

Original Research Paper

Amphetamine Stimulates Protein Kinase and Calcium Influx to Increase Corticosterone and Aldosterone Secretion from Male Rat Adrenal Cells

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Abstract: Amphetamine is a potent central nervous system stimulant. Clinical trials have demonstrated that in healthy adults, low (therapeutic) doses of amphetamine can improve i.e., cognition, memory, attention behavior. An amphetamine overdose can affect cardiovascular, central nervous system, musculoskeletal, respiratory, urinary, or sexual function. Furthermore, amphetamine can activate the hypothalamic-pituitary-adrenal axis to increase glucocorticoids and mineralocorticoids released from adrenal. The object of this research was to find out the effect of amphetamine *in vivo* and *in vitro* on the production of corticosterone and aldosterone by Zona Fasciculata-Reticularis (ZFR) cells and Zona Glomerulosa (ZG) cells from male rats. For the *in vivo* study, the rats were given intraperitoneal injections of saline (1 ml/kg/day, group 1), amphetamine (1 mg/ml/kg/day, group 2), or amphetamine (5 mg/ml/kg/day, group 3) for 7 days and then the ZFR or ZG cells from the sacrificed rats were incubated with other drugs. For the *in vitro* study, the adrenal cells of ZFR or ZG from untreated rats were incubated with amphetamine combined with other drugs. The corticosterone and aldosterone concentrations in samples of the medium were measured using radioimmunoassay. This *in vitro* and *in vivo* study illustrated that amphetamine can increase corticosterone secretion by ZFR cells and aldosterone secretion by ZG cells from male rats.

Keywords: Amphetamine, Corticosterone, Aldosterone

Introduction

Abuse of amphetamine-type Central Nervous System (CNS) stimulants is reaching an epidemic level around the world (United Nations Office on Drugs and Crime, 2010). Bazmi *et al.* (2017) found that Iranian patients with cardiovascular complications were usually amphetamine abusers. Phupong and Darojn (2007) found that the pregnant abusing amphetamine experienced more obstetric symptoms than non-drug abusers. Berman *et al.* (2008) found that amphetamine abuse causes brain structural abnormalities. Benitez-López *et al.* (2019) found that after abstinence for 6 months the amphetamine consumers still failed in stress regulation and inhibitory control. In the medical dose range (e.g., in the treatment of obesity, attention deficit/hyperactivity

disorder, or narcolepsy), amphetamine brings about mood and executive function changes, such as inducing good mood and the evolution of brain executive function. Very high-dose amphetamine causes damage to the dopamine system and nervous system in certain animals (Berman *et al.*, 2008; Carvalho *et al.*, 2012).

The Hypothalamic-Pituitary-Adrenal (HPA) axis is altered by both physiological and psychological processes to pathological condition as drug addiction, for example, involving amphetamines, cannabinoids, cocaine, ethanol, nicotine, or opiates (Charmandari *et al.*, 2005; Koob, 2008; Zuloaga *et al.*, 2015). Armario (2010) proposed that HPA axis can be activated by cocaine, amphetamine and its derivatives to increase levels of brain monoamines. It is well documented that amphetamine indirectly acts on the CNS, which stimulates the release of

dopamine in neural system (Dluzen and Ramirez, 1990a; 1990b; Folgering *et al.*, 2019) to increase prolactin release (Raptis *et al.*, 2004). Chen *et al.* (2003) showed that amphetamine can enhance progesterone production from MA-10 cells. Seibert *et al.* (2014) showed that 3,4-methylenedioxy-methamphetamine conditioned on no other stressors significantly stimulates the HPA axis increasing the levels of plasma concentration of corticosterone, cortisol, 11-deoxycorticosterone, 11-dehydrocorticosterone and aldosterone. Their study explored whether amphetamine could stimulate rat adrenal cells to release corticosterone and aldosterone. The mechanism of amphetamine's effect on ZFR and ZG release of corticosteroids was also examined.

