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Corticosterone in the ventral hippocampus differentially alters accumbal dopamine output in drug-naïve and amphetamine-withdrawn rats

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Abstract

Dysregulation in glucocorticoid stress and accumbal dopamine reward systems can alter reward salience to increase motivational drive in control conditions while contributing to relapse during drug withdrawal. Amphetamine withdrawal is associated with dysphoria and stress hypersensitivity that may be mediated, in part, by enhanced stress-induced corticosterone observed in the ventral hippocampus. Electrical stimulation of the ventral hippocampus enhances accumbal shell dopamine release, establishing a functional connection between these two regions. However, the effects of ventral hippocampal corticosterone on this system are unknown. To address this, a stress-relevant concentration of corticosterone (0.24ng/0.5μL) or vehicle were infused into the ventral hippocampus of urethane-anesthetized adult male rats in control and amphetamine withdrawn conditions. Accumbal dopamine output was assessed with *in vivo* chronoamperometry. Corticosterone infused into the ventral hippocampus rapidly enhanced accumbal dopamine output in control conditions, but produced a biphasic reduction of accumbal dopamine output in amphetamine withdrawal. Selectively blocking glucocorticoid-, mineralocorticoid-, or cytosolic receptors prevented the effects of corticosterone. Overall, these results suggest that the ability of corticosterone to alter accumbal dopamine output requires cooperative activation of mineralocorticoid and glucocorticoid receptors in the cytosol, which is dysregulated during amphetamine withdrawal. These findings implicate ventral hippocampal corticosterone in playing an important role in driving neural systems involved in positive stress coping mechanisms in

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BB and GF designed and conducted the experiments and analysed the data. KC, DB and MW conducted experiments and assisted with data analysis. All authors contributed to the writing of the manuscript.

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healthy conditions, whereas dysregulation of this system may contribute to relapse during withdrawal.

Keywords

Psychostimulant Withdrawal; Ventral Hippocampus; Corticosterone; Nucleus Accumbens Shell; Dopamine; Glucocorticoid Receptors

1. Introduction

Amphetamine dependence is a global health problem with high relapse potential and few effective interventions (Gossop, 2009; Sun et al., 2014). Amphetamine withdrawal is characterized by enhanced physiological and behavioral responses to stress (Bray et al., 2016; Li et al., 2014) as well as craving, anxiety, and dysphoria in humans (Gossop, 2009; Kosten, 2012; Shoptaw et al., 2009) and rodents (Bray et al., 2016; Cryan et al., 2003; Li et al., 2014; Russig et al., 2006; Tu et al., 2014). These negative affective states can induce relapse and maintain addiction (Gossop, 2009; Koob et al., 2014; Paliwal et al., 2008) and are mediated by alterations in dopamine reward- and corticosterone stress responses (Barr et al., 2017; Bray et al., 2016; Koob et al., 2014; Koob and Volkow, 2010).

At a neurobiological level, stress increases dopamine output in the nucleus accumbens shell (Enrico et al., 2013; Kalivas and Duffy, 1995), which can enhance incentive salience (“wanting”) and cue-triggered levels of motivation to pursue sucrose rewards (in rats) (Berridge and Robinson, 2016; Floresco, 2014; Hollon et al., 2015; Pecina and Berridge, 2013). However, stress can also *reduce* accumbal shell dopamine levels in psychostimulant withdrawal, and can prompt negative affect and dysphoria that drive drug-taking behaviors and predict relapse (Cleck and Blendy, 2008; Koob et al., 2014; Kwako and Koob, 2017; Paliwal et al., 2008; Sinha, 2007; Twining et al., 2014; Wheeler et al., 2008). Therefore, a greater understanding of the mechanisms that enable stress to alter accumbal dopamine output may help identify novel treatment targets for amphetamine withdrawal syndrome.

In addition to its effects on accumbal dopamine output, stress also increases free extracellular corticosterone levels in the dorsal- and ventral hippocampus in rodents (Bray et al., 2016; Droste et al., 2008; Droste et al., 2009), which are augmented in the ventral hippocampus during amphetamine withdrawal (Bray et al., 2016). Corticosterone is thought to be excitatory in the ventral hippocampus and can induce glutamate release *in vitro* (Karst et al., 2005; Wang and Wang, 2009). *In vivo*, the ventral hippocampus sends glutamatergic projections to the ventral tegmental area and nucleus accumbens shell (Barr et al., 2017; Sesack and Pickel, 1990; Strange et al., 2014), and electrical stimulation of the ventral hippocampus or *N*-Methyl-D-aspartic acid (NMDA) infusions into this region enhance accumbal shell dopamine output (Barr et al., 2014; Blaha et al., 1997; Britt et al., 2012; Floresco et al., 2001; Legault et al., 2000; Taepavarapruk et al., 2014; Valenti et al., 2011). Thus, we hypothesized that the local effects of corticosterone in the ventral hippocampus would enhance accumbal shell dopamine output in drug naïve conditions, enabling stress to enhance reward salience and motivate goal-oriented behavior. Here, we directly tested

whether corticosterone in the ventral hippocampus regulates dopamine levels in the nucleus accumbens shell.

At the cellular level, corticosterone induces its effects primarily by activating mineralocorticoid and glucocorticoid receptors, both of which are highly expressed in the ventral hippocampus (Herman et al., 1989; Reul and de Kloet, 1986). These receptors can be cytosolic or membrane-bound, genomic or non-genomic, and differ in their affinity for corticosterone, downstream signaling mechanisms, and temporal signatures in a regionally-dependent manner (Barr et al., 2017; Groeneweg et al., 2012; Joels and de Kloet, 2017). In the ventral hippocampus, non-genomic membrane mineralocorticoid receptors can be excitatory or disinhibitory, rapidly enhancing excitatory postsynaptic potential and glutamatergic transmission (Karst et al., 2005; Maggio and Segal, 2007) and reducing inhibitory postsynaptic currents (Maggio and Segal, 2009) *in vitro*. Non-genomic glucocorticoid receptors can be membrane-bound or cytosolic and are thought to act through retrograde signaling mechanisms to regulate interneuron inhibition and excitatory/inhibitory tone *in vitro* and *ex vivo* (Hu et al., 2010; Maggio and Segal, 2009; Zeise et al., 1992), and induce rapid serotonin release *in vivo* (Barr and Forster, 2011). In sum, corticosterone has rapid effects on local neurotransmission in the ventral hippocampus that have potential to influence activity of limbic structures targeted by this region of the hippocampus. Therefore, we also explored the receptor mechanisms that mediate the ability of corticosterone in the ventral hippocampus to alter accumbal dopamine output.

Glucocorticoid (but not mineralocorticoid) receptor expression and activity in the ventral hippocampus are reduced following 2 weeks of amphetamine treatment in male rats (Barr and Forster, 2011; Li et al., 2014). Furthermore, repeated cocaine exposure enhances the ability of NMDA infusions in the ventral hippocampus to stimulate accumbal dopamine release (Barr et al., 2014). These alterations may disrupt the ability of glucocorticoid receptors to regulate excitatory/inhibitory tone in the ventral hippocampus during withdrawal (Barr et al., 2017; Maggio and Segal, 2009), which in turn, would disrupt the ability of corticosterone in the ventral hippocampus to modulate accumbal dopamine release. Therefore, we also tested whether repeated amphetamine exposure disrupts the effects of glucocorticoid and mineralocorticoid receptor activation on accumbal dopamine output in rats undergoing 2 weeks of amphetamine withdrawal.

2. Materials and Methods

2.1. Animals

All experimental procedures were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (National Research Council Committee for the Update of the Guide for the and Use of Laboratory, 2011) and were approved by the Institutional Animal Care and Use Committee of the University of South Dakota. All efforts were made to minimize animal suffering and reduce the number of subjects used.

A total of 124 adult male Sprague-Dawley rats were used in this experiment ($367 \text{ g} \pm 35 \text{ g}$). Rats were obtained from the University of South Dakota Animal Resource Center at 3 weeks

of age and pair-housed in polysulfone cages (Tecniplast, Buguggiate, Varese, Italy; $16.73 \times 10.47 \times 7.28$ in, floor area: $800 \text{ cm}^2/124 \text{ in}^2$; corn husk bedding) held at a constant room temperature of 22°C (60% relative humidity) on a reverse 12-h light/dark cycle with lights off from 10:00 – 22:00. To eliminate a possible confound of enrichment-induced hippocampal neurogenesis and enrichment-induced alterations of stress responsiveness (Levone et al., 2015; Tanti et al., 2012), cages contained no enrichment but *ad lib* access to water and standard rat chow.

2.2. Rat model of amphetamine pretreatment and withdrawal

At 8 – 10 weeks of age, rats were randomly assigned to receive daily injections of physiological saline ($n = 74$) or d-amphetamine sulfate ($n = 50$) (2.5 mg/kg , ip.) for 14 days (Barr and Forster, 2011; Bray et al., 2016; Li et al., 2014) followed by a 14-day withdrawal period (Bray et al., 2016; Li et al., 2014; Solanki et al., 2016; Tu et al., 2014). To account for diurnal corticosterone levels (Tye et al., 2009; van Haarst et al., 1997), all injections were administered during the dark phase of the reverse photoperiod, between 11:00 and 14:00. This amphetamine protocol has been shown to enhance stress responses, including anxiety (Reinbold et al., 2014; Tu et al., 2014; Vuong et al., 2010), stress-induced behavioral arousal (Li et al., 2014), and corticosterone stress responses (Bray et al., 2016; Li et al., 2014), as well as reducing glucocorticoid receptor expression in the ventral hippocampus (Barr and Forster, 2013).

2.3. Stereotactic surgery

After the second week of withdrawal from amphetamine or saline pre-treatment, rats were anesthetized with urethane (1.8 g/kg , ip.). Urethane is a long-acting anesthetic that does not affect endogenous dopamine clearance (Barr and Forster, 2011; Blaha et al., 1997; Novick et al., 2015; Sabeti et al., 2003). Rats were placed into a stereotaxic frame (Kopf, Tujunga, CA, USA) with incisor bar set at -3.5 mm and body temperature held at $37^\circ \text{C} \pm 0.5^\circ \text{C}$ by a temperature-controlled heating pad (Harvard Apparatus, Holliston, MA, USA). Two 22-gauge stainless-steel guide cannulae were implanted side-by-side into the right or left ventral hippocampus (-5.2 mm AP from bregma; $\pm 4.5 \text{ mm}$ ML; -4.5 mm DV from dura) (Paxinos and Watson, 1998; Tu et al., 2014) and a silica infusion cannula ($2 \text{ mm} > \text{guide}$) was inserted through each guide cannula.

2.4. In vivo electrochemistry

A custom-made stearate-treated carbon paste recording electrode with $200 \mu\text{m}$ recording surface diameter (Blaha and Jung, 1991; Miller et al., 2005; Novick et al., 2015; Tye et al., 2009) was implanted into the ipsilateral medial nucleus accumbens shell (1.6 mm AP from bregma; $\pm 0.7 \text{ mm}$ ML; -7.0 mm DV from dura) (Miller et al., 2005; Paxinos and Watson, 1998) to measure dopamine oxidation current without interference from other oxidizing species (Blaha, 1996; Blaha and Lane, 1983; Miller et al., 2005; Novick et al., 2015; Tye et al., 2009). A custom-made reference electrode with AgCl-coated tip was placed touching the contralateral cortical tissue and a stainless-steel auxiliary electrode was fixed to the skull with a stainless steel surgical screw (Miller et al., 2005; Novick et al., 2015). Prior *in vitro* electrode recordings were conducted to confirm a distinct and measurable dopamine

oxidation signal after systemic addition of exogenous dopamine, norepinephrine, and ascorbic acid (Novick et al., 2015; Weber et al., 2018).

