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Impaired arginine–vasopressin-induced aldosterone release from adrenal gland cells in mice lacking the vasopressin V_{1A} receptor

Jun-ichi Birumachi, Masami Hiroyama, Yoko Fujiwara, Toshinori Aoyagi, Atsushi Sanbe, Akito Tanoue *

Department of Pharmacology, National Research Institute for Child Health and Development, 2-10-1 Okura Setagaya-ku, Tokyo 157-8535, Japan

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Abstract

We examined aldosterone release in response to stimulation with arginine–vasopressin (AVP) using adrenal gland cells. AVP caused a significant increase in aldosterone release from the dispersed adrenal gland cells of wild-type mice ($V_{1A}R^{+/+}$) at concentrations from 0.1 μM to 1 μM. In contrast, AVP-induced aldosterone release was impaired in adrenal gland cells from mice lacking the vasopressin V_{1A} receptor ($V_{1A}R^{-/-}$), while adrenocorticotropic hormone (ACTH)-induced aldosterone release in $V_{1A}R^{-/-}$ mice was not significantly different from that in $V_{1A}R^{+/+}$ mice. In addition, a vasopressin V_{1A} receptor-selective antagonist 1-[1-[4-(3-acetylaminopropoxy)benzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (OPC-21268) potently inhibited AVP-induced aldosterone release. Thus, our study clearly demonstrates that AVP-induced aldosterone release from adrenal gland cells is mediated via the vasopressin V_{1A} receptor in mice.

Keywords: Arginine–vasopressin; Vasopressin V_{1A} receptor-deficient mice; Aldosterone; Adrenal gland cells

1. Introduction

The neurohypophyseal peptide, arginine–vasopressin (AVP), plays a major role in regulating water excretion by the kidney. It also participates in other physiological functions such as vasoconstriction and glycogenolysis through vasopressin receptors, which are divided into at least three types: vasopressin V_{1A}, V_{1B}, and V_2 receptors (Thibonnier et al., 2002). The vasopressin V_{1A} receptor, which mainly mediates blood pressure control, is expressed in the liver, brain, heart, kidney, spleen, uterus, and adrenal glands, as well as in vessels. The vasopressin V_{1A} receptor also mediates mineralocorticoid (aldosterone) secretion from zona glomerulosa cells in the human adrenal cortex (Guillon et al., 1995). Pharmacological studies have shown that the application of a non-specific vasopressin V_1 receptor antagonist (Des-Gly-(Pha^1, D-Try(Et)^2, Lys^6, Arg^8)-AVP) inhibited AVP-induced aldosterone release from the rat adrenal cortex (Mazzocchi et al., 1993). These findings suggest that AVP plays a crucial role in stimulating aldosterone release via the vasopressin V_{1A} receptor in human and rat adrenal glands. Recently, we successfully generated a mouse lacking the vasopressin V_{1A} receptor ($V_{1A}R^{-/-}$) (Koshimizu et al., 2006; Egashira et al., 2004). $V_{1A}R^{-/-}$ mice are not lethal and have no apparent anatomical anomaly in organs, including the heart, brain, liver, muscle, and kidney. In our previous study, we observed a decrease in the corticosterone response to ACTH in mutant mice (Koshimizu et al., 2006). In the present study, we investigated the functional role of AVP, in addition to that of a V_{1A} selective antagonist, 1-[1-[4-(3-acetylaminopropoxy)benzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (OPC-21268), on aldosterone secretion from mouse adrenal glands with vasopressin V_{1A} receptor-deficient mice ($V_{1A}R^{-/-}$).

2. Materials and methods

2.1. Animals

The generation of vasopressin V_{1A} receptor-deficient ($V_{1A}R^{-/-}$) mice was previously described (Egashira et al., 2004; Koshimizu et al., 2006). Briefly, by homologous

* Corresponding author. Tel.: +81 3 5494 7120x4650; fax: +81 3 5494 7057.
E-mail address: atanoue@nch.go.jp (A. Tanoue).