Along with corticosteroid release, the mechanisms by which amphetamine mediates steroid release have been examined. Two important mechanisms are (1) adenylate cyclase activation, increasing cAMP concentration, which activates Protein Kinase A (PKA) (Gold, 2019; Ould Amer and Hebert-Chatelain, 2018); and (2) an elevation of cytosolic free calcium via Ca^{2+} entry from the extracellular space and/or via Ca^{2+} mobilization from a sequestered intracellular Ca^{2+} pool, which activates protein kinase C or Ca^{2+} -calmodulin kinase (Anderson and Kane, 1998; Hughes *et al.*, 1990). Because amphetamine can be ingested orally or by injection or smoking, it might interfere with the CNS or HPA axis to affect physiology. Here we explore the effects of amphetamine on adrenal cells both *in vitro* and *in vivo*. To my understanding, this is the first study to examine the direct effects of amphetamine on adrenal cells.

Materials and Methods

Chemicals

A23187 (calcium ionophore), Adrenocorticotrophic Hormone (ACTH, which increases the production and secretion of cortisol from the cortex of the adrenal gland), amphetamine, angiotensin II (AngII, which stimulates the secretion of aldosterone from the adrenal gland), Bovine Serum Albumin (BSA, a component of KRBGA medium), 8-Br-cyclic AMP (8-Br-cAMP, cAMP analog), Cyclopiazonic Acid (CPA, specific inhibitor of SERCA ATPase in intracellular Ca^{2+} storage sites), deoxycorticosterone (a precursor for the synthesis of cortisol), Forskolin (FSK, an adenylate cyclase agonist) and H89 (a protein kinase A inhibitor) were bought from Sigma Chemical Co. (St. Louis, MO, USA). Except BSA and deoxycorticosterone, the above drugs were dissolved in water as stock solutions. Deoxycorticosterone was dissolved in ethanol as a stock solution. When both stock solutions challenging cells, they were diluted in Krebs-Ringer bicarbonate buffer with 3.6 mM K^+ , 11.1 mM glucose, 0.2% BSA medium (KRBGA). [^3H]-aldosterone and [^3H]-corticosterone were bought from Amersham Life Science (Buckinghamshire, UK).

Animals

The National Yang-Ming University supplied Sprague-Dawley male rats weighing 300-350 g (age: 2 months). Those were housed conditioned on temperature control at $22\pm 1^\circ\text{C}$ and light control with on at 6:00 am and off at 8:00 pm. Food and water were supplied ad libitum. For the *in vivo* study, rats were randomly divided into three groups. Rats received intraperitoneal injections of saline (1 ml/kg/day, group 1), amphetamine (1 mg/ml/kg/day, group 2), or amphetamine (5 mg/ml/kg/day, group 3), respectively, for 7 days. The next morning after the last injection, all rats were sacrificed. To avoid variation caused by the adrenal rhythm, the sacrifice of rats started at 8:00 am and followed a specific pattern. The pattern was to sacrifice a rat from group 1, followed by a rat from group 2, then a rat from group 3 and repeat until done. The whole process was complete before 10:00 am.

The animal protocols adopted in this study were approved by the Institutional Animal Care and Use Committee of the National Yang-Ming University. All animals were treated in humane care complying with the Principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals, published by the National Science Council, Taiwan, ROC.

Preparation of Zona Fasciculata-Reticularis (ZFR) and Zona Glomerulosa (ZG) Cells for Cell Culture

The amphetamine treatment included both an *in vivo* and an *in vitro* model. The *in vivo* model included groups 1, 2 and 3 described above. For the *in vitro* model, adrenal glands were obtained from rats without any treatment. Preparation of ZFR and ZG cells from the glands followed our previous report (Lo *et al.*, 1998; Chang *et al.*, 2008). In brief, adrenal glands (from the *in vivo* and *in vitro* models) were taken with adipose tissues being removed then kept in ice-cold 0.9% (w/v) NaCl solution. The glands were separated into capsule (mainly zona glomerulosa) and inner zone (mainly zona fasciculata-reticularis) fractions. The inner zone or capsule fractions from 10-20 adrenals coming from the same group of rats were put together as a single dispersion. The cells (5×10^4 cells/ml) were pre-incubated with KRBGA medium for 1 h at 37°C in a shaker bath (50 cycles/min) aerated with 95% O_2 and 5% CO_2 . Then, the supernatant was dropped out after centrifugation at $200\times g$ for 10 min. Finally, the cells were suspended and incubated with fresh incubation medium for 1, 4, or 24 h and centrifuged, respectively. The medium was stored at -20°C for corticosterone or aldosterone Radioimmunoassay (RIA).