Following a thirty-minute recovery period, voltammetry sweeps were conducted using an electrometer (Echempro, GMA Technologies, Inc., Vancouver, Canada) to confirm dopamine detection and identify the range of potentials to be applied to the electrode during chronoamperometry (Miller et al., 2005; Novick et al., 2015). This was done by applying an incrementally increasing range of electrical potentials to the working electrode (–150 mV to +450 mV vs. Ag/AgCl, ramp rate 10 mV/second; (Novick et al., 2015)). A 300 mV voltammetric range encompassing the distinct dopamine signal was then selected and the electrometer was set to repetitively apply that range of potential (typically –150 mV to +150 mV vs. Ag/AgCl reference electrode) to the working electrode in brief (1 s) pulses at 30 s intervals, with changes in dopamine oxidation current recorded in ampere at the end of each pulse and converted to nA for analysis (Borland and Michael, 2007; Novick et al., 2015).

After 30 min of stable chronoamperometric baseline recordings, agents were infused into the ventral hippocampus as described below (Section 2.5). Dopamine oxidation current recordings were subsequently collected until they returned to basal levels (~2 hours post-infusion). Rats were then euthanized with a lethal dose of FatalPlus (Vortech, Dearborn, MI, USA; 0.5 mL, ip.) and brains were removed and fixed for confirmation of cannulae and electrode placements.

2.5. Microinfusions

All infusions were administered through a silica infusion cannula using a microinfusion pump (Stoelting, Wood Dale, IL, USA), with 0.5 μ L total volume infused over one minute. Infusions were administered during the dark phase of the reverse photoperiod, between 13:00 and 18:00 (average infusion time was 15:30 \pm 1:18). Corticosterone (Sigma-Aldrich) was dissolved in 2-hydroxypropyl- β -cyclodextrin [HBC] (Tocris) (0.05%) then diluted with artificial cerebrospinal fluid (aCSF) to produce a 0.48ng/ μ L concentration (0.24 ng total delivered, equal to 6.927×10^{-13} M of corticosterone). This concentration mimics stress-induced corticosterone levels previously observed in the hippocampus (Bray et al., 2016; Droste et al., 2008). When more than one infusion was made into the ventral hippocampus (e.g. receptor antagonist or vehicle pretreatment prior to corticosterone infusion; Table 1), 10 minutes was allowed between infusions.

The effects of corticosterone infusion on accumbal dopamine levels, and which receptor types were responsible for these effects, were assessed in both saline and amphetamine pretreated rats with the drug infusion combinations outlined for groups 1–12 of Table 1. Mifepristone and spironolactone (Sigma-Aldrich) were dissolved in vehicle [1:1 solution of 100% ethanol (Fisher Scientific) and 5% Kolliphor EL (Sigma-Aldrich)], and then diluted in aCSF to a concentration of 2.91 nM mifepristone or 2.99 nM spironolactone (1.25 μ g total delivery). Vehicle infusions were thus 5% ethanol in aCSF. Concentrations of mifepristone and spironolactone were based on those used previously to inhibit glucocorticoid and mineralocorticoid receptors, respectively (Barr and Forster, 2011; Garthwaite and McMahon, 2004). Mifepristone is also a progesterone receptor antagonist with a higher affinity for progesterone vs. glucocorticoid receptors (Heikinheimo, 1997; Heikinheimo and

Kekkonen, 1993; Mahajan and London, 1997). Thus, progesterone receptor inhibition also occurred with these infusions, and we cannot exclude the possibility that the effect of mifepristone on accumbal dopamine output was observed in response to its antagonism of progesterone receptors, as has been suggested by others (Perez et al., 2014).

To determine whether the observed effects of ventral hippocampal corticosterone infusions on accumbal dopamine output in saline-pretreated rats were mediated by cytosolic receptors, corticosterone 3-carboxymethyloxime : bovine serum albumin, (Corticosterone 3-CMO : BSA, Steraloids, Inc.) was used (Table 1 groups 13–14), in which corticosterone was commercially conjugated to bovine serum albumin (BSA). BSA is hydrophobic and thus prevents corticosterone from crossing the plasma membrane to act on cytosolic receptors (Groeneweg et al., 2011; Morozov et al., 1988). The corticosterone 3-CMO : BSA conjugate was dissolved in 0.05% HBC then diluted with aCSF to produce a 5.95 ng/ μ L concentration (2.97 ng total delivered, for a total of 0.24 ng of corticosterone delivered per 0.5 μ L infusion to match corticosterone concentrations described above).

2.6. Histology

Following euthanasia, rat brains were removed and fixed in 10% buffered formalin (Fisher Scientific) for ≥ 72 hours, sectioned on a sliding microtome (60 μ m at -12° C maintained with dry ice), and analyzed under a light microscope by two individuals blind to treatment, to confirm cannulae and electrode placement and identify anatomical controls (Barr and Forster, 2011; Novick et al., 2015).

2.7. Data analysis and statistics

All statistical analyses were performed using IBM® SPSS® Statistics v25- (SPSS Inc., Armonk, NY) and SigmaPlot 13.0 (Systat Software, Inc., San Jose, CA) software with alpha level set at 0.05 throughout.

To analyze chronoamperometry results, pre- and post-infusion recordings for each individual subject were separately normalized to zero current values, with changes after microinfusions reported as absolute changes in dopamine oxidation current, as previously published (Novick et al., 2015; Weber et al., 2018). Data points were collected every 30 s, but were collapsed into 90 s time bins to facilitate repeated measure of time analysis. Grubbs outlier tests (Grubbs, 1969) were run at the two independent (non-adjacent) points farthest from zero in each treatment group. All data from rats whose dopamine oxidation current values were identified to be Grubbs outliers at both of the two non-adjacent points were excluded as outliers, for a total of six rats. These six rats were evenly spread across the treatment groups and included saline pre-treated rats receiving infusions of: vehicle + corticosterone ($n = 1$), spironolactone + corticosterone ($n = 1$), and BSA-HBC ($n = 1$); and amphetamine pre-treated rats receiving infusions of: corticosterone ($n = 1$), mifepristone + HBC ($n = 1$), and spironolactone + corticosterone ($n = 1$).

An initial three-way analysis of variance (ANOVA) with one repeated measure (pre-treatment \times drug infusions into the ventral hippocampus \times repeated measure of time) was used to compare dopamine responses across time between pre-treatment and drug infusions into the ventral hippocampus (groups 1–12 of Table 1). Missing values at a single time point

in two saline- and two amphetamine pre-treated rats precluded the inclusion of these subjects' datum from use in this ANOVA. Significant interactions were further analyzed by two-way ANOVAs (one repeated measure of time) or one-way ANOVA performed separately in saline- and amphetamine pre-treatment groups or across drug infusion groups. Main effects of time were followed by separate *post hoc* Holm-Sidak tests to identify significant changes across time within each pre-treatment group (–2 to –0.5 min time bin set as the baseline control), or between drug infusion groups.

A separate two-way ANOVA with one repeated measure (drug infusion × repeated measure of time) was used to determine whether changes in dopamine output differed over time as a function of Corticosterone 3-CMO : BSA infusion (compared to BSA-HBC infusion) in saline pre-treated rats (groups 13–14 of Table 1).

One-way ANOVA with a repeated measure of time were also separately performed in saline pre-treated rats receiving drug infusions into the dorsoventral hippocampus and amygdala (posterior medial cortical regions) as anatomical controls (groups 15–16 of Table 1), to identify whether infusions of corticosterone outside of the ventral portion of the ventral hippocampus had effects on accumbal dopamine output in saline pre-treated controls.

3. Results

3.1. Electrode and infusion cannula placements

Electrode and infusion cannula placements were similarly distributed in saline- and amphetamine pre-treated rats across all experiments and all infusion conditions (Figs. 1, 3B – C, and 4B – C). Data from rats in which the electrode placements missed the nucleus accumbens shell were excluded from subsequent analyses. However, drug cannulae that missed the ventral hippocampus target region were analyzed separately as anatomical control groups. These drug infusion cannulae were found to be placed in the dorsal aspect of the ventral hippocampus or below the ventral hippocampus in the amygdala (posterior medial cortical regions, Fig. 4C).

3.2. The effects of corticosterone on accumbal dopamine output differ in drug-naïve- and amphetamine withdrawn rats

An initial three-way ANOVA with one repeated measure (pre-treatment × drug infusion × repeated measure of time) revealed a significant interaction between pre-treatment, time, and infusion(s) ($F(18,257) = 3.187$, $P < 0.0001$; Fig. 2). This was followed up with Holm-Sidak post hoc two- and one way ANOVA and repeated measures ANOVAs, as reported below.

3.2.1. Stress-relevant concentrations of corticosterone infused into the ventral hippocampus of saline pre-treated rats enhance accumbal dopamine output—In saline pre-treated rats, infusing vehicle + corticosterone into the ventral hippocampus significantly increased accumbal dopamine output relative to pre-infusion levels and to vehicle + HBC infusions, peaking at 57.5 min post-infusion (Fig. 2A). A two-way ANOVA (drug infusion × repeated measure of time) revealed a significant interaction between drug infusion and time ($F(2,37) = 3.137$, $P = 0.049$), with vehicle + corticosterone infusions resulting in greater accumbal dopamine output at 28 – 75.5 min post-infusion as

compared to vehicle + HBC control levels (Holm-Sidak $P < 0.05$). A one-way repeated measures ANOVA performed in vehicle + corticosterone infused rats revealed a significant effect of time ($F(2,21) = 4.534$, $P = 0.021$), with vehicle + corticosterone infusions resulting in a significantly greater accumbal dopamine output at 36 – 67.5 min post-infusion relative to baseline levels (–2 to –0.5 min time bin) (Holm-Sidak, $p < 0.05$). In contrast, vehicle + HBC infusions into the ventral hippocampus did not significantly alter accumbal dopamine output over time in saline pre-treated rats ($F(4,21) = 1.025$, $P = 0.410$).

3.2.2. Stress-relevant concentrations of corticosterone infused into the ventral hippocampus reduce accumbal dopamine output in amphetamine withdrawal—

In rats undergoing two weeks of withdrawal from amphetamine pre-treatment, vehicle + corticosterone infusions into the ventral hippocampus significantly reduced accumbal dopamine output relative to pre-infusion levels and to vehicle + HBC infusions, peaking at 34.5 and 67.5 min post-infusion (Fig. 2A), with a significant interaction between drug infusion and time ($F(4,68) = 3.770$, $P = 0.007$). Here, vehicle + corticosterone infusions resulted in a reduction of accumbal dopamine output compared to vehicle + HBC infusions at 16 – 39.5 and 48 – 99.5 min post-infusion (Holm-Sidak, $P < 0.05$). Further, in vehicle + corticosterone infused rats, a one-way repeated measures ANOVA revealed a significant effect of time ($F(3,29) = 5.454$, $P = 0.004$), with reduced accumbal dopamine output at 56 – 85.5 min time points as compared to baseline levels (Holm-Sidak, $P < 0.05$). Infusing vehicle + HBC into the ventral hippocampus was not found to alter accumbal dopamine output over time ($F(3,19) = 0.846$, $P = 0.474$).

3.2.3. Stress-relevant concentrations of corticosterone infused into the ventral hippocampus differentially alter accumbal dopamine output in saline- and amphetamine pre-treated rats—

To assess whether corticosterone in the ventral hippocampus alters accumbal dopamine output differently in amphetamine withdrawal (relative to saline pre-treated controls), a two-way ANOVA (pre-treatment \times repeated measure of time) was performed in saline- and amphetamine pre-treated rats receiving infusions of vehicle + corticosterone into the ventral hippocampus (Fig. 2A). This revealed a significant interaction between pre-treatment and time ($F(3,49) = 6.877$, $P = 0.001$), with accumbal dopamine output differing significantly between the two pre-treatment groups at 18 – 87.5- and 94 – 101.5 min post-infusion (Holm-Sidak, $P < 0.05$). When comparing the effects of vehicle + HBC infusions in saline- vs amphetamine pre-treated rats over time, there were no main effects of time ($F(4,54) = 0.954$, $P = 0.443$) or pre-treatment ($F(1,13) = 0.114$, $P = 0.741$) and no significant interactions between pre-treatment and time ($F(4,54) = 0.904$, $P = 0.471$).