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recombination, we disrupted exon 1, which contains the translation initiation codon. Non-vasopressin V_{1A} receptor-deficient littermates ($V_{1A}R^{+/+}$) were used as age-matched control subjects for $V_{1A}R^{-/-}$ mice. Animals were housed in micro-isolator cages in a pathogen-free barrier facility. $V_{1A}R^{+/+}$ and $V_{1A}R^{-/-}$ mice were placed on a 12-h day/night cycle with ad libitum access to food and water except when specified by the experimental protocol. Animals were used at 8–12 weeks of age. All data presented here were obtained from male mice. All experimentation was performed according to approved institutional guidelines.

2.2. Reverse-transcribed (RT)-PCR analysis

RNA was prepared from a whole adrenal gland, and reverse-transcribed (RT)-PCR was performed as described previously (Oshikawa et al., 2004; Tanoue et al., 2004). Thermal cycling was performed for 30 s at 94 °C, 30 s at 57 °C, and 2 min at 72 °C for 30 cycles. The upstream and downstream primer sequences, located within the first exon of the mouse vasopressin V_{1A}, V_{1B}, and V_2 and oxytocin (OT) receptor genes, were 5′-CCGTGCTGGGTAATAGCAGT-3′ upstream and 5′-TCTTCACTGTGCGGATCTTG-3′ downstream for the vasopressin V_{1A} receptor (806 base pairs (bp)), 5′-TCACCTGGACCACCATGGCCATC-3′ upstream and 5′-GCCACATTGGTAGAATCTT-3′ downstream for the V_{1B} receptor (348 bp), 5′-ATTGTCTACGTGCTGTGCTG-3′ upstream and 5′-GAAGGTCTATTGGTCCTATCCT-3′ downstream for the V_2 receptor (618 bp), and 5′-TGGAGCGTCTGGGACGTCAAT-3′ upstream and 5′-ATGGTTGAGAACAGCTCCTC-3′ downstream for the OT receptor (251 bp). The GAPDH sequences (5′ → 3′) were 5′-GGTCATCATCTCCGCCCCTTC-3′ for the sense primers and 5′-CCACCACCCTGTTGCTGTAG-3′ for the antisense primers (662 bp). A control PCR reaction was also performed on non-reverse-transcribed RNA to exclude any contamination by genomic DNA.

2.3. Adrenal gland cell culture and aldosterone measurements

Adrenal gland cells from male $V_{1A}R^{+/+}$ or $V_{1A}R^{-/-}$ mice (8–12 weeks old) were cultured, and aldosterone radioimmunoassays were performed as described (Oshikawa et al., 2004; Tanoue et al., 2004). Briefly, male $V_{1A}R^{+/+}$ or $V_{1A}R^{-/-}$ mice were killed by decapitation, and their adrenal glands were then rapidly removed. The adrenal glands were enzymatically dispersed by the methods of Guillon et al. (1995) with a slight modification. The glands were incubated for 30 min at 37 °C with Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum, 100 U/ml penicillin G potassium, and 1 mg/ml streptomycin sulfate. To disperse cells, 2.5% collagenase was added to the medium. The suspension of glands was sieved through a 100-μm-pore nylon mesh and then centrifuged at 400 ×*g* for 10 min. The pellets were resuspended with DMEM culture media, and the cells were then seeded into 24-well plates (1 to 3×10^5 cells/well). The cells were cultured in a humid incubator at 37 °C in 5% CO_2 and 95% air. After preincubation for 1 h with the incubation medium, the cells were incubated with or without AVP (Peptide Institute, Inc., Osaka, Japan), angiotensin II (Peptide Institute, Inc.), ACTH (Peptide Institute, Inc.), or co-treatment with AVP and ACTH for an additional hour. In experiments with OPC-21268 or (2S,4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-*N*,*N*-dimethyl-2-pyrrolidine carboxamide (SSR149415), the effect of vasopressin V_{1A} or V_{1B} receptor antagonists on AVP-induced aldosterone release was examined in these cultured cells. OPC-21268 (a gift from Otsuka Pharmaceutical Co., Tokushima, Japan) was added 10 min prior to the administration of AVP (0.1 μM). At the end of the incubation period, the medium was collected and stored at −20 °C until the aldosterone assay could be performed. The aldosterone released into the cultured medium was measured by an aldosterone immunoradiometric assay (Yamasa Shoyu Inc., Tokyo, Japan). The aldosterone concentration was expressed as the amount released per 1×10^5 cells.

