New Topics in Vasopressin Receptors and Approach to Novel Drugs: Effects of Vasopressin Receptor on Regulations of Hormone Secretion and Metabolisms of Glucose, Fat, and Protein

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Received September 25, 2008; Accepted November 10, 2008

Abstract. The neurohypophyseal peptide [Arg⁸]-vasopressin (AVP) is involved in diverse functions such as the regulation of body fluid homeostasis, metabolism, and hormone secretion. In this study, we analyzed the functional roles of AVP in hormone release and metabolisms of glucose, fat, and protein in mutant mice lacking the V₁a (V₁aR-KO) or V₁b receptor (V₁bR-KO). Our study suggests that antagonists for the receptors could affect the hormone secretions and metabolisms.

Keywords: arginine vasopressin, metabolism, hormone, adrenocorticotropic hormone (ACTH)

Introduction

The neurohypophyseal peptide [Arg⁸]-vasopressin (AVP) is involved in diverse functions such as the regulation of body fluid homeostasis, metabolism, and hormone secretion (1). Here, I report the functional roles of AVP in hormone release and metabolisms of glucose, fat, and protein in mutant mice lacking the V₁a (V₁aR-KO) or V₁b receptor (V₁bR-KO).

Adrenocorticotropic hormone (ACTH) release from the anterior pituitary glands in response to AVP or oxytocin (OT) stimulation

The vasopressin V₁b receptor is specifically expressed in pituitary cells and mediates the stimulatory effect of AVP on ACTH release (2). To investigate the functional roles of V₁b-receptor subtypes, plasma ACTH levels and ACTH secretion from anterior pituitary cells were examined in V₁bR-KO mice. Under resting conditions, circulating concentrations of ACTH and corticosterone were lower in V₁bR-KO mice compared with wild type (WT) mice. AVP-induced ACTH release from primary cultured pituitary cells in V₁bR-KO mice was also blunted. Furthermore, the increase in ACTH after a forced swim stress was significantly suppressed in V₁bR-KO mice. These results indicate that the V₁b receptor plays a crucial role in regulating hypothalamic–pituitary–adrenal axis activity by maintaining ACTH and corticosterone levels, not only under stress but also under basal conditions (3).

Oxytocin (OT) is also one of the secretagogues for stress-induced ACTH release and OT-induced ACTH release is reported to be mediated by the vasopressin V₁b receptor in the rat pituitary gland (4). OT-induced ACTH release was examined using primary cultures of anterior pituitary cells from WT and V₁bR-KO mice. OT stimulated similar levels of ACTH release from pituitary cells of WT and V₁bR-KO mice. OT-induced ACTH release was significantly inhibited by the selective V₁b-receptor antagonist SSR149415 and by the OT-receptor antagonist CL-14-26 in WT mice. In addition, co-treatment with SSR149415 and CL-14-26 inhibited OT-induced ACTH release to the control level in WT mice. In V₁bR-KO mice, OT-induced ACTH release was completely inhibited by CL-14-26. These results indicate that OT induces the ACTH response via OT and V₁b receptors in WT mice but via only OT receptors in V₁bR-KO mice (5).

Aldosterone release in response to AVP stimulation

Aldosterone release in response to stimulation with AVP was examined with adrenal gland cells. AVP...
caused a significant increase in aldosterone release from the dispersed adrenal gland cells of WT mice. In contrast, AVP-induced aldosterone release was impaired in adrenal gland cells from V1aR-KO mice. In addition, the selective V1a-receptor antagonist OPC-21268 potently inhibited AVP-induced aldosterone release. These findings indicate that AVP-induced aldosterone release from adrenal gland cells is mediated via the vasopressin V1a receptor in mice (6).

**Glucagon and insulin release in response to AVP and/or OT stimulation**

AVP and OT have been reported to stimulate insulin and glucagon release from the pancreas (7). To investigate the type of receptors involved in AVP- and OT-induced glucagon secretion, the effect of these peptides on glucagon secretion was evaluated in islets of WT and V1bR-KO mice. AVP-induced glucagon secretion was significantly inhibited by SSR149415 and OT-induced glucagon secretion was significantly inhibited by CL-14-26 in islets of WT mice. AVP- and OT-induced glucagon secretions were not completely inhibited by the antagonist of each, but co-treatment with both SSR149415 and CL-14-26 further inhibited AVP- and OT-induced glucagon secretions in islets of WT mice. In addition, both AVP and OT stimulated glucagon secretion with the same efficacy in V1bR-KO mice as in WT mice. AVP- and OT-induced glucagon secretion in V1bR-KO mice was significantly inhibited by CL-14-26. These results indicate that V1b receptors can mediate OT-induced glucagon secretion and OT receptors can mediate AVP-induced glucagon secretion in islets from WT mice in the presence of a heterologous antagonist, while AVP and OT can stimulate glucagon secretion through the OT receptors in V1bR-KO mice, suggesting that the other receptor can compensate when one receptor is absent (8).