3.2.4. Blocking either glucocorticoid- or mineralocorticoid receptors in the ventral hippocampus prevents ventral hippocampal corticosterone from altering accumbal dopamine output—

Both glucocorticoid- and mineralocorticoid receptor antagonism independently blocked the effects of corticosterone in the ventral hippocampus on accumbal dopamine output in saline pre-treated rats (Fig. 2B). A two-way ANOVA with one repeated measure of time, comparing the effects of mifepristone + corticosterone infusions to those observed following mifepristone + HBC infusions in saline

pre-treated rats, revealed no main effects of drug infusion ($F(1,10) = 3.853$, $P = 0.078$) or time ($F(3,34) = 1.257$, $P = 0.306$) and no significant interactions between drug infusion and time ($F(3,34) = 1.379$, $P = 0.265$; Fig. 2B). Similarly, when comparing the accumbal dopamine responses to ventral hippocampus infusions of spironolactone + corticosterone vs spironolactone + HBC infusions (over time), there were no main effects of drug infusion ($F(1,11) = 1.400$, $P = 0.262$) or time ($F(5,51) = 0.864$, $P = 0.504$) and no significant interactions between drug infusion and time ($F(5,51) = 1.298$, $P = 0.281$; Fig. 2B).

Likewise, in rats undergoing two weeks of withdrawal from amphetamine pre-treatment, accumbal dopamine responses to corticosterone in the ventral hippocampus were blocked by either glucocorticoid or mineralocorticoid receptor antagonism (Fig. 2C). A two-way repeated measures ANOVA revealed no main effects of drug infusion ($F(1,10) = 0.850$, $P = 0.378$) or time ($F(4,35) = 0.881$, $P = 0.474$), and there was no significant interaction between drug infusion and time ($F(4,35) = 0.863$, $P = 0.484$; Fig. 2C). When comparing the accumbal dopamine responses to ventral hippocampus infusions of spironolactone + corticosterone vs spironolactone + HBC infusions (over time) there were also no main effects of drug infusion ($F(1,10) = 3.229$, $P = 0.103$) or time ($F(4,42) = 1.748$, $P = 0.154$) and no significant interaction between drug infusion and time ($F(4,42) = 0.410$, $P = 0.811$; Fig. 2C).

3.3. Stress-relevant concentrations of membrane-impermeable corticosterone infused into the ventral hippocampus of saline pre-treated rats fail to alter accumbal dopamine output relative to vehicle infusions

Within saline pre-treated rats receiving infusions of membrane impermeable corticosterone 3-CMO : BSA or its vehicle (BSA-HBC) into the ventral hippocampus, drug infusion was not found to have a significant effect on accumbal dopamine output ($F(1,12) = 0.00555$, $P = 0.942$), and there was no main effect of time ($F(68,816) = 1.098$, $P = 0.280$) nor a significant interaction between time and infusion ($F(68,816) = 0.951$, $P = 0.590$) (Fig. 3).

3.4. Effect of location of corticosterone infusion on accumbal dopamine output in saline pretreated controls

To determine the specificity of corticosterone infusions in the ventral portion of the ventral hippocampus, we also tested whether vehicle + corticosterone infusions made into the dorsoventral hippocampus ($n = 5$) or below the ventral hippocampus into the posterior medial cortical regions of the amygdala ($n = 4$) (including the amygdalohippocampal area (AHiPM, $n = 1$), posteromedial cortical area (PMCO, $n = 2$), and amygdalopiriform atransitional area (APir, $n = 1$)) produced alterations in accumbal dopamine output (Fig. 4). A one-way repeated measures ANOVA revealed that vehicle + corticosterone infusions into the dorsoventral hippocampus did produce a significant increase in accumbal dopamine output over time ($F(65, 260) = 1.974$, $P < 0.001$). However, no specific time period was greater over time when multiple comparisons were assessed vs. pre-infusion controls (Holm Sidak, $P > 0.05$). Similar to the effects of dorsoventral hippocampal infusions, infusions into the posterior medial cortical regions of the amygdala produced a significant increase in accumbal dopamine output over time ($F(60,180) = 1.860$, $P < 0.001$), but no specific time period was greater over time when multiple comparisons were assessed vs. pre-infusion controls (Holm Sidak, $P > 0.05$).

4. Discussion

4.1. Ventral hippocampal corticosterone enhances accumbal dopamine output in controls

Corticosterone is thought to be excitatory in the ventral hippocampus and can induce rapid glutamate release *in vitro* (Bekkers and Stevens, 1989; Karst et al., 2005). Electrical or NMDA activation of the ventral hippocampus enhances accumbal dopamine output (Barr et al., 2014; Blaha et al., 1997; Karst et al., 2005; Taepavarapruk et al., 2014). As predicted by these previous observations, infusing corticosterone into the ventral hippocampus of saline pre-treated control rats rapidly enhanced accumbal dopamine release. This effect was most prominent in the ventral portion of the ventral hippocampus where subicular output to the nucleus accumbens is known to arise (Britt et al., 2012; Brog et al., 1993; Goto and Grace, 2005; Groenewegen et al., 1987; O'Donnell and Grace, 1995; Strange et al., 2014). The dorsal aspect of the ventral hippocampus has high expression of glucocorticoid- and mineralocorticoid receptors (Reul and de Kloet, 1985, 1986), but projects to the nucleus accumbens core rather than to the shell (Strange et al., 2014). As such, we observed that infusions of corticosterone into this more dorsal aspect of the ventral hippocampus were less effective at increasing dopamine in the accumbens shell. A more transient effect of corticosterone was also observed when infusions were made deeper than the ventral hippocampus, into the posterior medial cortical regions of the amygdala. These regions of the amygdala have functional connectivity with the ventral hippocampus and other regions of the amygdala, but not to the nucleus accumbens shell (Belujon et al., 2016; Groeneweg et al., 2012; Sah et al., 2003; Salgado and Kaplitt, 2015; Schmitt et al., 2012; Zorrilla and Koob, 2013). Therefore, the effect of corticosterone infusions on accumbal dopamine output observed in posterior medial cortical regions of the amygdala most likely occurred through connectivity with the ventral hippocampus and/or from some corticosterone diffusion into the ventral sub-regions of the hippocampus. However, this conclusion warrants further investigation with larger sample sizes.

The finding that corticosterone infused into the ventral hippocampus stimulates accumbal dopamine has several implications for the ability of stress to alter motivated behaviors. For example, stress-enhanced corticosterone in the ventral hippocampus (Bray et al., 2016; Droste et al., 2008) may contribute to the ability of stressors to enhance reward salience and motivate goal-oriented behavior in control conditions (Berridge and Robinson, 2016; Floresco, 2014; Hollon et al., 2015). Furthermore, acute psychostimulant exposure enhances corticosterone secretion (Bayer et al., 1995; Knysch and Eisenberg, 1979; Swerdlow et al., 1993; Zuloaga et al., 2014). Therefore, our findings also suggest that accumbal dopamine responses to corticosterone in the ventral hippocampus may contribute to positive reinforcement of initial psychostimulant use (Robinson and Berridge, 2000).

4.2. Receptor mechanisms in the ventral hippocampus mediating corticosterone stimulation of accumbal dopamine.

The effects of corticosterone were abolished when the steroid was prevented from crossing cellular membranes (conjugated to BSA), suggesting that the rapid stimulatory effects of ventral hippocampal corticosterone on accumbal dopamine release are dependent upon

binding of cytosolic receptors. Typically, steroid effects within 30 minutes of onset are associated with non-genomic mechanisms (Barr et al., 2017; de Kloet et al., 2008; Groeneweg et al., 2012; Haller et al., 2008; Makara and Haller, 2001; Prager and Johnson, 2009; Stahn and Buttgerit, 2008; Stahn et al., 2007). Furthermore, the non-genomic effects of corticosterone are most often attributed to membrane-associated mechanisms (Barr et al., 2017; Groeneweg et al., 2012; Joels and de Kloet, 2017; Tasker et al., 2006). However, cytosolic mineralocorticoid and glucocorticoid receptors and receptor complexes can also induce non-genomic effects (Croxtall et al., 2002; Horvath and Wanner, 2006; Liu et al., 2010; Tumlin et al., 1997), supporting the idea that non-genomic cytosolic receptors are involved in mediating the rapid ability of ventral hippocampal corticosterone to alter accumbal dopamine release. Alternatively, the approach used here does not rule out the possibility that concomitant activation of both membrane-bound and cytosolic mechanisms are required for ventral hippocampal corticosterone to alter accumbal dopamine release. This possibility warrants future investigation, when molecular tools advance to differentiate membrane-associated and cytosolic receptor activity and associated signaling cascades.

Furthermore, we have only used one isoform of BSA-conjugated corticosterone, at one dose. It is possible that the carboxymethyloxime-ketone conjugation of BSA to corticosterone's terminal ketone group (employed in the synthesis of the Corticosterone 3-CMO : BSA isoform used in these studies) blocks corticosterone receptor binding. We believe this is unlikely as prior research has shown similar increases in glutamate transmission induced by both BSA-conjugated corticosterone and corticosterone alone (Karst et al., 2005). Further, intrahippocampal infusions of BSA-conjugated corticosterone and acute stress elicit similar changes in behavioral performance on a spatial discrimination task (Chauveau et al., 2010). However, this possibility still warrants future investigation through the use of other commercially available isoforms of BSA-conjugated corticosterone and a dose-response study.

We anticipated that blocking mineralocorticoid receptors would isolate corticosterone's effects to glucocorticoid receptors and vice versa, thus revealing the role of each receptor in the ventral hippocampus in mediating accumbal dopamine output *in vivo*. Surprisingly, selectively blocking either glucocorticoid- or mineralocorticoid receptors in the ventral hippocampus prevented ventral hippocampal corticosterone from altering accumbal dopamine output. This suggests that neither glucocorticoid- nor mineralocorticoid receptors in the ventral hippocampus can sufficiently enable ventral hippocampal corticosterone to alter accumbal dopamine output independently of one another. At the genomic level, a variety of literature suggests specific glucocorticoid target genes may require concomitant activation of mineralocorticoid- and glucocorticoid receptors (Mifsud and Reul, 2018; Mifsud and Reul, 2016). This is thought to occur through heterodimerization of mineralocorticoid and glucocorticoid receptor complexes (Liu et al., 1995; Mifsud and Reul, 2018; Mifsud and Reul, 2016; Ou et al., 2001; Trapp and Holsboer, 1996). This cooperative ability has been demonstrated in ventral hippocampal tissue, and can increase the functional diversity of corticosterone's genomic actions (Trapp and Holsboer, 1996). Our data raises the intriguing possibility that cooperative activity of the two corticosterone receptor types in the ventral hippocampus is also required to induce distinct non-genomic effects.