RIA of Corticosterone and Aldosterone

Concentrations of corticosterone in the media were determined by RIA (Chang *et al.*, 2002; Lo *et al.*, 1998). The RIA with antiserum PSW#4-9 was set up to measure

plasma corticosterone levels. The sensitivity of the corticosterone RIA was 5 pg/tube and the variation of intra- and inter-assay coefficients were 3.3% (n = 5) and 9.2% (n = 4), respectively.

The concentration of aldosterone in the medium was determined by RIA (Kau *et al.*, 2000). A RIA with the antiserum JJC-088 was set up to measure plasma aldosterone levels. The sensitivity of the aldosterone RIA was 4 pg/tube. The variation of intra-(assay) and inter-assay coefficients were 3.9% (n = 5) and 8.2% (n = 4), respectively.

Statistical Analysis

The results are shown as the mean ± S.E.M. A one-way Analysis Of Variance (ANOVA) test (Steel and Torrie, 1960) was used to assess differences among the mean values of all groups. A t-test compares the difference between groups conditioned on significant difference being established. The result of $P < 0.05$ was statistically significant.

Results

In Vitro Study

Effects of Amphetamine with ACTH, Forsolin, 8-Br-cAMP, or Deoxycorticosterone on the Release of Corticosterone by Rat ZFR Cells

Incubation of ZFR cells for 4h with ACTH (10^{-9} M), forskolin (10^{-5} M), 8-Br-cAMP (10^{-5} M), or deoxycorticosterone (10^{-6} M) enhanced corticosterone release (Fig. 1A and 1B; $P < 0.01$). Incubation of these reagents (except ACTH and forskolin) with amphetamine (10^{-7} - 10^{-5} M) caused dose proportionally dependent increment of corticosterone release from ZFR cells (Fig. 1A and 1B; $P < 0.05$ or 0.01). Amphetamine did not increase the

ACTH- or forskolin-induced corticosterone release from ZFR cells. It could be that the ACTH- or forskolin-induced corticosterone arrived at the plateau level after ZFR cells 4h incubation with ACTH or forskolin, which makes the effects of amphetamine disappeared.

Effects of Amphetamine with AngII, KCl, CPA, or A23187 on the Release of Aldosterone by Rat ZG Cells in Vitro

Incubation of ZG cells for 4 h with AngII (10^{-8} M), or KCl (10^{-2} M) enhanced aldosterone release (Fig. 2A, $P < 0.05$ or 0.01). Incubation of KCl and CPA (10^{-5} M) with amphetamine (10^{-6} or 10^{-5} M) for 4 h caused dose proportionally dependent increment of aldosterone released from ZG cells (Fig. 2A, $P < 0.05$). Although amphetamine did not increase vehicle or AngII-induced aldosterone release from ZG cells after 4 h, amphetamine (10^{-5} M) increased vehicle or AngII-induced aldosterone release after 24 h (Fig. 2B, $P < 0.05$ or 0.01).