2.4. Real-time quantitative PCR

Adrenal cortex and medulla were separated from adrenal glands using a substantial microscope. RNA preparation and real-time PCR were performed as described previously (Oshikawa et al., 2004; Tanoue et al., 2004). PCRs were performed using an ABI PRISM 7900 sequence detection system instrument and software (Applied Biosystems, Tokyo, Japan). The primer sequences for the mouse vasopressin V_{1A} receptor genes were as follows: 5′-TGGCAAGCTGGAGTTTACC-3′ (forward) and 5′-GGTGTCGGATGAAGAGATGCA-3′ (reverse). The TaqMan probe for the vasopressin V_{1A} receptor (5′-CATCGCACGCCACGCAAGACAT-3′) was labeled at the 5′ end with the reporter dye FAM and at the 3′ end with the quencher TAMRA. RNA samples were normalized to the level of GAPDH RNA (Applied Biosystems, Tokyo, Japan). The probe for GAPDH RNA (Applied Biosystems, Tokyo, Japan) was labeled with VIC (a reporter dye) and TAMRA (a quencher dye).

2.5. Plasma aldosterone and ACTH concentration

To determine the basal aldosterone and ACTH levels, $V_{1A}R^{+/+}$ and $V_{1A}R^{-/-}$ mice weighing 25–30 g were anesthetized and killed in the light phase. Blood samples were collected and centrifuged as described (Tanoue et al., 2004). Plasma aldosterone and ACTH were measured from a 100-μl plasma sample using an aldosterone immunoradiometric assay kit (Yamasa Shoyu Inc., Tokyo, Japan) or an ACTH immunoradiometric assay kit (Mitsubishi Kagaku Iatron, Inc., Tokyo, Japan).

2.6. Plasma aldosterone response to ACTH

Between 16:00 and 17:00, 2 mg/kg of ACTH was i.p. injected into $V_{1A}R^{+/+}$ and $V_{1A}R^{-/-}$ mice weighing 20–25 g as reported (Coll et al., 2004). Blood was collected before and 30 min after ACTH injection as reported (Koshimizu et al., 2006). Plasma aldosterone levels were measured using an aldosterone immunoradiometric assay kit (Yamasa Shoyu Inc., Tokyo, Japan).

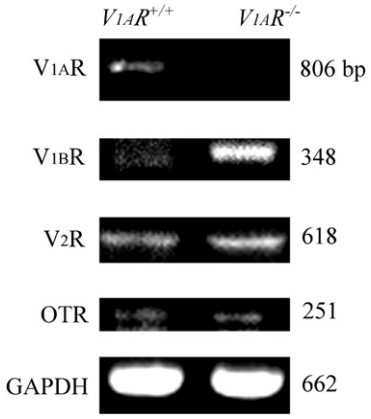

Fig. 1. RT-PCR analysis of the vasopressin receptor family in adrenal gland cells from $V_{1A}R^{+/+}$ or $V_{1A}R^{-/-}$ mice. The RT-PCR fragments were stained with ethidium bromide. The transcripts of the V_{1A}, V_{1B}, V_2, and OT receptors were detected as 806, 348, 618, and 251 bp fragments, respectively. RT-PCR analysis was controlled by the detection of the 662 bp fragment of the GAPDH and is shown in the lower panel.

2.7. Statistics

All values are expressed as the means±S.E.M. Differences between the groups were tested using two-way analysis of variance (ANOVA), followed by Fisher's PLSD and Student's *t*-test as post-hoc test using Statview version 5.0 software (Concepts, Inc., Berkeley, CA, USA). A *P* value below 0.05 was considered statistically significant.