4.3. An overall model for how ventral hippocampal corticosterone modulates accumbal dopamine

The ventral hippocampus has an extensive interneuronal network responsible for regulating local excitation (Fig. 5) (Chamberland and Topolnik, 2012; Freund and Buzsaki, 1996; Leranath and Hajszan, 2007). We propose the glutamatergic efferents from the ventral hippocampus responsible for stimulating accumbal dopamine release are under tonic inhibition in basal conditions (Fig. 5). Non-genomic glucocorticoid receptors can regulate interneuron inhibition (Zeise et al., 1992). This may occur in part through their recruitment of serotonin- and membrane-permeable retrograde signaling mechanisms such as nitric oxide (NO, a gas) and the endocannabinoid 2-arachidonoylglycerol (2-AG, an ester/lipid), which activate excitatory and inhibitory serotonin receptors, NO-sensitive guanylyl cyclase (NO-GC), and inhibitory Type I cannabinoid receptors (CB1) (respectively; Fig. 5). These signal transducers are expressed on excitatory glutamatergic terminals and inhibitory GABAergic terminals (Figure 5), including specific subpopulations of GABAergic interneurons and interneuron-inhibiting interneurons (IS-Is), and augment, inhibit, or disinhibit presynaptic interneuron activity (Barr and Forster, 2011; Di et al., 2016; Di et al., 2003; Hu et al., 2010; Li et al., 2014).

The presence of local interneurons, interneuron-*inhibiting* interneurons (IS-Is) and long-range GABAergic projections in the hippocampus (Fig. 5) (Chamberland and Topolnik, 2012; Freund and Buzsaki, 1996; Jinno, 2009) make it difficult to discern whether glucocorticoid-receptor-mediated effects on interneuron and IS-I transmission (Liu et al., 2010; Maggio and Segal, 2009) would translate to inhibitory or disinhibitory effects locally and/or in the nucleus accumbens shell *in vivo*. This is because it is not known whether these glucocorticoid-receptor effects impact interneurons or interneuron *inhibiting* neurons (IS-Is), or both. Furthermore, we previously found that corticosterone acting on glucocorticoid receptors rapidly increases serotonin levels in the ventral hippocampus (Barr and Forster, 2011). The hippocampus is enriched with all subtypes of excitatory and inhibitory 5-HT receptors, localized to 5-HT presynaptic terminals, GABAergic interneurons, and glutamatergic neurons (Berumen et al., 2012). The combined effects of these 5-HT actions in the hippocampus are complex, however serotonin's inhibitory 5-HT_{1A} receptors are localized to GABAergic interneurons in this region (Aznar et al., 2003) and 5-HT_{1A} receptors in the hippocampus are thought to provide inhibitory regulation of GABAergic interneurons (Matsuyama et al., 1997). Additionally, serotonin's excitatory 5-HT₃ receptors are preferentially expressed on IS-Is in the ventral hippocampus, reinforcing a disinhibiting effect of serotonin in this region (Berumen et al., 2012; Chamberland and Topolnik, 2012; Freund and Buzsaki, 1996; Pelkey et al., 2017). Thus, it is possible that cytosolic non-genomic glucocorticoid receptor activation results in disinhibition of glutamatergic efferents from the ventral hippocampus to the mesolimbic dopamine system via serotonergic (and retrograde NO or 2-AG) signals acting on local GABAergic neurons (Fig. 5).

Based on our current findings, glucocorticoid receptor-mediated disinhibition of the glutamate efferents from the ventral hippocampus may be insufficient to stimulate accumbal dopamine release without concomitant excitation. Electrophysiology studies suggest pre- and postsynaptic membrane mineralocorticoid receptors can rapidly and reversibly

potentiate glutamate release in the hippocampus (Bekkers and Stevens, 1989; Karst et al., 2005). Therefore, we propose concomitant activation of non-genomic mineralocorticoid receptors (Fig. 5) is also required to potentiate glutamate release from the glutamatergic efferents that project from the ventral hippocampus to stimulate accumbal dopamine release when these neurons are disinhibited by glucocorticoid receptor activation. Overall, the model and interactions proposed by Figure 5 require testing in the future to confirm the mechanisms by which corticosterone in the ventral hippocampus modifies accumbal dopamine efflux.

4.4 Ventral hippocampal corticosterone reduces accumbal dopamine output in amphetamine withdrawal

In amphetamine pre-treated rats, corticosterone infusions into the ventral hippocampus produced a biphasic reduction in accumbal dopamine output, highlighting disrupted ventral hippocampal corticosterone modulation of accumbal dopamine in amphetamine withdrawal. This may be due, in part, to reduced glucocorticoid receptor expression and function in the ventral hippocampus of this amphetamine withdrawal model (Barr and Forster, 2011; Li et al., 2014), which we predict would result in an inability to suppress GABAergic inhibition of glutamatergic efferents from the hippocampus to the nucleus accumbens (Figure 5). Interestingly, mineralocorticoid receptor expression in the ventral hippocampus does not change during amphetamine withdrawal (Barr and Forster, 2011). Our current findings suggest that synergistic activation of glucocorticoid and mineralocorticoid receptors in the ventral hippocampus are required to observe increased dopamine efflux in the nucleus accumbens. Thus, the prominent reduction in glucocorticoid receptor function in the ventral hippocampus during amphetamine withdrawal (Barr and Forster, 2011; Li et al., 2014) is likely to negate any stimulatory effect of corticosterone's actions on mineralocorticoid receptors (Figure 5) in withdrawn rats. However, our model would predict that corticosterone in the ventral hippocampus would be ineffective in altering accumbal dopamine efflux in the absence of glucocorticoid receptor signaling. The observed decrease in dopamine signal within the nucleus accumbens is thus likely due to other molecular changes induced by amphetamine exposure (Barr et al., 2017) that are revealed when corticosterone is infused into the ventral hippocampus. A likely candidate are corticosterone-sensitive organic cation transporters (OCTs) which play an important role in transport monoamine neurotransmitters within the brain (Gasser, 2019). The expression and function of OCT-3 are increased in the ventral hippocampus of our amphetamine withdrawal rat model (Barr et al., 2013; Solanki et al., 2016) and whether these changes can result in altered glutamatergic neuronal activity in the ventral hippocampus should be explored in the future.

Our findings lead to the implication that disrupted ventral hippocampal corticosterone responses may promote dysphoric states during amphetamine withdrawal by contributing to accumbal dopamine deficiency, which in turn, contributes to stress-related drug-taking behavior and relapse (Brischoux et al., 2009; Haake et al., 2018; Hurley et al., 2017; Paliwal et al., 2008; Robinson et al., 2014; Roitman et al., 2008; Sinha, 2007; Twining et al., 2014; Ungless et al., 2004; Weise-Kelly and Siegel, 2001; Wheeler et al., 2011; Wheeler and Carelli, 2009; Wheeler et al., 2008). The opponent-process theory of addiction suggests that

blunted dopamine reward responses and glucocorticoid stress responses contribute to negative reinforcement of drug-taking (Koob and Le Moal, 2008a, b). Previous research has focused on the role of corticotrophin releasing factor (CRF) in the amygdala as contributing to the disruption of reward processes thought to prompt addiction (Koob, 2009; Koob and Le Moal, 2008a, b; Koob and Zorrilla, 2010; Zorrilla et al., 2014). Our findings implicate corticosterone in the ventral hippocampus as a key contributor to the dysregulated opponent processes thought to negatively reinforce drug dependence (Barr et al., 2017).

5. Conclusions

Here we demonstrate for the first time that a stress-relevant concentration of corticosterone in the ventral hippocampus significantly enhances accumbal dopamine output in control conditions, and reduces accumbal dopamine output in protracted amphetamine withdrawal. Our findings suggest that the ability of corticosterone in the ventral hippocampus to alter accumbal dopamine output requires cytosolic access as well as activation of both mineralocorticoid and glucocorticoid receptors that are likely to be at least partly mediated by non-genomic mechanisms. Thus, we propose the ability of corticosterone in the ventral hippocampus to alter accumbal dopamine output requires cooperative activation of excitatory mineralocorticoid receptors and glucocorticoid-receptor-mediated disinhibition to produce excitatory output onto the mesolimbic dopamine circuit. Disruption to this balance within the ventral hippocampus thus appears to reduce accumbal dopamine output during amphetamine withdrawal.

Overall, our findings suggest the ventral hippocampal corticosterone stress response as a potential mechanism that enables stress to enhance incentive salience and promote goal-oriented behavior. This response may also contribute to positive reinforcement of initial drug exposure, and when altered by chronic psychostimulant exposure, contributes to the dysphoric states thought to negatively reinforce drug dependence and relapse during withdrawal.

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Abbreviations

2-AG

2-arachidonoylglycerol

aCSF

artificial cerebrospinal fluid

AHiPM

amygdalohippocampal area of the amygdala

AMP

amphetamine pre-treatment and withdrawal

ANOVA

analysis of variance

APir

amygdalaopiriform atransitional area of the amygdala

BSA

bovine serum albumin

BSA

Corticosterone, infusions of corticosterone

3-CMO

BSA (corticosterone conjugated to membrane-impermeable BSA)

CB1

Inhibitory G_{i/o}-coupled type I cannabinoid receptor

CORT

corticosterone

CRF

corticotrophin releasing factor

BSA-HBC

infusion of bovine serum albumin in 0.05% 2-hydroxypropyl- β -cyclodextrin

Corticosterone 3-CMO : BSA

corticosterone 3-corticosterone methyl oxidase conjugated to bovine serum albumin (4-pregnen-11b, 21-diol-3, 20-dione 3-carboxymethyloxime : bovine serum albumin), a membrane-impermeable corticosterone conjugate

GABA

gamma-aminobutyric acid

HBC

2-hydroxypropyl- β -cyclodextrin

IS-I

interneuron specific interneuron

MIF

mifepristone infusion

NMDA

N-Methyl-D-aspartic acid

NO

nitrous oxide

NO-GC

nitrous oxide-sensitive guanylyl cyclase

PMCO

posteriomedial cortical area of the amygdala

SAL

saline pre-treatment

SPIR

spironolactone infusion

Vehicle

vehicle infusion

vHipp

ventral hippocampus.

References:

- Aznar S, Qian Z, Shah R, Rahbek B, Knudsen GM, 2003 The 5-HT1A serotonin receptor is located on calbindin- and parvalbumin-containing neurons in the rat brain. *Brain Research* 959(1), 58–67. [PubMed: 12480158]
- Barr JL, Bray B, Forster GL, 2017 The Hippocampus as a Neural Link between Negative Affect and Vulnerability for Psychostimulant Relapse In: Stuchlik A, (Ed), *The Hippocampus*, IntechOpen.
- Barr JL, Forster GL, 2011 Serotonergic neurotransmission in the ventral hippocampus is enhanced by corticosterone and altered by chronic amphetamine treatment. *Neuroscience* 182, 105–114. [PubMed: 21420472]
- Barr JL, Forster GL, Unterwald EM, 2014 Repeated cocaine enhances ventral hippocampal-stimulated dopamine efflux in the nucleus accumbens and alters ventral hippocampal NMDA receptor subunit expression. *J Neurochem* 130, 583–590. [PubMed: 24832868]
- Bayer BM, Mulroney SE, Hernandez MC, Ding XZ, 1995 Acute infusions of cocaine result in time- and dose-dependent effects on lymphocyte responses and corticosterone secretion in rats. *Immunopharmacology* 29, 19–28. [PubMed: 7768668]
- Bekkers JM, Stevens CF, 1989 NMDA and non-NMDA receptors are co-localized at individual excitatory synapses in cultured rat hippocampus. *Nature* 341, 230–233. [PubMed: 2571090]
- Belujon P, Jakobowski NL, Dollish HK, Grace AA, 2016 Withdrawal from Acute Amphetamine Induces an Amygdala-Driven Attenuation of Dopamine Neuron Activity: Reversal by Ketamine. *Neuropsychopharmacology* 41, 619–627. [PubMed: 26129677]
- Berumen LC, Rodriguez A, Miledi R, Garcia-Alcocer G, 2012 Serotonin receptors in the hippocampus. *Scientific World Journal*, 823493–823508. [PubMed: 22629209]
- Berridge KC, Robinson TE, 2016 Liking, wanting, and the incentive-sensitization theory of addiction. *Am Psychol* 71, 670–679. [PubMed: 27977239]
- Blaha CD, 1996 Evaluation of stearate-graphite paste electrodes for chronic measurement of extracellular dopamine concentrations in the mammalian brain. *Pharmacol Biochem Behav* 55, 351–364. [PubMed: 8951976]