In Vivo Study

Effects of Intraperitoneally Injected Amphetamine, with ACTH, Forsolin, 8- Br-cAMP, or H89, on the Release of Corticosterone by Rat ZFR Cells in Vivo

Incubation of ZFR cells (from group 1) for 1h with ACTH (10^{-9} M), forskolin (10^{-5} M), or 8- Br-cAMP (10^{-4} M) enhanced corticosterone release (Fig. 3, $P < 0.01$) but suppressed corticosterone release (Fig. 3, $P < 0.01$) when incubated with H89 (10^{-6} M) (Fig. 3, $P < 0.01$). Amphetamine increased basal corticosterone release from ZFR cells (from group 3) (Fig. 3, $P < 0.01$). ZFR cells (from group 2 or 3) incubated with ACTH, forskolin, 8-Br-cAMP, or H89 showed increment of corticosterone release (Fig. 3, $P < 0.05$ or 0.01).

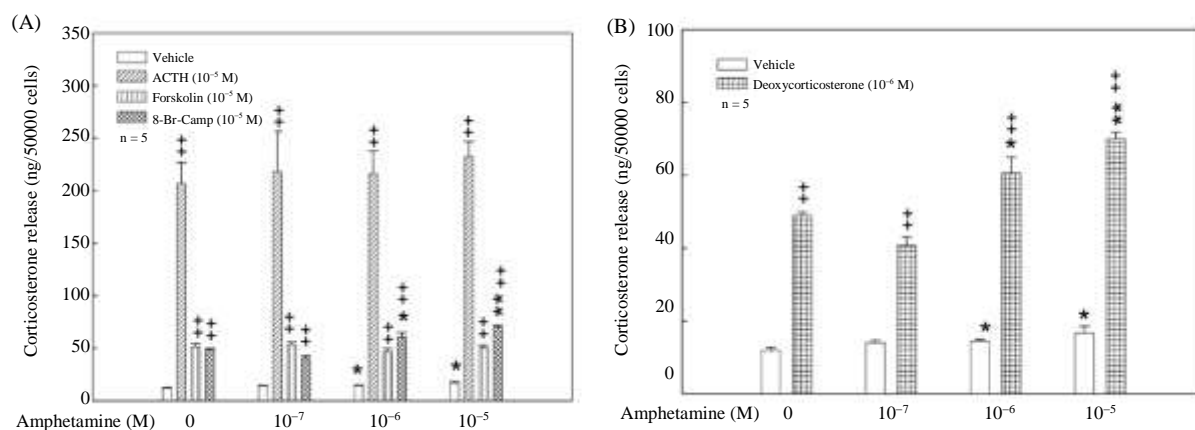


Fig. 1: Effects of amphetamine (0, 10^{-7} - 10^{-5} M) on the release of corticosterone by rat ZFR cells *in vitro* in response to the action of (A) ACTH (10^{-9} M), forskolin (10^{-5} M), 8- Br-cAMP (10^{-5} M) or (B) deoxycorticosterone (10^{-6} M). ++: $P < 0.01$ as compared with vehicle group in the same amphetamine concentration. *, **: $P < 0.05$ or 0.01 as compared with amphetamine equals to zero in each group. Each value represents the mean ± SEM