3. Results

3.1. Expression of vasopressin receptors in the mouse adrenal glands

To determine whether vasopressin receptors are involved in the response of aldosterone release to AVP, RT-PCR was used to assess the expression of the AVP receptor subtypes and the OT receptor in adrenal gland tissues from male $V_{1A}R^{+/+}$ and $V_{1A}R^{-/-}$ mice. As shown in Fig. 1, vasopressin V_{1A} receptor mRNA was detected in the adrenal gland tissues from $V_{1A}R^{+/+}$ mice but not from $V_{1A}R^{-/-}$ mice. Vasopressin V_{1B}, V_2, and OT receptor mRNAs were also detected in the adrenal gland tissues from both $V_{1A}R^{+/+}$ and $V_{1A}R^{-/-}$ mice. Furthermore, since the vasopressin V_{1A} receptor was reported to express in the adrenal cortex rather than in the adrenal medulla (Grazzini et al., 1996; Guillon et al., 1995), we assessed the mRNA level of the vasopressin V_{1A} receptor by a quantitative real-time PCR assay. The expression ratio of vasopressin V_{1A} receptor/GAPDH was greater in the adrenal cortex than in the adrenal medulla of $V_{1A}R^{+/+}$ mice (1± 0.3 in the cortex, $n=6$, vs. 0.06±0.03 in the medulla, $n=6$, $P<0.05$). In $V_{1A}R^{-/-}$ mice, no mRNA of the vasopressin V_{1A} receptor was detected in the cortex or medulla (data not shown).

3.2. Aldosterone release from primary cultured adrenal gland cells

In order to determine whether AVP stimulates aldosterone release via the vasopressin V_{1A} receptor, we treated the cells from $V_{1A}R^{+/+}$ mice with antagonists. Although the V_{1B} receptor-selective antagonist, SSR149415, was ineffective at a concentration of 1 μM (data not shown), the vasopressin V_{1A} receptor-selective antagonist, OPC-21268, significantly inhibited AVP-induced aldosterone release (% of 0 M AVP was 122.5±6.0 in $V_{1A}R^{+/+}$ mice and 99.2±3.6 in $V_{1A}R^{-/-}$ mice, $n=6$ each, $P<0.05$) at a concentration of 1 μM (Fig. 2A). Application of the antagonist alone did not change aldosterone release at any of the concentrations used (data not shown). This result indicates that AVP stimulates aldosterone release via the vasopressin V_{1A} receptor. Aldosterone release from primary cultured adrenal gland cells from mutant mice was examined.

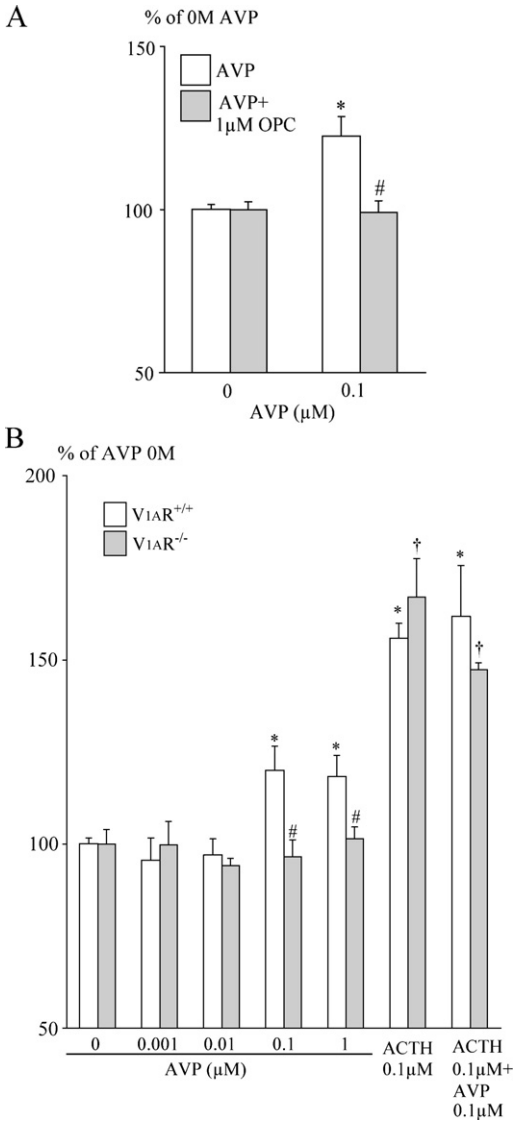

Fig. 2. Effects of AVP or ACTH on aldosterone secretion from adrenal gland cells of $V_{1A}R^{+/+}$ and $V_{1A}R^{-/-}$ mice. (A) The cells from male $V_{1A}R^{+/+}$ mice were incubated with AVP (10^{-7} M) with (open columns) or without (solid columns) OPC-2128 (OPC, 10^{-6} M), which was added 10 min prior to the administration of AVP. (B) The cells from male $V_{1A}R^{+/+}$ (open columns) or $V_{1A}R^{-/-}$ (solid columns) mice were incubated without or with AVP, ACTH (10^{-7} M), or ACTH+AVP (10^{-7} M). The values are represented as the means±S.E.M. of six experiments. *$P<0.001$ vs. AVP 0M in $V_{1A}R^{+/+}$. †$P<0.001$ vs. AVP 0M in $V_{1A}R^{-/-}$. #$P<0.001$ vs. $V_{1A}R^{+/+}$.

