal levels of (6.6±0.71 ng/ml; Fig. 2A; ~100%; Fig. 2B) to (11.10±0.9 ng/ml; Fig. 2A; 137.07%; Fig. 2B) at 30 min and to (12.18±0.58ng/ml; Fig. 2A; 140.56%; Fig. 2B) at 60 min, compared with saline injection (basal level: 8.11±0.84; at 30 min: 8.00±1.01 and at 60 min: 8.07±0.58, Fig. 2A).

Sulpiride significantly decreased ($P<0.001$) plasma leptin from the basal levels of (8.14±0.99 ng/ml, Fig. 2A; ~100%; Fig. 2B) to (4.73±0.58 ng/ml; Fig. 2A;

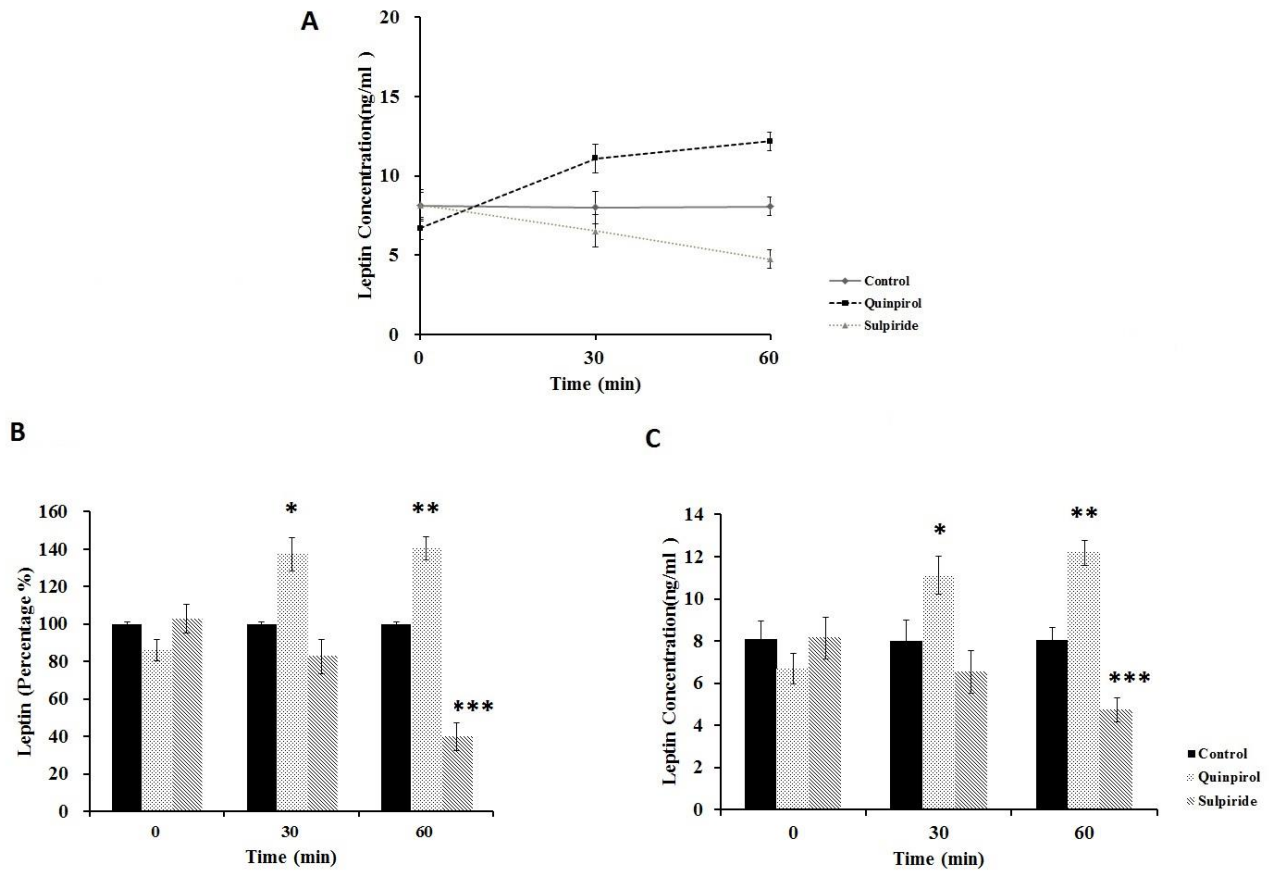

Fig.2. Effect of VMH injection of the D2R agonist (quinpirole: 0.5µg) and D2R antagonist (slpride: 0.005µg) on plasma leptin concentrations in 20 h fasted rats. A: the leptin secretion pattern over time (a period of 1 h) following microinjection of saline (0.5µl), quinpirole (0.5µg) and sulpiride (0.005µg) into the VMH. B: comparative time-dependent leptin concentration changes as percentage between groups (n=5-6). C: differences in mean concentration of leptin at one time between groups (n=5-6). Each point represents mean ±SEM.
$^{***}P$<0.001, $^{**}P$< 0.01 and $^{*}P$<0. 05 compared with VMH saline-injected controls.

39.71%; Fig.2B) at 60 min, compared with saline injection (basal level: 8.11±0.84; at 30 min: 8.00±1.01 and at 60 min: 8.07±0.58, Fig. 2A). Sulpiride injection had no significant effect on leptin concentration at time of 30 compared with saline (Figs. 2A and 2B) treated rats. Also, the results obtained from one-way ANOVA for leptin analysis at one time showed a