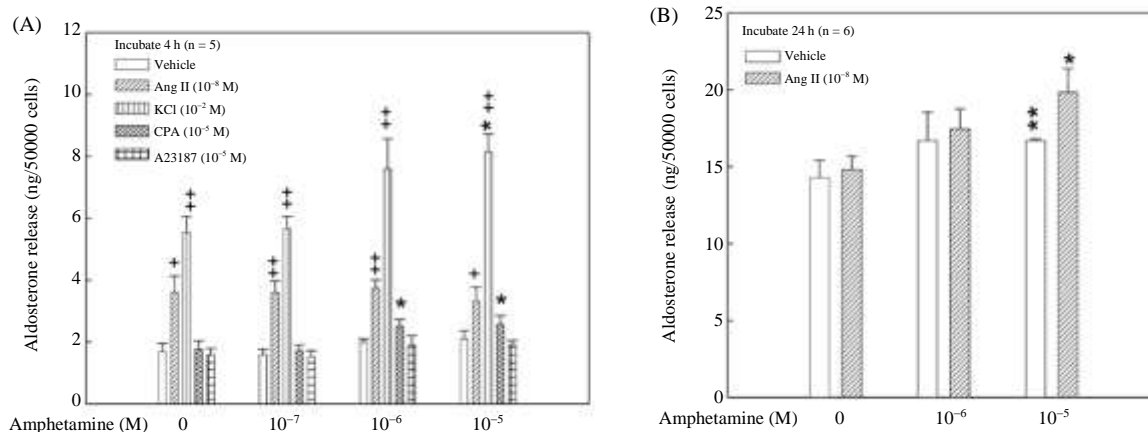


Fig. 2: Effects of amphetamine (0, 10^{-7} - 10^{-5} M) on the release of aldosterone by rat ZG cells *in vitro* in response to the action of AngII (10^{-8} M), KCl (10^{-2} M), CPA (10^{-5} M) or A23187 (10^{-5} M). (A) ZG cells incubated for 4 h (B) ZG cells incubated for 24 h. +, ++: $P < 0.05$ or 0.01 as compared with vehicle group in the same amphetamine concentration. *, **: $P < 0.05$ or 0.01 as compared with amphetamine equals to zero in each group. Each value represents the mean \pm SEM

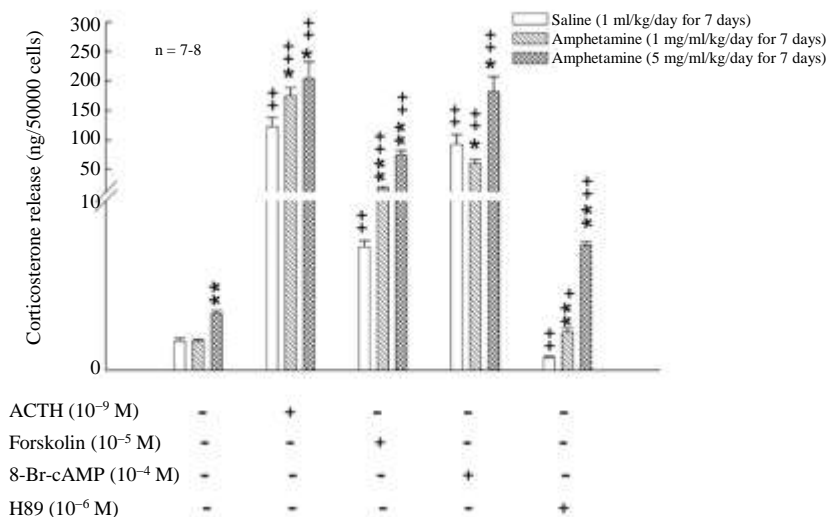


Fig. 3: Effects of amphetamine intraperitoneal injected (with saline (1 ml/kg/day, group 1), amphetamine (1 mg/ml/kg/day, group 2) or amphetamine (5 mg/ml/kg/day, group 3), respectively for 7 days) on the release of corticosterone by rat ZFR cells *in vivo* in response to the action of ACTH (10^{-9} M), forskolin (10^{-5} M), 8- Br-cAMP (10^{-4} M) or H89 (10^{-6} M). +, ++: $P < 0.05$ or 0.01 as compared with basal in the same intraperitoneal injection amphetamine. *, **: $P < 0.05$ or 0.01 as compared with intraperitoneal injecting saline in the same stimulant.

Effects of Intraperitoneally Injected Amphetamine with AngII, KCl, CPA, or A23187 on the Release of Aldosterone by Rat ZG Cells in Vivo

ZG cells (from group 1) incubated for 1 h with AngII (10^{-8} M), KCl (10^{-2} M), CPA (10^{-5} M), or A23187 (10^{-5} M) enhanced aldosterone release (Fig. 4, $P < 0.01$). Amphetamine increased ZG cells (group 3) aldosterone release in response to KCl or CPA (Fig. 4, $P < 0.05$ or 0.01). Amphetamine increased ZG cells (group 2 or 3) aldosterone release, whether basal or induced by AngII or A23187 (Fig. 4, $P < 0.05$ or 0.01).