- Blaha CD, Jung ME, 1991 Electrochemical evaluation of stearate-modified graphite paste electrodes: selective detection of dopamine is maintained after exposure to brain tissue. *J Electroanal Chem Interfacial Electrochem* 310, 317–334.
- Blaha CD, Lane RF, 1983 Chemically modified electrode for in vivo monitoring of brain catecholamines. *Brain Res Bull* 10, 861–864. [PubMed: 6616277]
- Blaha CD, Yang CR, Floresco SB, Barr AM, Phillips AG, 1997 Stimulation of the ventral subiculum of the hippocampus evokes glutamate receptor-mediated changes in dopamine efflux in the rat nucleus accumbens. *Eur J Neurosci* 9, 902–911. [PubMed: 9182943]
- Borland LM, Michael AC, 2007 An Introduction to Electrochemical Methods in Neuroscience In: Michael AC, Borland LM, (Eds), *Electrochemical Methods for Neuroscience*. CRC Press/Taylor & Francis, Boca Raton (FL), pp. 1–39.
- Bray B, Scholl JL, Tu W, Watt MJ, Renner KJ, Forster GL, 2016 Amphetamine withdrawal differentially affects hippocampal and peripheral corticosterone levels in response to stress. *Brain Res* 1644, 278–287. [PubMed: 27208490]
- Brischoux F, Chakraborty S, Brierley DI, Ungless MA, 2009 Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *Proc Natl Acad Sci U S A* 106, 4894–4899. [PubMed: 19261850]
- Britt JP, Benaliouad F, McDevitt RA, Stuber GD, Wise RA, Bonci A, 2012 Synaptic and behavioral profile of multiple glutamatergic inputs to the nucleus accumbens. *Neuron* 76, 790–803. [PubMed: 23177963]
- Brog JS, Salyapongse A, Deutch AY, Zahm DS, 1993 The patterns of afferent innervation of the core and shell in the “accumbens” part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluoro-gold. *J Comp Neurol* 338, 255–278. [PubMed: 8308171]
- Chamberland S, Topolnik L, 2012 Inhibitory control of hippocampal inhibitory neurons. *Front Neurosci* 6, 165. [PubMed: 23162426]
- Chauveau F, Tronche C, Pierard C, Liscia P, Drouet I, Coutan M, Beracochea D, 2010 Rapid stress-induced corticosterone rise in the hippocampus reverses serial memory retrieval pattern. *Hippocampus* 20, 196–207. [PubMed: 19360856]
- Cleck JN, Blendy JA, 2008 Making a bad thing worse: adverse effects of stress on drug addiction. *J Clin Invest* 118, 454–461. [PubMed: 18246196]
- Croxtall JD, van Hal PT, Choudhury Q, Gilroy DW, Flower RJ, 2002 Different glucocorticoids vary in their genomic and non-genomic mechanism of action in A549 cells. *Br J Pharmacol* 135, 511–519. [PubMed: 11815387]
- Cryan JF, Hoyer D, Markou A, 2003 Withdrawal from chronic amphetamine induces depressive-like behavioral effects in rodents. *Biol Psychiatry* 54, 49–58. [PubMed: 12842308]
- de Kloet ER, Karst H, Joels M, 2008 Corticosteroid hormones in the central stress response: quick-and-slow. *Front Neuroendocrinol* 29, 268–272. [PubMed: 18067954]
- Di S, Itoga CA, Fisher MO, Solomonow J, Roltsch EA, Gilpin NW, Tasker JG, 2016 Acute Stress Suppresses Synaptic Inhibition and Increases Anxiety via Endocannabinoid Release in the Basolateral Amygdala. *J Neurosci* 36, 8461–8470. [PubMed: 27511017]
- Di S, Malcher-Lopes R, Halmos KC, Tasker JG, 2003 Nongenomic Glucocorticoid Inhibition via Endocannabinoid Release in the Hypothalamus: A Fast Feedback Mechanism. *The Journal of Neuroscience* 23, 4850–4857. [PubMed: 12832507]
- Droste SK, de Groote L, Atkinson HC, Lightman SL, Reul JM, Linthorst AC, 2008 Corticosterone levels in the brain show a distinct ultradian rhythm but a delayed response to forced swim stress. *Endocrinology* 149, 3244–3253. [PubMed: 18356272]
- Droste SK, de Groote L, Lightman SL, Reul JM, Linthorst AC, 2009 The ultradian and circadian rhythms of free corticosterone in the brain are not affected by gender: an in vivo microdialysis study in Wistar rats. *J Neuroendocrinol* 21, 132–140. [PubMed: 19076270]
- Enrico P, Sirca D, Mereu M, Peana AT, Mercante B, Diana M, 2013 Acute restraint stress prevents nicotine-induced mesolimbic dopaminergic activation via a corticosterone-mediated mechanism: a microdialysis study in the rat. *Drug Alcohol Depend* 127, 8–14. [PubMed: 22809896]
- Floresco SB, 2014 The Nucleus Accumbens: An Interface Between Cognition, Emotion, and Action. *Annu Rev Psychol* 66, 25–52. [PubMed: 25251489]

- Floresco SB, Todd CL, Grace AA, 2001 Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. *J Neurosci* 21, 4915–4922. [PubMed: 11425919]
- Freund TF, Buzsaki G, 1996 Interneurons of the hippocampus. *Hippocampus* 6, 347–470. [PubMed: 8915675]
- Garthwaite SM, McMahon EG, 2004 The evolution of aldosterone antagonists. *Mol Cell Endocrinol* 217, 27–31. [PubMed: 15134797]
- Gasser PJ, 2019 Roles for uptake 2 transporter OCT3 in regulation of dopaminergic neurotransmission and behavior. *Neurochemistry International* 123, 46–49. [PubMed: 30055194]
- Gossop M, 2009 Review: limited evidence to support pharmacological therapy for amphetamine withdrawal. *Evid Based Ment Health* 12, 122. [PubMed: 19854784]
- Goto Y, Grace AA, 2005 Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. *Nat Neurosci* 8, 805–812. [PubMed: 15908948]
- Groeneweg FL, Karst H, de Kloet ER, Joels M, 2011 Rapid non-genomic effects of corticosteroids and their role in the central stress response. *J Endocrinol* 209, 153–167. [PubMed: 21357682]
- Groeneweg FL, Karst H, de Kloet ER, Joels M, 2012 Mineralocorticoid and glucocorticoid receptors at the neuronal membrane, regulators of nongenomic corticosteroid signalling. *Mol Cell Endocrinol* 350, 299–309. [PubMed: 21736918]
- Groenewegen HJ, Vermeulen-Van der Zee E, te Kortschot A, Witter MP, 1987 Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of Phaseolus vulgaris leucoagglutinin. *Neuroscience* 23, 103–120. [PubMed: 3683859]
- Grubbs FE, 1969 Procedures for detecting outlying observations in samples. *Technometrics* 11, 1–21.
- Haake RM, West EA, Wang X, Carelli RM, 2018 Drug-induced dysphoria is enhanced following prolonged cocaine abstinence and dynamically tracked by nucleus accumbens neurons. *Addict Biol.*
- Haller J, Mikics E, Makara GB, 2008 The effects of non-genomic glucocorticoid mechanisms on bodily functions and the central neural system. A critical evaluation of findings. *Front Neuroendocrinol* 29, 273–291. [PubMed: 18054070]
- Heikinheimo O, 1997 Clinical pharmacokinetics of mifepristone. *Clin Pharmacokinet* 33, 7–17. [PubMed: 9250420]
- Heikinheimo O, Kekkonen R, 1993 Dose-response relationships of RU 486. *Ann Med* 25, 71–76. [PubMed: 8382070]
- Herman JP, Patel PD, Akil H, Watson SJ, 1989 Localization and regulation of glucocorticoid and mineralocorticoid receptor messenger RNAs in the hippocampal formation of the rat. *Mol Endocrinol* 3, 1886–1894. [PubMed: 2558306]
- Hollon NG, Burgeno LM, Phillips PE, 2015 Stress effects on the neural substrates of motivated behavior. *Nat Neurosci* 18, 1405–1412. [PubMed: 26404715]
- Horvath G, Wanner A, 2006 Inhaled corticosteroids: effects on the airway vasculature in bronchial asthma. *Eur Respir J* 27, 172–187. [PubMed: 16387951]
- Hu W, Zhang M, Czeh B, Flugge G, Zhang W, 2010 Stress impairs GABAergic network function in the hippocampus by activating nongenomic glucocorticoid receptors and affecting the integrity of the parvalbumin-expressing neuronal network. *Neuropsychopharmacology* 35, 1693–1707. [PubMed: 20357756]
- Hurley SW, West EA, Carelli RM, 2017 Opposing Roles of Rapid Dopamine Signaling Across the Rostral-Caudal Axis of the Nucleus Accumbens Shell in Drug-Induced Negative Affect. *Biol Psychiatry* 82, 839–846. [PubMed: 28624112]
- Jinno S, 2009 Structural organization of long-range GABAergic projection system of the hippocampus. *Front Neuroanat* 3, 13. [PubMed: 19649167]
- Joels M, de Kloet ER, 2017 30 YEARS OF THE MINERALOCORTICOID RECEPTOR: The brain mineralocorticoid receptor: a saga in three episodes. *J Endocrinol* 234, T49–t66. [PubMed: 28634266]
- Kalivas PW, Duffy P, 1995 Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress. *Brain Res* 675, 325–328. [PubMed: 7796146]