The basal aldosterone concentration was not significantly different between $V_{1A}R^{+/+}$ and $V_{1A}R^{-/-}$ mice (162.6± 11.9 pg/ml/105 cells in $V_{1A}R^{+/+}$ mice, $n=90$; and 129.1± 22.2 pg/ml/105 cells in $V_{1A}R^{-/-}$ mice, $n=21$, $P=0.09$). As shown in Fig. 2B, 0.1 μM and 1 μM AVP potently stimulated aldosterone release in the adrenal gland cells from $V_{1A}R^{+/+}$ mice. An approximately 30% increase in the aldosterone level was observed with AVP stimulation at 0.1 μM and 1 μM. In contrast, there was no increase in aldosterone release after AVP stimulation in cells from $V_{1A}R^{-/-}$ mice.

Since AVP-induced aldosterone release was decreased in $V_{1A}R^{-/-}$ mice, we studied ACTH-induced aldosterone release. When the adrenal cells were treated with ACTH, an increase in the aldosterone level was 1.7-fold to the basal level in both mice at 0.1 μM ACTH, and there was no significant difference in the response between the two genotypes (Fig. 2B). Co-treatment with ACTH and AVP did not lead to any further increase in aldosterone production compared to that with stimulation of ACTH in $V_{1A}R^{+/+}$ and $V_{1A}R^{-/-}$ mice (Fig. 2B).

3.3. Plasma aldosterone and ACTH concentration, and aldosterone response to ACTH

As AVP-induced aldosterone release was impaired in adrenal gland cells from $V_{1A}R^{-/-}$ mice in vitro, we measured the plasma aldosterone level in vivo. The basal plasma aldosterone level was significantly lower in $V_{1A}R^{-/-}$ mice than in $V_{1A}R^{+/+}$ mice (7.4±1.1 ng/dl in $V_{1A}R^{+/+}$ mice, $n=4$, vs. 4.7±0.4 ng/dl in $V_{1A}R^{-/-}$ mice, $n=4$, $P<0.05$, Fig. 3). Since ACTH is one of the major stimulators of aldosterone secretion in vivo, we measured the plasma ACTH level and aldosterone secretion in response to ACTH stimulation. The plasma ACTH concentration did not differ between $V_{1A}R^{+/+}$ and $V_{1A}R^{-/-}$ mice (12.9±4.2 ng/dl in $V_{1A}R^{+/+}$, $n=5$, vs. 18.8±2.0 ng/dl in $V_{1A}R^{-/-}$, $n=5$, $P=0.12$). The aldosterone level was increased 30 min after ACTH injection (2 mg/kg, i.p.) in $V_{1A}R^{-/-}$ as well as in $V_{1A}R^{+/+}$ mice (aldosterone levels: 15.4±1.5 ng/dl in $V_{1A}R^{+/+}$, $n=4$, $P<0.01$ vs. without treatment; 14.2±1.6 ng/dl in $V_{1A}R^{-/-}$ mice, $n=4$, $P<0.01$ vs. without treatment, Fig. 3), but the increase in the aldosterone level did not significantly differ between the two groups.

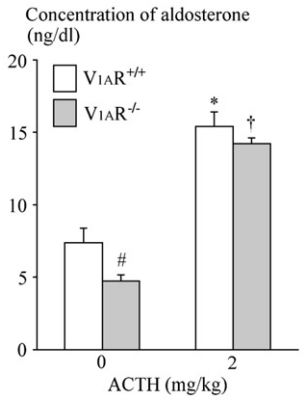

Fig. 3. Plasma aldosterone levels before (open columns) and after (solid columns) ACTH (2 mg/kg, i.p.) stimulation. The values are represented as the means±S.E.M. of four animals. *$P<0.01$ vs. without treatment in $V_{1A}R^{+/+}$. †$P<0.01$ vs. without ACTH treatment in $V_{1A}R^{-/-}$. #$P<0.05$ vs. $V_{1A}R^{+/+}$.