Discussion

It is well documented that amphetamine can stimulate dopamine release in the nervous system (Dluzen and Ramirez, 1990a; 1990b; Folgering *et al.*, 2019) to increase prolactin release (Raptis *et al.*, 2004). Vislobokov *et al.* (1993) found that amphetamine at concentration 10^{-9} - 10^{-7} M can activate inward calcium current in neurons of the snail *Lymnaea*, but at higher concentration it inhibits. DiLullo and Martin-Iverson (1992) have shown that, in rats, the unconditioned response and conditioned locomotor response to

amphetamine are blocked by nimodipine (L-type calcium-channel antagonist) combined with haloperidol. Cameron *et al.* (2015) showed that amphetamine induces dopamine transporter depolarization to activate L-type Ca^{2+} channel currents. Thus, amphetamine might affect prolactin and calcium ion release.

The object of this research was to explore the effects of amphetamine on adrenal cells *in vitro* and *in vivo*. In the *in vitro* study, broth ZFR and ZG cells were incubated with amphetamine for 4 or 24 h. In the *in vivo* study, ZFR and ZG cells from rats that received intraperitoneal injections of amphetamine for 7 days were incubated for 1 h. The amphetamine affected basal or AngII-induced aldosterone release from ZG cells at 24 h but not at 4 h *in vitro*.

Adrenal ZG cells producing aldosterone is controlled by AngII, KCl and ACTH. All inputs are mediated through increasing cAMP production and calcium mobilization. (Ehrhart-Bornstein *et al.*, 1998; Spat and Hunyady, 2004). In ZG cells, AngII binding to the AngII receptor type 1 activates phosphoinositide-specific phospholipase C to generate inositol 1,4,5-triphosphate and diacylglycerol G (DAG) (Ganguly and Davis, 1994; Rasmussen *et al.*, 1995). Calcium from an intracellular storage site was released to enhance cytosolic calcium levels and activate calcium/calmodulin-dependent protein kinase C to regulate sustained aldosterone production by Inositol 1,4,5-triphosphate (Ganguly and Davis, 1994; Rasmussen *et al.*, 1995). Elevation of

extracellular potassium concentration by KCl activates voltage-dependent calcium channels and enhances Ca^{2+} influx (Ganguly and Davis, 1994), which increases steroidogenesis. Together, the effects of AngII and KCl are likely reconciled through intracellular Ca^{2+} . Studies have demonstrated that increasing in cytosolic Ca^{2+} comes out increment in aldosterone production (Payet *et al.*, 2006; Python *et al.*, 1995). Demarex *et al.* (1992) showed that CPA induces Ca^{2+} secretion from Ins (1,4,5) P3-sensitive Ca^{2+} stores and promotes Ca^{2+} influx across the plasma membrane. The ionophore A23187 increases intracellular Ca^{2+} levels. It also inhibits mitochondrial ATPase activity and in some cells it induces apoptosis. In this *in vitro* and *in vivo* study, AngII and KCl stimulated aldosterone production by ZG cells (Fig. 2 and 4, $P < 0.05$ or 0.01). CPA or A23187 stimulated aldosterone secretion from ZG cells incubated for 1 h *in vivo*, but could not stimulate aldosterone release for 4 h *in vitro*. The reason might be cell toxicity from long-term incubation of ZG cells with CPA or A23187. Amphetamine increased basal and AngII-, KCl- and CPA-induced aldosterone secretion from ZG cells (Fig. 2 and 4, $P < 0.05$ or 0.01) in the *in vitro* and *in vivo* experiments, but it increased only A23187-induced aldosterone secretion from ZG cells in the *in vivo* study. Taken together, the results suggest that amphetamine might be stimulating calcium influx to increase aldosterone production.