- Karst H, Berger S, Turiault M, Tronche F, Schutz G, Joels M, 2005 Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. *Proc Natl Acad Sci U S A* 102, 19204–19207. [PubMed: 16361444]
- Knych ET, Eisenberg RM, 1979 Effect of amphetamine on plasma corticosterone in the conscious rat. *Neuroendocrinology* 29, 110–118. [PubMed: 503280]
- Koob GF, 2009 Brain stress systems in the amygdala and addiction. *Brain Res* 1293, 61–75. [PubMed: 19332030]
- Koob GF, Buck CL, Cohen A, Edwards S, Park PE, Schlosburg JE, Schmeichel B, Vendruscolo LF, Wade CL, Whitfield TW Jr., George O, 2014 Addiction as a stress surfeit disorder. *Neuropharmacology* 76 Pt B, 370–382. [PubMed: 23747571]
- Koob GF, Le Moal M, 2008a Addiction and the brain antireward system. *Annu Rev Psychol* 59, 29–53. [PubMed: 18154498]
- Koob GF, Le Moal M, 2008b Review. Neurobiological mechanisms for opponent motivational processes in addiction. *Philos Trans R Soc Lond B Biol Sci* 363, 3113–3123. [PubMed: 18653439]
- Koob GF, Volkow ND, 2010 Neurocircuitry of addiction. *Neuropsychopharmacology* 35, 217–238. [PubMed: 19710631]
- Koob GF, Zorrilla EP, 2010 Neurobiological mechanisms of addiction: focus on corticotropin-releasing factor. *Curr Opin Investig Drugs* 11, 63–71.
- Kosten TR, 2012 Diagnoses, symptoms, and assessment In: Kosten TR, Newton TF, De La Garza R II, Haile CN, (Eds), *Cocaine and methamphetamine dependence: Advances in treatment*. American Psychiatric Publishing, Inc, Arlington, VA US, pp. 85–104.
- Kwako LE, Koob GF, 2017 Neuroclinical Framework for the Role of Stress in Addiction. *Chronic Stress* 1, 247054701769814.
- Legault M, Rompre PP, Wise RA, 2000 Chemical stimulation of the ventral hippocampus elevates nucleus accumbens dopamine by activating dopaminergic neurons of the ventral tegmental area. *J Neurosci* 20, 1635–1642. [PubMed: 10662853]
- Leranth C, Hajszan T, 2007 Extrinsic afferent systems to the dentate gyrus. *Prog Brain Res* 163, 63–84. [PubMed: 17765712]
- Levone BR, Cryan JF, O'Leary OF, 2015 Role of adult hippocampal neurogenesis in stress resilience. *Neurobiol Stress* 1, 147–155. [PubMed: 27589664]
- Li H, Scholl JL, Tu W, Hassell JE, Watt MJ, Forster GL, Renner KJ, 2014 Serotonergic responses to stress are enhanced in the central amygdala and inhibited in the ventral hippocampus during amphetamine withdrawal. *Eur J Neurosci* 40, 3684–3692. [PubMed: 25234335]
- Liu W, Wang J, Sauter NK, Pearce D, 1995 Steroid receptor heterodimerization demonstrated in vitro and in vivo. *Proc Natl Acad Sci U S A* 92, 12480–12484. [PubMed: 8618925]
- Liu X, Zeng J, Zhao Y, Xiao Z, Fang C, Ruan H, 2010 Inhibition of ATP-induced Ca²⁺ influx by corticosterone in dorsal root ganglion neurons. *Neurochem Res* 35, 804–810. [PubMed: 20180019]
- Maggio N, Segal M, 2007 Striking variations in corticosteroid modulation of long-term potentiation along the septotemporal axis of the hippocampus. *J Neurosci* 27, 5757–5765. [PubMed: 17522319]
- Maggio N, Segal M, 2009 Differential corticosteroid modulation of inhibitory synaptic currents in the dorsal and ventral hippocampus. *J Neurosci* 29, 2857–2866. [PubMed: 19261881]
- Mahajan DK, London SN, 1997 Mifepristone (RU486): a review. *Fertil Steril* 68, 967–976. [PubMed: 9418681]
- Makara GB, Haller J, 2001 Non-genomic effects of glucocorticoids in the neural system. Evidence, mechanisms and implications. *Prog Neurobiol* 65, 367–390. [PubMed: 11527573]
- Matsuyama S, Nei K, Tanaka C, 1997 Regulation of GABA release via NMDA and 5-HT_{1A} receptors in guinea pig dentate gyrus. *Brain Research* 761(1), 105–112. [PubMed: 9247072]
- Mifsud KR, Reul J, 2018 Mineralocorticoid and glucocorticoid receptor-mediated control of genomic responses to stress in the brain. *Stress*, 1–14.
- Mifsud KR, Reul JM, 2016 Acute stress enhances heterodimerization and binding of corticosteroid receptors at glucocorticoid target genes in the hippocampus. *Proc Natl Acad Sci U S A* 113, 11336–11341. [PubMed: 27655894]

- Miller AD, Forster GL, Yeomans JS, Blaha CD, 2005 Midbrain muscarinic receptors modulate morphine-induced accumbal and striatal dopamine efflux in the rat. *Neuroscience* 136, 531–538. [PubMed: 16216430]
- Morozov VI, Chaikovskii VS, Priiatkin SA, Rogozkin VA, Savchenko ON, 1988 [Radioimmunologic analysis of steroids. Scientific and practical aspects]. *Fiziol Zh SSSR Im I M Sechenova* 74, 1049–1072. [PubMed: 3058518]
- National Research Council Committee for the Update of the Guide for the Care and Use of Laboratory Animals, 2011 The National Academies Collection: Reports funded by National Institutes of Health Guide for the Care and Use of Laboratory Animals. National Academies Press (US) National Academy of Sciences., Washington (DC).
- Novick AM, Forster GL, Hassell JE, Davies DR, Scholl JL, Renner KJ, Watt MJ, 2015 Increased dopamine transporter function as a mechanism for dopamine hypoactivity in the adult infralimbic medial prefrontal cortex following adolescent social stress. *Neuropharmacology* 97, 194–200. [PubMed: 26056032]
- O'Donnell P, Grace AA, 1995 Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. *J Neurosci* 15, 3622–3639. [PubMed: 7751934]
- Ou XM, Storrington JM, Kushwaha N, Albert PR, 2001 Heterodimerization of mineralocorticoid and glucocorticoid receptors at a novel negative response element of the 5-HT1A receptor gene. *J Biol Chem* 276, 14299–14307. [PubMed: 11278286]
- Paliwal P, Hyman SM, Sinha R, 2008 Craving predicts time to cocaine relapse: further validation of the Now and Brief versions of the cocaine craving questionnaire. *Drug Alcohol Depend* 93, 252–259. [PubMed: 18063320]
- Paxinos G, Watson C, 1998 The rat brain in stereotaxic coordinates, 4th edition Academic Press (Imprint of Elsevier), San Diego, CA.
- Pecina S, Berridge KC, 2013 Dopamine or opioid stimulation of nucleus accumbens similarly amplify cue-triggered 'wanting' for reward: entire core and medial shell mapped as substrates for PIT enhancement. *Eur J Neurosci* 37, 1529–1540. [PubMed: 23495790]
- Pelkey KA, Chittajallu R, Craig MT, Triccoire L, Wester JC, McBain CJ, 2017 Hippocampal GABAergic Inhibitory Interneurons. *Physiol Rev* 97, 1619–1747. [PubMed: 28954853]
- Perez SM, Chen L, Lodge DJ, 2014 Alterations in dopamine system function across the estrous cycle of the MAM rodent model of schizophrenia. *Psychoneuroendocrinology* 47, 88–97. [PubMed: 25001958]
- Prager EM, Johnson LR, 2009 Stress at the synapse: signal transduction mechanisms of adrenal steroids at neuronal membranes. *Sci Signal* 2, re5.
- Reinbold ED, Scholl JL, Oliver KM, Watt MJ, Forster GL, 2014 Central CRF receptor antagonism reduces anxiety states during amphetamine withdrawal. *Neurosci Res* 89, 37–43. [PubMed: 25205625]
- Reul JM, de Kloet ER, 1985 Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology* 117, 2505–2511. [PubMed: 2998738]
- Reul JM, de Kloet ER, 1986 Anatomical resolution of two types of corticosterone receptor sites in rat brain with in vitro autoradiography and computerized image analysis. *J Steroid Biochem* 24, 269–272. [PubMed: 3702410]
- Robinson TE, Berridge KC, 2000 The psychology and neurobiology of addiction: an incentive-sensitization view. *Addiction* 95 Suppl 2, S91–117.
- Robinson TE, Yager LM, Cogan ES, Saunders BT, 2014 On the motivational properties of reward cues: Individual differences. *Neuropharmacology* 76 Pt B, 450–459. [PubMed: 23748094]
- Roitman MF, Wheeler RA, Wightman RM, Carelli RM, 2008 Real-time chemical responses in the nucleus accumbens differentiate rewarding and aversive stimuli. *Nat Neurosci* 11, 1376–1377. [PubMed: 18978779]
- Russig H, Pryce CR, Feldon J, 2006 Amphetamine withdrawal leads to behavioral sensitization and reduced HPA axis response following amphetamine challenge. *Brain Res* 1084, 185–195. [PubMed: 16563358]

- Sabeti J, Gerhardt GA, Zahniser NR, 2003 Chloral hydrate and ethanol, but not urethane, alter the clearance of exogenous dopamine recorded by chronoamperometry in striatum of unrestrained rats. *Neurosci Lett* 343, 9–12. [PubMed: 12749985]
- Sah P, Faber ES, Lopez De Armentia M, Power J, 2003 The amygdaloid complex: anatomy and physiology. *Physiol Rev* 83, 803–834. [PubMed: 12843409]
- Salgado S, Kaplitt MG, 2015 The Nucleus Accumbens: A Comprehensive Review. *Stereotact Funct Neurosurg* 93, 75–93. [PubMed: 25720819]
- Schmitt O, Eipert P, Philipp K, Kettlitz R, Fuellen G, Wree A, 2012 The intrinsic connectome of the rat amygdala. *Front Neural Circuits* 6, 81. [PubMed: 23248583]
- Sesack SR, Pickel VM, 1990 In the rat medial nucleus accumbens, hippocampal and catecholaminergic terminals converge on spiny neurons and are in apposition to each other. *Brain Res* 527, 266–279. [PubMed: 1701338]
- Shoptaw SJ, Kao U, Heinzerling K, Ling W, 2009 Treatment for amphetamine withdrawal. *Cochrane Database Syst Rev*, Cd003021.
- Sinha R, 2007 The role of stress in addiction relapse. *Curr Psychiatry Rep* 9, 388–395. [PubMed: 17915078]
- Solanki RR, Scholl JL, Watt MJ, Renner KJ, Forster GL, 2016 Amphetamine Withdrawal Differentially Increases the Expression of Organic Cation Transporter 3 and Serotonin Transporter in Limbic Brain Regions. *J Exp Neurosci* 10, 93–100. [PubMed: 27478387]
- Stahn C, Buttgerit F, 2008 Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol* 4, 525–533. [PubMed: 18762788]
- Stahn C, Lowenberg M, Hommes DW, Buttgerit F, 2007 Molecular mechanisms of glucocorticoid action and selective glucocorticoid receptor agonists. *Mol Cell Endocrinol* 275, 71–78. [PubMed: 17630118]
- Strange BA, Witter MP, Lein ES, Moser EI, 2014 Functional organization of the hippocampal longitudinal axis. *Nat Rev Neurosci* 15, 655–669. [PubMed: 25234264]
- Sun HQ, Chen HM, Yang FD, Lu L, Kosten TR, 2014 Epidemiological trends and the advances of treatments of amphetamine-type stimulants (ATS) in China. *Am J Addict* 23, 313–317. [PubMed: 24724890]
- Swardlow NR, Koob GF, Cador M, Lorang M, Hauger RL, 1993 Pituitary-adrenal axis responses to acute amphetamine in the rat. *Pharmacol Biochem Behav* 45, 629–637. [PubMed: 8392732]
- Taepavarapruk P, Butts KA, Phillips AG, 2014 Dopamine and glutamate interaction mediates reinstatement of drug-seeking behavior by stimulation of the ventral subiculum. *Int J Neuropsychopharmacol* 18, 1461–1457.
- Tanti A, Rainer Q, Minier F, Surget A, Belzung C, 2012 Differential environmental regulation of neurogenesis along the septo-temporal axis of the hippocampus. *Neuropharmacology* 63, 374–384. [PubMed: 22561281]
- Tasker JG, Di S, Malcher-Lopes R, 2006 Minireview: rapid glucocorticoid signaling via membrane-associated receptors. *Endocrinology* 147, 5549–5556. [PubMed: 16946006]
- Trapp T, Holsboer F, 1996 Heterodimerization between mineralocorticoid and glucocorticoid receptors increases the functional diversity of corticosteroid action. *Trends Pharmacol Sci* 17, 145–149. [PubMed: 8984741]
- Tu W, Cook A, Scholl JL, Mears M, Watt MJ, Renner KJ, Forster GL, 2014 Serotonin in the ventral hippocampus modulates anxiety-like behavior during amphetamine withdrawal. *Neuroscience* 281c, 35–43.
- Tumlin JA, Lea JP, Swanson CE, Smith CL, Edge SS, Someren JS, 1997 Aldosterone and dexamethasone stimulate calcineurin activity through a transcription-independent mechanism involving steroid receptor-associated heat shock proteins. *J Clin Invest* 99, 1217–1223. [PubMed: 9077529]
- Twining RC, Wheeler DS, Ebben AL, Jacobsen AJ, Robble MA, Mantsch JR, Wheeler RA, 2014 Aversive Stimuli Drive Drug Seeking in a State of Low Dopamine Tone. *Biol Psychiatry*.
- Tye SJ, Miller AD, Blaha CD, 2009 Differential corticosteroid receptor regulation of mesoaccumbens dopamine efflux during the peak and nadir of the circadian rhythm: a molecular equilibrium in the midbrain? *Synapse* 63, 982–990. [PubMed: 19598178]