4. Discussion

Our analysis of AVP receptor expression in the adrenal gland indicates that the vasopressin V_{1A} receptor is predominantly expressed in the cortex rather than in the medulla. This finding for the mouse adrenal gland is in good agreement with previous studies of the human and rat adrenal glands (Grazzini et al., 1999, 1996; Guillon et al., 1995; Mazzocchi et al., 1993). In human and rat, AVP is reported to stimulate aldosterone secretion via activation of the vasopressin V_{1A} receptor, which is predominantly expressed in the zona glomerulosa and zona fasciculata of the cortex (Guillon et al., 1995). Similar to human and rat, in the mouse adrenal cortex, the vasopressin V_{1A} receptor is expressed and mediates AVP-induced aldosterone release. Our study using $V_{1A}R^{-/-}$ mice and the selective antagonist demonstrates that the blockade of the AVP/V_{1A}R pathway could lead to suppression of the signaling pathways of aldosterone production and/or secretion in the adrenal cortex, resulting in a decrement in the plasma aldosterone level.

Thus, in the present study, we found that the plasma aldosterone level was decreased in $V_{1A}R^{-/-}$ mice. Aldosterone secretion is known to be regulated by factors such as angiotensin-II, ACTH and AVP (Guillon et al., 1995; Bird et al., 1990; Quinn and William, 1992). In our previous study, we reported that plasma angiotensin II concentrations were not significantly different between $V_{1A}R^{+/+}$ and $V_{1A}R^{-/-}$ mice (Koshimizu et al., 2006), while the plasma AVP level was increased in $V_{1A}R^{-/-}$ mice (Aoyagi et al., in press). Therefore, we investigated the plasma ACTH level and aldosterone response to ACTH in this study. In our study, ACTH stimulated aldosterone secretion more than AVP did, which implies that ACTH is a more potent stimulator of aldosterone secretion from the adrenal cortex than AVP is. While the aldosterone secretion response to ACTH did not differ between $V_{1A}R^{+/+}$ and $V_{1A}R^{-/-}$ mice, the response to AVP was blunted in $V_{1A}R^{-/-}$ mice. In good agreement with the in vitro study, the plasma aldosterone level was lower in $V_{1A}R^{-/-}$ mice than in $V_{1A}R^{+/+}$ mice, suggesting that AVP plays a crucial role in maintaining the plasma aldosterone level. In addition, impaired aldosterone secretion by stimulation with AVP could not be compensated for by other stimulators. These results suggest that the low aldosterone level in $V_{1A}R^{-/-}$ mice could be due to the absence of the vasopressin V_{1A} receptor and not due to the loss of response to ACTH.

Since AVP plays a significant role in regulating aldosterone secretion, inhibition of the vasopressin V_{1A} receptor may be useful for treating patients with Cushing's syndrome caused by adrenal adenoma or ACTH-independent macronodular adrenocortical hyperplasia (AIMAH), in which the hyper-responsiveness of plasma cortisol and aldosterone to AVP has been reported (Bertherat et al., 2005; Lacroix et al., 2001). In addition, Mune et al. (2002) suggested that eutopic vasopressin V_{1A} receptor overexpression is involved in the etiology of AIMAH. Thus, the antagonism of the vasopressin V_{1A} receptor may be effective for treating these disorders. Indeed, orally

active OPC-21268, a nonpeptide-selective vasopressin V_{1A} receptor antagonist, partially suppressed cortisol excretion into urine in patients with AIMAH and suppressed AVP-induced cortisol release from AIMAH adrenal cells in vitro (Daidoh et al., 1998). Similarly, antagonists for the vasopressin V_{1A} receptor could also be effective for suppressing aldosterone secretion.

In conclusion, the vasopressin V_{1A} receptor in mouse adrenal gland cells mediated aldosterone secretion from the cells. Control of vasopressin V_{1A} receptor expression would be an approach to the successful treatment of Cushing's syndrome, which is caused by an aberrant expression and/or function of the vasopressin V_{1A} receptor.

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