Next, the AVP-receptor subtype responsible for stimulation of insulin release from pancreatic β cells was determined by using subtype-selective antagonists and V1bR-KO mice. AVP increased insulin release from isolated mouse islet cells, and AVP-induced insulin release from pancreatic islet cells was significantly inhibited by SSR149415, but not by OPC-21268. Furthermore, the AVP effect on insulin release was entirely lost in V1bR-KO mice. These results indicate that vasopressin-stimulated insulin release from islet cells is mediated via V1b receptors (9).

**Regulation of glucose metabolism by AVP**

AVP-resistance is observed in poorly controlled NIDDM subjects, suggesting that AVP is involved in maintaining glucose homeostasis (10). Therefore, the roles of the AVP/V1a receptor in regulating glucose homeostasis were investigated using V1aR-KO and V1bR-KO mice. The plasma glucose levels at the baseline or during a GTT were higher in V1aR-KO than in WT mice. Also, a hyperinsulinemic-euglycemic clamp study revealed that a glucose infusion rate was significantly lower in V1aR-KO mice than in WT mice and that hepatic glucose production during the clamp state was higher in V1aR-KO mice than in WT mice. In contrast to increased hepatic glucose production, liver glycogen content was decreased in the mutant mice. These results indicated that the mutant mice had impaired glucose tolerance. Furthermore, feeding V1aR-KO mice a high-fat diet resulted in significantly overt obesity relative to WT mice, accompanied with increased calorie intake. In addition, the circulating plasma volume and aldosterone level were decreased in V1aR-KO mice, although the plasma AVP level was increased. These results suggest that the effect of AVP on water recruitment is disturbed in V1aR-KO mice and indicate that one of the AVP-resistance conditions resulting from deficiency of the V1a receptor leads to decreased plasma volume as well as impaired glucose homeostasis, which exacerbates obesity under the enriched energy condition (11).

We next examined the physiological role of the V1b receptor in regulating blood glucose levels in vivo, and the fasting plasma glucose, insulin, and glucagon levels were found to be lower in V1bR-KO mice than in WT mice. Then, we evaluated glucose tolerance by performing the GTT. The plasma glucose and insulin levels during the GTT were lower in V1bR-KO mice than in WT mice. An insulin tolerance test (ITT) revealed that after insulin administration, plasma glucose levels were lower in V1bR-KO mice than in WT mice. In addition, a hyperinsulinemic-euglycemic clamp study showed that the glucose infusion rate was increased in V1bR-KO mice, indicating that insulin sensitivity was enhanced at the in vivo level in V1bR-KO mice. Furthermore, we found that the V1b receptor was expressed in white adipose tissue and that insulin-stimulated Akt phosphorylation was increased in adipocytes isolated from V1bR-KO mice. Thus, the blockade of the V1b receptor could result, at least in part, in enhanced insulin sensitivity by altering insulin signaling in adipocytes (12).

**Regulation of fat metabolism by AVP**

We examined the involvement of the V1a receptor in the anti-lipolytic effect of AVP using V1aR-KO mice. The levels of blood glycerol were increased in V1aR-KO
mice. The levels of ketone bodies, such as acetoacetic acid and 3-hydroxybutyric acid, the products of the lipid metabolism, were increased in V1aR-KO mice under a fasting condition. Triacylglyceride and free fatty acid levels in blood were decreased in V1aR-KO mice. These results suggest that the lipid metabolism is enhanced in V1aR-KO mice. The cAMP level was enhanced in V1aR-KO mice in response to isoproterenol and phosphorylation of Akt by insulin stimulation was reduced in V1aR-KO mice, indicating that insulin signaling is suppressed in V1aR-KO mice. In addition, the total bile acid, taurine, and cholesterol levels in blood were increased, and an enlargement of the cholecyst was observed in V1aR-KO mice. These results indicated that the production of bile acid was enhanced by the increased level of cholesterol and taurine. Taking together, these results indicated that AVP could modulate the lipid metabolism by its antilipolytic action and synthesis of bile acid via the V1a receptor (13).

Regulation of protein metabolism by AVP

Since the analysis with V1aR-KO mice revealed that glucose homeostasis and lipid metabolism were altered in the mutant mice, we investigated whether the deficiency of the V1a receptor affected protein metabolism. The proteasome activity of the skeletal muscle and the serum 3-methylhistidine level were increased in V1aR-KO mice under a fasting condition. Triacylglyceride and free fatty acid levels in blood were decreased in V1aR-KO mice. These results suggest that the lipid metabolism is enhanced in V1aR-KO mice. The cAMP level was enhanced in V1aR-KO mice in response to isoproterenol and phosphorylation of Akt by insulin stimulation was reduced in V1aR-KO mice, indicating that insulin signaling is suppressed in V1aR-KO mice. In addition, the total bile acid, taurine, and cholesterol levels in blood were increased, and an enlargement of the cholecyst was observed in V1aR-KO mice. These results indicated that the production of bile acid was enhanced by the increased level of cholesterol and taurine. Taking together, these results indicated that AVP could modulate the lipid metabolism by its antilipolytic action and synthesis of bile acid via the V1a receptor (13).

Concluding remarks

In summary, AVP is involved in regulating hormone secretion and metabolism via the V1a and V1b receptors, and the blockade of the receptors could affect these physiological functions.

References