- Ungless MA, Magill PJ, Bolam JP, 2004 Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. *Science* 303, 2040–2042. [PubMed: 15044807]
- Valenti O, Lodge DJ, Grace AA, 2011 Aversive stimuli alter ventral tegmental area dopamine neuron activity via a common action in the ventral hippocampus. *J Neurosci* 31, 4280–4289. [PubMed: 21411669]
- van Haarst AD, Oitzl MS, de Kloet ER, 1997 Facilitation of feedback inhibition through blockade of glucocorticoid receptors in the hippocampus. *Neurochem Res* 22, 1323–1328. [PubMed: 9355104]
- Vuong SM, Oliver HA, Scholl JL, Oliver KM, Forster GL, 2010 Increased anxiety-like behavior of rats during amphetamine withdrawal is reversed by CRF2 receptor antagonism. *Behav Brain Res* 208, 278–281. [PubMed: 19958793]
- Wang CC, Wang SJ, 2009 Modulation of presynaptic glucocorticoid receptors on glutamate release from rat hippocampal nerve terminals. *Synapse* 63, 745–751. [PubMed: 19484722]
- Weber MA, Graack ET, Scholl JL, Renner KJ, Forster GL, Watt MJ, 2018 Enhanced dopamine D2 autoreceptor function in the adult prefrontal cortex contributes to dopamine hypoactivity following adolescent social stress. *Eur J Neurosci* 48, 1833–1850. [PubMed: 29904960]
- Weise-Kelly L, Siegel S, 2001 Self-administration cues as signals: drug self-administration and tolerance. *J Exp Psychol Anim Behav Process* 27, 125–136. [PubMed: 11296488]
- Wheeler RA, Aragona BJ, Fuhrmann KA, Jones JL, Day JJ, Cacciapaglia F, Wightman RM, Carelli RM, 2011 Cocaine cues drive opposing context-dependent shifts in reward processing and emotional state. *Biol Psychiatry* 69, 1067–1074. [PubMed: 21481843]
- Wheeler RA, Carelli RM, 2009 Dissecting motivational circuitry to understand substance abuse. *Neuropharmacology* 56 Suppl 1, 149–159.
- Wheeler RA, Twining RC, Jones JL, Slater JM, Grigson PS, Carelli RM, 2008 Behavioral and electrophysiological indices of negative affect predict cocaine self-administration. *Neuron* 57, 774–785. [PubMed: 18341996]
- Zeise ML, Teschemacher A, Arriagada J, Zieglansberger W, 1992 Corticosterone Reduces Synaptic Inhibition in Rat Hippocampal and Neocortical Neurons in vitro. *J Neuroendocrinol* 4, 107–112. [PubMed: 21554584]
- Zorrilla EP, Koob GF, 2013 Amygdalostratial projections in the neurocircuitry for motivation: a neuroanatomical thread through the career of Ann Kelley. *Neurosci Biobehav Rev* 37, 1932–1945. [PubMed: 23220696]
- Zorrilla EP, Logrip ML, Koob GF, 2014 Corticotropin releasing factor: a key role in the neurobiology of addiction. *Front Neuroendocrinol* 35, 234–244. [PubMed: 24456850]
- Zuloaga DG, Johnson LA, Agam M, Raber J, 2014 Sex differences in activation of the hypothalamic-pituitary-adrenal axis by methamphetamine. *J Neurochem* 129, 495–508. [PubMed: 24400874]

Bray et al Highlights

- Corticosterone in ventral hippocampus increases accumbal dopamine release.
- Mineralocorticoid and glucocorticoid receptors both mediate this response.
- Amphetamine withdrawal attenuates corticosterone-induced accumbal dopamine release.
- Dysregulated hippocampal corticosterone may promote dysphoria during drug withdrawal.

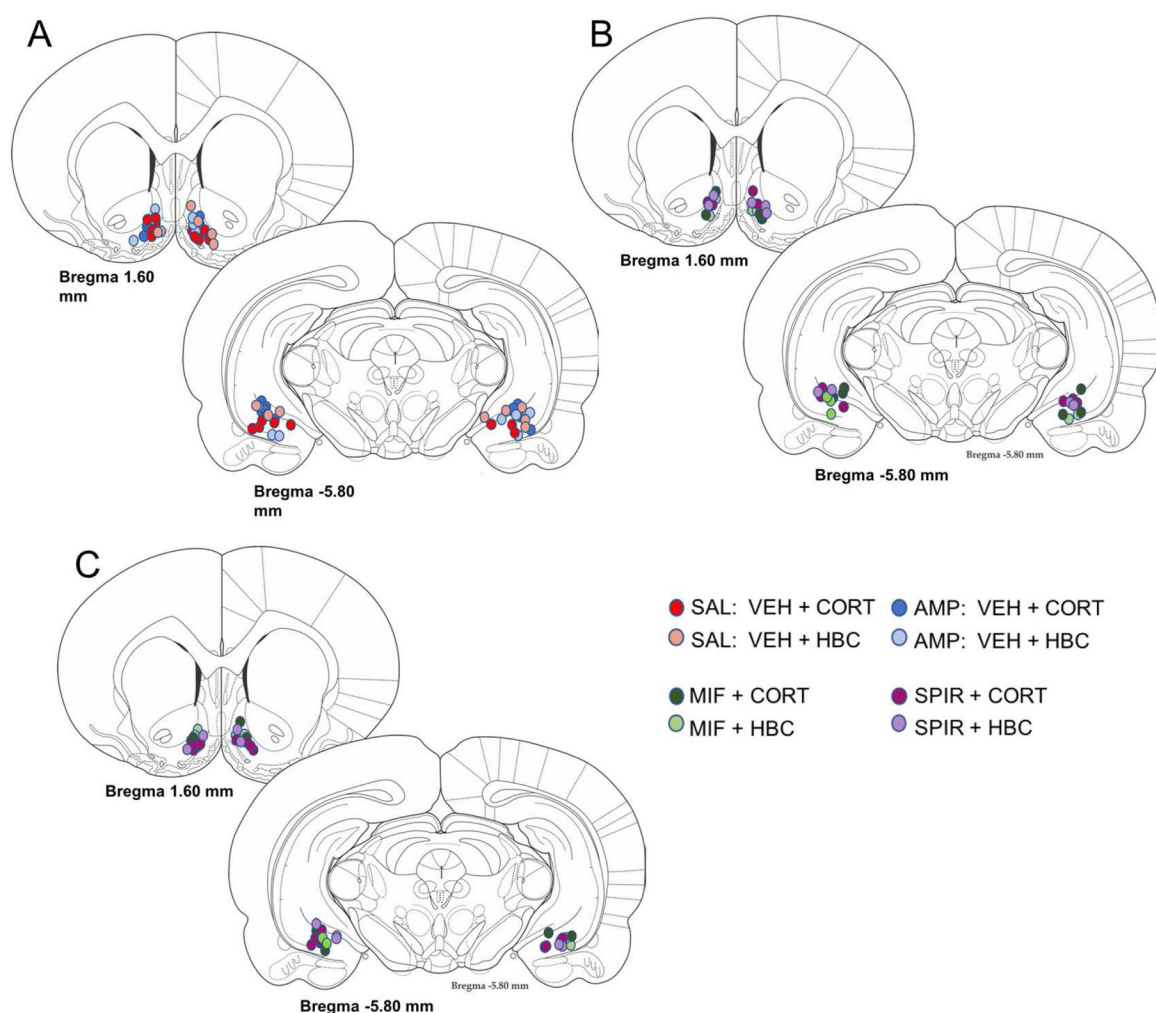


Figure 1. Representative diagrams of carbon paste electrode placements in the medial nucleus accumbens shell (left panel) and infusion cannula placements in the ventral subiculum and ventral dentate gyrus regions of the hippocampus (right panel).

A) Electrode/cannulae placements corresponding with results shown in Fig. 2A for saline and amphetamine pre-treated rats infused with corticosterone or vehicle, as outlined in Table 1. **B and C)** Electrode/cannulae placements corresponding with Figs. 2B and 2C respectively, conducted in saline- (**B**) and amphetamine (**C**) pre-treated rats receiving mifepristone or spironolactone infusions, as outlined in Table 1. Figures adapted from Paxinos and Watson (1998). AMP: Amphetamine pre-treatment; CORT: Corticosterone; HBC: hydroxypropyl- β -cyclodextrin; MIF: Mifepristone; SAL: Saline pre-treatment; SPIR: Spironolactone; VEH: Vehicle for antagonists.

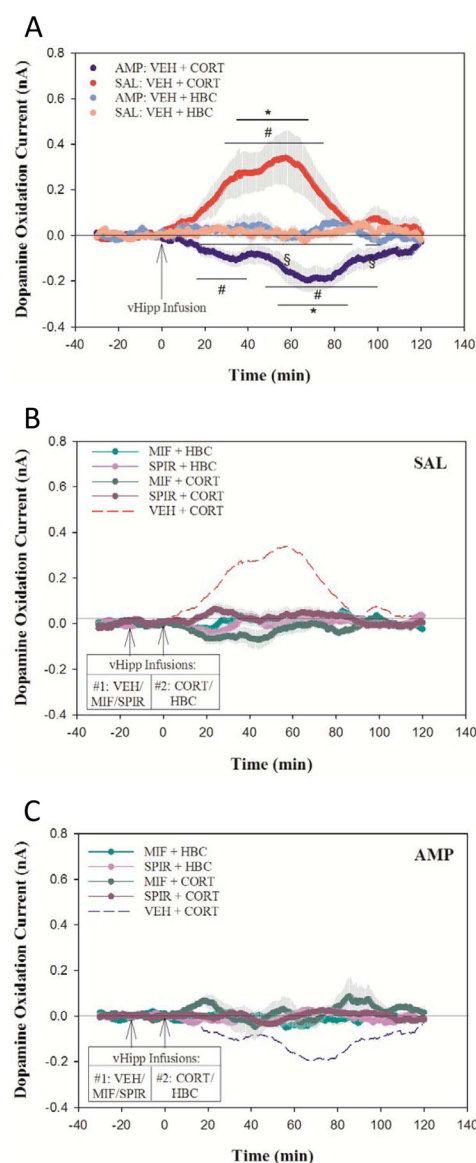


Figure 2. Corticosterone infusions into the ventral hippocampus differentially alter accumbal dopamine output in (A) saline- and amphetamine pre-treated rats, and (B-C) antagonism of either glucocorticoid- or mineralocorticoid receptors in the ventral hippocampus blocks the effects of corticosterone.

Data corresponds to mean \pm SEM nA. A) Saline- and amphetamine pre-treated rats receiving corticosterone and vehicle infusions into the ventral hippocampus (Table 1). B) saline- or C) amphetamine pre-treated rats receiving ventral hippocampus infusions of mifepristone or spironolactone in combination with corticosterone or vehicle (Table 1), with tracings for vehicle + corticosterone infusions from Fig. 2A shown as dotted lines for comparison. * $P < 0.05$ vs -2 to -0.5 min (within pre-treatment). # $P < 0.05$ vs VEH + HBC (within pre-treatment). § $P < 0.05$ vs pre-treatment. AMP: Amphetamine pre-treatment; CORT: Corticosterone; HBC: hydroxypropyl- β -cyclodextrin; MIF: Mifepristone; SAL: Saline pre-treatment; SPIR: Spironolactone; VEH: Vehicle for antagonists.