significant increase at times of 30 and 60 min for quinpirole group compared to control group at 30 min and at 60 min (Fig. 2C, P<0.01). Leptin concentration in sulpiride group also showed a significant decrease at time 60 compared to control group (Fig. 2C). Differences were maximum 1h post-injection (P<0.001, Fig. 2C).

Effect of D2R agonist and antagonist on the plasma concentration of glucose

As shown in Figure 3A, quinpirole significantly changed plasma glucose levels in different groups (P<0.05). Further analysis revealed a significant decrease in plasma glucose from the basal levels of 142±5 mg/dl to 113±6 (79.4%, Fig. 3A) (Fig. 3B) at 30 min, and to 116±7 mg/dl (Fig. 3A) (81 %; Fig. 3B) at 60 min compared with control group (at basal level: 139±11; at 30 min: 140±9 and at 60 min: 138±8, Fig. 3A; P<0.05). Performing one-way ANOVA for glucose analysis at one time showed a significant decrease at times of 30 and 60 min for quinpirole group compared to control group (Fig. 2C). Moreover, glucose concentration in sulpiride showed a significant increase from the basal levels of (129±14 ng/ml, Fig. 2A) to 171±10 (152.8%; Fig. 3C) (Fig. 3B) at 30 min, and to 233±12 mg/dl (Fig. 3A) (178.5 %; Fig. 3B) at 60 min, compared with saline injection (at basal level: 139±11; at 30 min: 140±9 and at 60 min: 138±8; Fig. 3A) (P<0.001). Also, the results obtained from one-way ANOVA for glucose analysis at one time showed a significant decrease at times of 30 and 60 min for