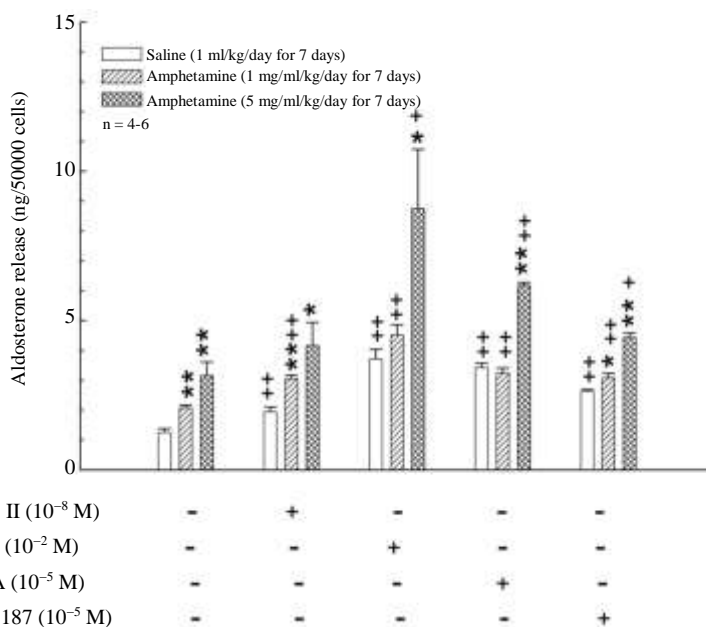


Fig. 4: Effects of amphetamine intraperitoneal injected (with saline (1 ml/kg/day, group 1), amphetamine (1 mg/ml/kg/day, group 2) or amphetamine (5 mg/ml/kg/day, group 3), respectively for 7 days) on the release of aldosterone by rat ZG cells *in vivo* in response to the action of AngII (10^{-8} M), KCl (10^{-2} M), CPA (10^{-5} M) or A23187 (10^{-5} M). +, ++: $P < 0.05$ or 0.01 as compared with basal in the same intraperitoneal injection amphetamine. *, **: $P < 0.05$ or 0.01 as compared with intraperitoneal injecting saline in the same stimulant

ACTH is secreted from the anterior pituitary. It regulates acute glucocorticoid secretion and supports functions specific to cells of the adrenal cortex (Penhoat *et al.*, 1994). ACTH mediates cAMP second-messenger systems to activate cAMP-dependent Protein Kinase A (PKA) (Wong *et al.*, 1992). Forskolin increases cAMP levels by activating adenylate cyclase to stimulate corticosterone release from ZFR cells (Uneyama *et al.*, 1993). 8-Br-cAMP is an activator of cAMP-dependent protein kinase. *In vitro* and *in vivo*, ACTH, forskolin and 8-Br-cAMP stimulated corticosterone production from ZFR cells (Fig. 1A and 3, $P < 0.01$). H89, a PKA inhibitor, inhibited corticosterone production by ZFR cells (Fig. 3, $P < 0.01$). Amphetamine increased basal and 8-Br-cAMP-induced corticosterone secretion from ZFR cells (Fig. 1A, 3, $P < 0.05$ or 0.01) *in vitro* and *in vivo*, but it only increased ACTH-, or forskolin-inducing corticosterone secretion from ZFR cells (Fig. 3, $P < 0.05$ or 0.01) exposed to amphetamine *in vivo*. The reason might be that ACTH- or forskolin-induced corticosterone secretion reached a plateau, which blunted the effect of amphetamine. High-dose amphetamine (group 3) blunted the inhibitory effects of H89 (Fig. 3, $P < 0.01$). Taken together, the results suggest amphetamine's stimulatory effects might be mediated through stimulation of the PKA pathway in ZFR cells.

We conclude that (1) amphetamine can stimulate rat adrenals to release corticosterone and aldosterone and (2) amphetamine might be stimulating the PKA pathway to enhance calcium influx, thereby increasing ZFR and ZG cell release of corticosterone and aldosterone.

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Author Contribution

Ling-Ling Chang: Planned and executed all experiments, data-analysis, organization and writing of the manuscript.

Wan-Song Alfred Wun and Paulus S. Wang: Designed the research plan, organized and revised writing of the manuscript.

Cai-Yun Jian: Worked in part of experiments.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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