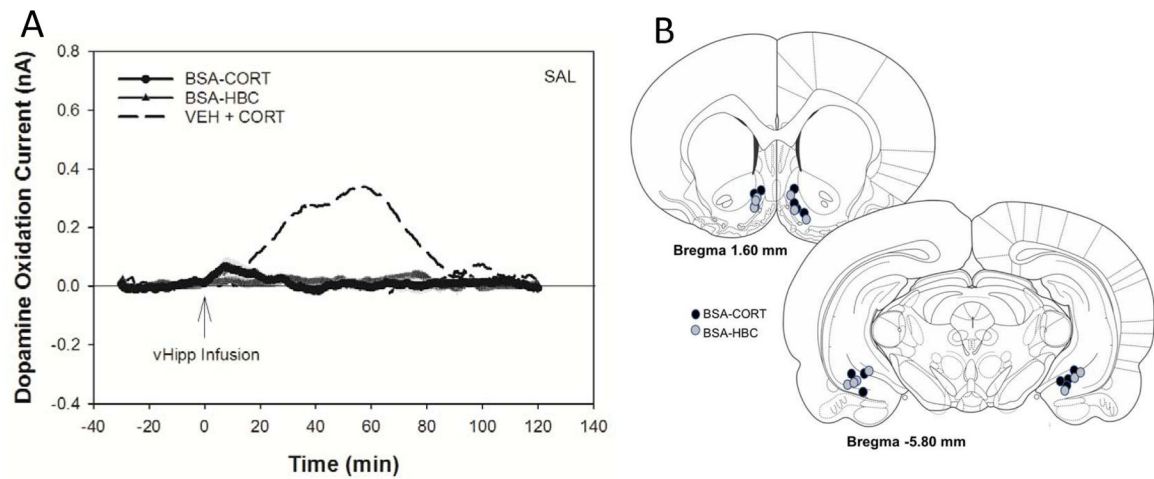


Figure 3. Stress-relevant concentrations of membrane-impermeable corticosterone infused into the ventral hippocampus of saline pre-treated rats fail to alter accumbal dopamine output relative to vehicle infusions.

A) Saline pre-treated rats receiving ventral hippocampus infusions of BSA-corticosterone conjugate or vehicle (BSA-HBC), with tracing for vehicle + corticosterone infusions from Fig. 2A shown as dotted lines for comparison. Data represent mean \pm SEM nA. **B)** Representative diagrams of carbon paste electrode placements in the medial nucleus accumbens shell and infusion cannula placements in the ventral hippocampus. Figures adapted from Paxinos and Watson (1998). BSA: bovine serum albumin; CORT: Corticosterone; HBC: hydroxypropyl- β -cyclodextrin; VEH: Vehicle.

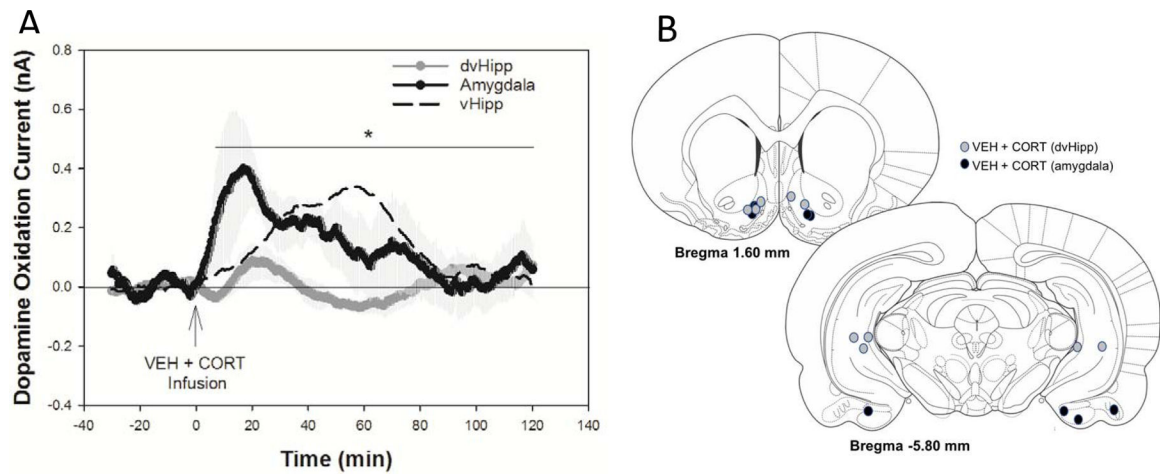


Figure 4. Location of corticosterone infusion differentially affects accumbal dopamine output in saline pre-treated controls.

A) Saline pre-treated rats receiving infusions of vehicle + corticosterone into the dorsoventral hippocampus (dvHipp) or posterior medial cortical regions of the amygdala, with tracing for accumbal dopamine output following vehicle + corticosterone infusions (VEH+CORT) into the ventral hippocampus (vHipp) from Fig. 2A shown as dotted line for reference. Data represent mean \pm SEM nA *significant effect of time ($P < 0.05$) but no specific time points identified as significantly different from pre-infusion levels ($P > 0.05$, Holm Sidak). **B)** Representative diagrams of carbon paste electrode placements in the medial nucleus accumbens shell and corresponding infusion cannula placements in the dorsoventral hippocampus and posterior medial cortical amygdala. Figures adapted from Paxinos and Watson (1998).

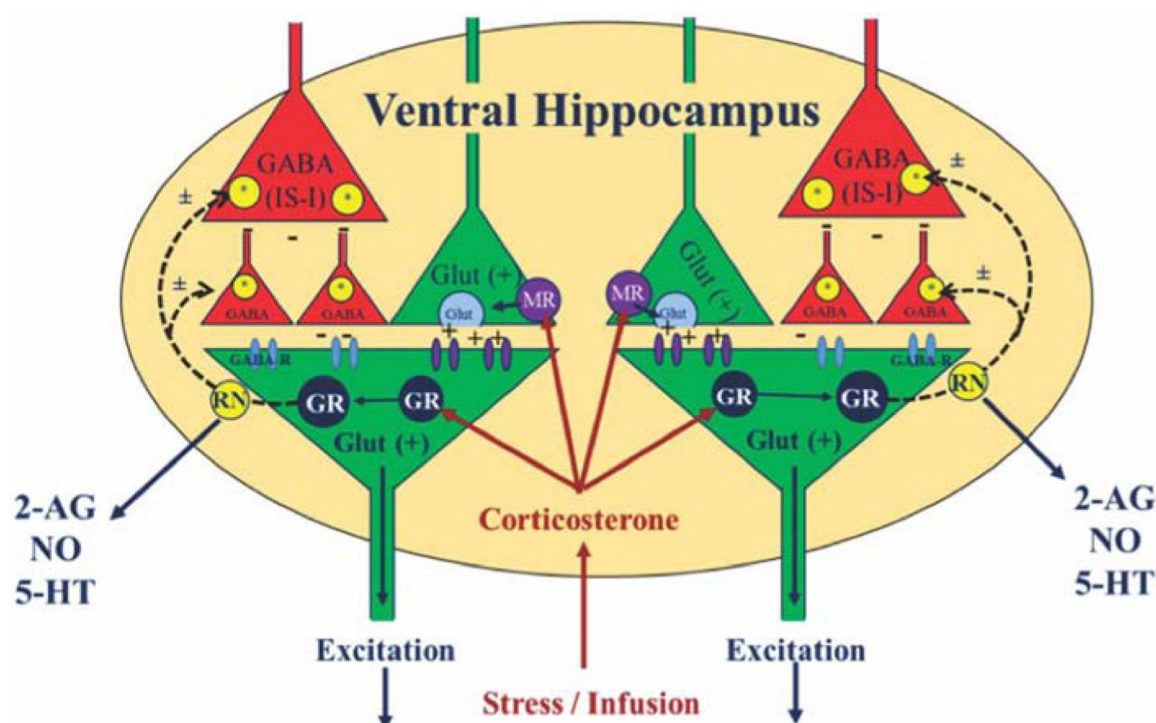


Figure 5. Cellular and molecular mechanisms proposed to mediate corticosterone excitation within the ventral hippocampus.

The ventral hippocampus is known to have an extensive interneuronal network (shown in red) responsible for regulating local excitation (Chamberland and Topolnik, 2012; Freund and Buzsaki, 1996; Leranth and Hajszan, 2007). Therefore, we propose the ventral hippocampus' glutamatergic efferents responsible for stimulating accumbal dopamine release (shown in green) may be under tonic inhibition by GABAergic interneuron- and interneuron-inhibiting interneurons (called interneuron-specific interneurons, IS-Is) under basal conditions. We conclude that corticosterone activation of presynaptic membrane mineralocorticoid receptors (MR, purple circles) potentiates local glutamate release onto the ventral hippocampus' glutamatergic efferents (Bekkers and Stevens, 1989; Karst et al., 2005). Membrane mineralocorticoid receptors also exist postsynaptically and can rapidly and reversibly potentiate glutamate release in the hippocampus; these have not been shown in the figure for the sake of simplicity. However, we propose activation of postsynaptic cytosolic glucocorticoid receptors (GR, blue circles) is also required to induce top-down disinhibition of the glutamatergic efferents whose terminal actions regulate accumbal dopamine output (Liu et al., 2010; Maggio and Segal, 2009; Zeise et al., 1992). The disinhibiting effects of GR activation are thought to occur through its induction of the retrograde signaling (RN: retrograde neurotransmitter) components 2-Arachidonoylglycerol (2-AG; an ester/lipid endocannabinoid), nitric oxide (NO; a gas), and/or serotonin (5-HT; an amino acid), which have been shown to act on inhibitory $G_{i/o}$ -coupled Type I cannabinoid (CB1) receptors, NO-sensitive guanylyl cyclase, and inhibitory 5-HT_{1A}- and excitatory 5-HT₃ receptors (respectively) on the presynaptic terminals of presynaptic GABAergic interneurons (Barr and Forster, 2011; Di et al., 2016; Di et al., 2003; Hu et al., 2010; Li et al., 2014). Overall, we propose GR activation disinhibits GABAergic suppression of the

ventral hippocampus' principal glutamatergic efferents that project to the mesolimbic dopamine system, enabling MR-induced depolarizing events to regulate accumbal excitation/inhibition and dopamine release.

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Table 1

Treatment Groups

Group	Pre-treatment	Region	Infusion 1	Infusion 2	N
1	Saline	Ventral vHipp	Vehicle	HBC Vehicle	9
2	Saline	Ventral vHipp	Vehicle	Corticosterone	13 *
3	Saline	Ventral vHipp	Mifepristone	HBC Vehicle	6
4	Saline	Ventral vHipp	Mifepristone	Corticosterone	6
5	Saline	Ventral vHipp	Spironolactone	HBC Vehicle	7
6	Saline	Ventral vHipp	Spironolactone	Corticosterone	8 *
7	Amphetamine	Ventral vHipp	Vehicle	HBC Vehicle	10
8	Amphetamine	Ventral vHipp	Vehicle	Corticosterone	11 *
9	Amphetamine	Ventral vHipp	Mifepristone	HBC Vehicle	7 *
10	Amphetamine	Ventral vHipp	Mifepristone	Corticosterone	7
11	Amphetamine	Ventral vHipp	Spironolactone	HBC Vehicle	7
12	Amphetamine	Ventral vHipp	Spironolactone	Corticosterone	8 *
13	Saline	Ventral vHipp	-	BSA-HBC	9 *
14	Saline	Ventral vHipp	-	BSA-Corticosterone	7
15	Saline	Dorsal vHipp	Vehicle	Corticosterone	5
16	Saline	Posterior Amygdala	Vehicle	Corticosterone	4

BSA: bovine serum albumin; HBC: 2-hydroxypropyl- β -cyclodextrin; vHipp: ventral hippocampus.

* One subject's data was excluded from use in this treatment group, based on its data being identified as a Grubbs outlier at two non-adjacent points farthest from zero in the treatment group's average datum. Therefore, the number of subjects whose data were used in this treatment group equals N-1.