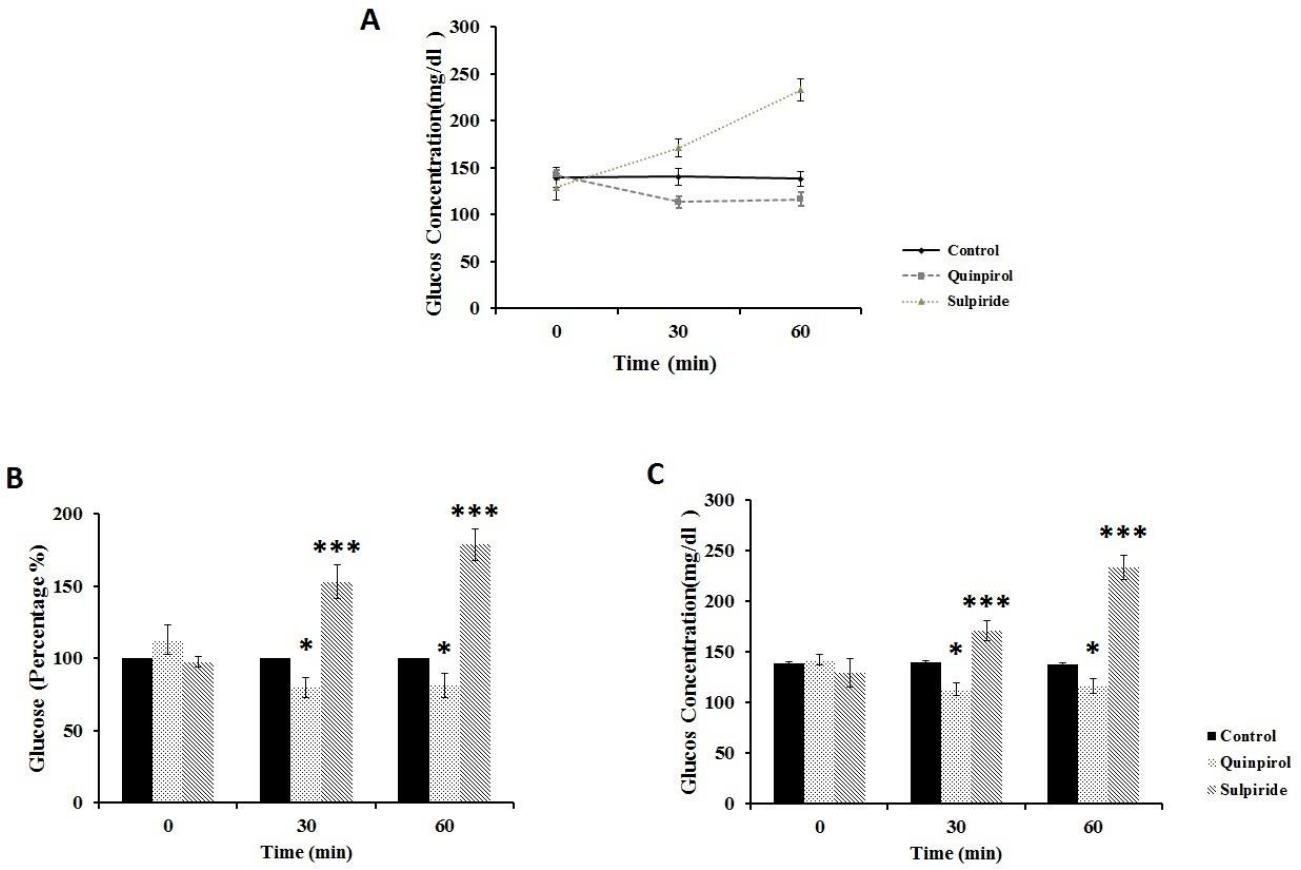

Fig.3. Effect of VMH injection of the D2R agonist (quinpirole: 0.5µg) and D2R antagonist (slpride: 0.005µg) on plasma glucose concentrations in 20 h fasted rats. A: the glucose secretion pattern over time (a period of 1 h) following microinjection of saline (0.5µl), quinpirole (0.5µg) and sulpiride (0.005µg) into the VMH. B: comparative time-dependent glucose concentration changes as percentage between groups (n=5-6). C: differences in mean concentration of glucose at one time between groups (n=5-6). Each point represents mean ±SEM.
$^{***}P$<0.001 and $^{*}P$<0. 05 compared with VMH saline-injected controls.

quinpirole group compared to control group (Fig. 3C). Leptin concentration in sulpiride also showed significant increase at times of 30 and 60 min for sulpiride group compared to control group (Fig. 3C). Differences were maximum 1h post-injection (P<0.001; Fig 2C).

Correlation between plasma concentration of glucose and leptin under VMH dopamine changes

We also examined the possibility that the leptin secretion may affect glucose metabolism by VMH injection of quinpirole. Analysis revealed a significant negative correlation between the plasma leptin and glucose concentration in the quinpirole (Pearson's correlation; r=0.71, P< 0.05) and sulpiride (r=0.88, P< 0.01) groups (Fig. 4) at 60 min after injection drugs. These findings supported the idea that plasma glucose levels were affected by leptin secretion under ventromedial D2 receptor activity.

Discussion

Although dopamine has been shown to involve in the regulation of food intake via the mesolimbic and hypothalamic circuitries (Baptista, 1999; Kuo, 2002; Volkow et al., 2011), specific role of hypothalamic nuclei including VMH in regulation of food intake is elusive. In the present study, we provide first evidence that dopaminergic signaling in the VMH can play an important role in the regulation of leptin levels. Activation of the VMH D2 receptors by quinpirole increased plasma levels of leptin, while D2 receptors blockade by sulpiride reduced the stimulatory effect of dopamine receptor activation. Our results also demonstrate that change in the VMH dopaminergic transmission by a dopamine D2 agonist or antagonist can modulate glucose metabolism. The VMH D2 activation by quinpirole tended to reduce

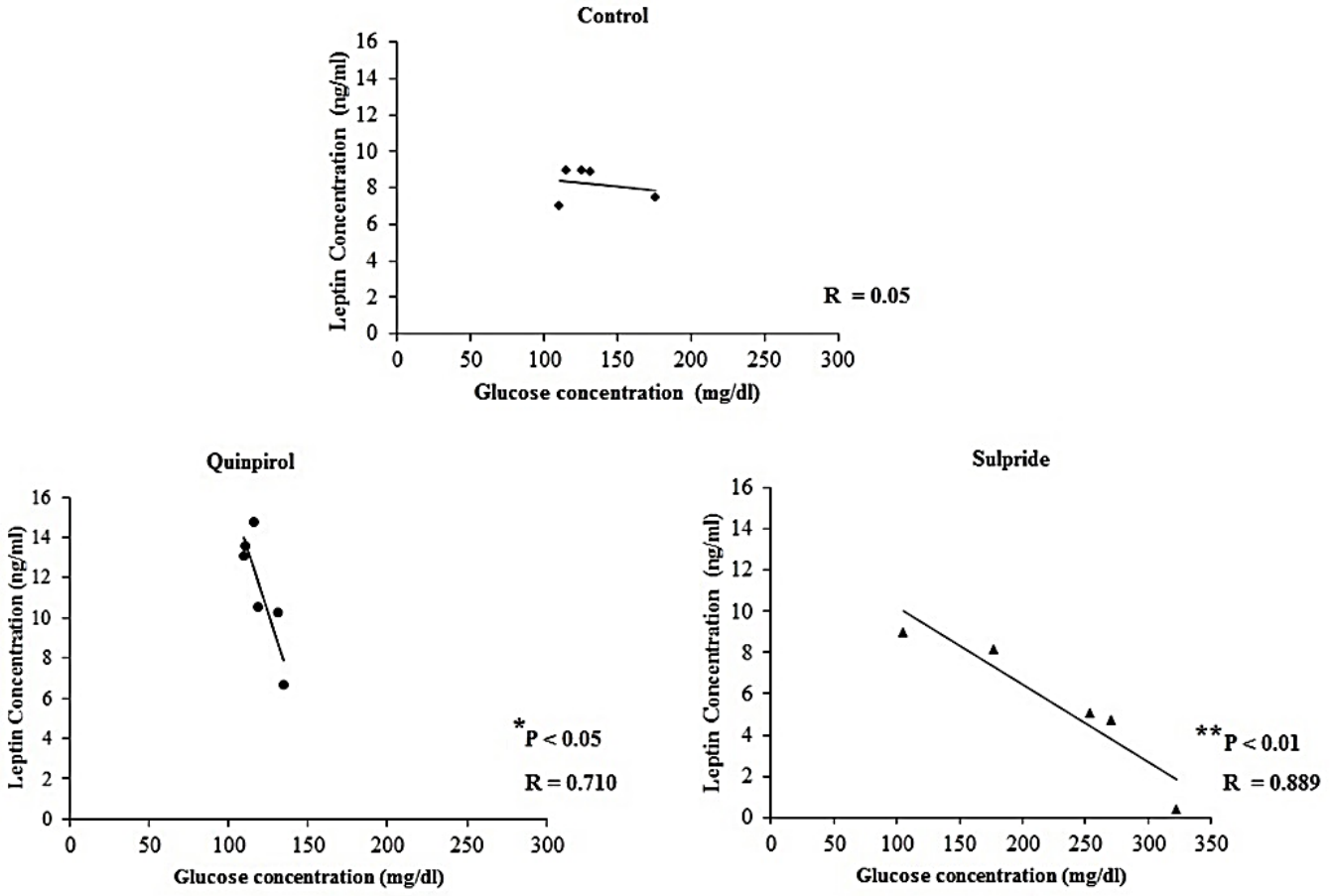

Fig.4. Correlation analysis between the plasma concentration of leptin and glucose in different groups (n = 5-6). Results are expressed as mean±SEM (Pearson's correlation test; *P*<0.05 and *P*< 0.01 in quinpirole and sulpiride-treated animals).

fasting plasma glucose concentration, while blocking dopamine D2R by sulpiride increased glucose level.In obese humans and animals, dopamine D2 receptor availability is lower in some regions of the brain including hypothalamic nuclei which in turn, results in increased seeking behaviors for food intake (de Leeuw van Weenen et al, 2011; Fetissov et al., 2002; Pijl, 2003; Wang et al., 2001). Hence, it has been suggested that there is a dopamine deficiency in obese subjects which might promote compensatory eating response to activate reward/feeding circuits regulated by the activity of dopamine D2 receptors (Noble et al., 1994). Moreover, it has been indicated that leptin attends as the dominant adiposity anorexic signal in the hypothalamus circuits after meal and can promote suppression of appetite (Park and Ahima, 2015). It seems that one mechanism under the hypothalamic D2 receptor activation is regulation of peripherally appetite or satiety hormones. Hence, we suggest both blockade D2 receptors and low dopamine D2 receptor availability might result in a reduction of plasma leptin level. These results are consistent with a study performed after bariatric surgery that indicated a regional decrease in the hypothalamic D2 receptors was accompanied by significant decreases in plasma insulin and leptin levels (Dunn et al., 2010). Although, some studies have provided direct evidence for an inhibitory effect of dopamine D2 agonist (alpha-bromoergocryptine) on leptin release in obese human, indicating that dopaminergic neurotransmission is involved in the control of leptin release in humans (Kok et al., 2006b; Mastronardi et al., 2001). Since obese individuals have a deficit in dopamine transmission and D2 receptor signaling, therefore, improving dopamine function and leptin circulating might be useful in treating them.

Our results also demonstrate that change in the VMH dopaminergic transmission by a dopamine D2 agonist or antagonist can modulate glucose metabolism. The VMH D2 activation by quinpirole tended to reduce fasting plasma glucose concentration, while blocking dopamine D2R by sulpiride increased glucose level. Previous studies have demonstrated that VMH is closely involved in the control of glucose and lipid homeostasis through glucose and leptin sensing

neurons, while destruction of the VMH causes hyperphagia, obesity and hyperglycemia (Poca et al., 2005; Shimizu et al., 1987; Van Den Hoek et al., 2004). Moreover, it has been established that brain dopaminergic transmission profoundly affects glucose metabolism (de Leeuw van Weenen et al. 2011; Kok et al., 2006a) and that the VMH is regarded as an area with high DRD2 expression levels (Fetissov et al., 2002). Hence, the VMH dopamine D2R modulation may affect energy homeostasis via glucose metabolism. Pharmacological activation of dopamine D2R ameliorates various metabolic anomalies and improves glycemic control in obese animal models and human (Cincotta et al., 1999; Kok et al., 2006a; Kuo, 2002; Luo et al., 1999). In accordance with this, short-term and long term administration of dopamine D2 agonists improve glucose and lipid metabolism in patients with type 2 diabetes and hyperprolactinemia (dos Santos Silva et al., 2011; Pijl, 2003). Furthermore, Luo et al. (1999) showed intracerebroventricular administration of bromocriptine recovers insulin sensitivity in obese. Conversely, our results showed that D2 receptor blockade increases glucose levels, consistent with data reporting an increased occurrence of diabetes among individuals treated with dopamine D2 antagonist (Buse et al., 2003; Xu et al., 2002). Also, blocking dopamine D2R in animals and humans induces insulin resistance of glucose metabolism in addition to appetite enhancement (Baptista et al., 1987; Baptista et al., 2002). Additionally, we propose activation/ inactivation of dopamine D2R by quinpirole and sulpiride may alter glucose metabolism via modulation of circulating regulatory metabolic peptides such as leptin, since we observed a negative correlation between the plasma concentration of glucose and leptin in quinpirole and sulpiride-treated animals. The impact of activation of dopamine D2R by bromocriptine on leptin level as well as insulin sensitivity improvement is well established (de Leeuw van Weenen et al., 2011). Both ghrelin and leptin affect insulin sensitivity and glucose homeostasis (Chabot et al., 2014; Van Den Hoek et al., 2004). There is a strong positive correlation between fasting leptin and insulin concentrations which confirms that high leptin levels might be reversely associated with the hypoglycemia (Korek et al., 2013).

Conclusion

Together, these data suggest an association between D2 receptor activity and alteration in metabolic signals including leptin and that pharmacological or pathological altered D2R-mediated neurotransmission might contribute to change the metabolic phenotype of individuals. The VMH D2-mediated dopaminergic signaling might follow a mechanism through which the hypothalamus controls glucose metabolism and metabolic profile of appetite peptides in rats, although further studies are needed to assess the mechanism (s) involved in the hypothalamic dopamine regulation of food intake. Generally, these findings suggest that the VMH dopamine is a physiological regulator for leptin release and support the role of hypothalamic dopamine in the control of glucose concentration.

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Conflict of interest

The authors declare that no competing interests exist.

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