CANDIDATE
REVIEWS

Glucocorticoid Receptor-Mediated Effects within the Extended Amygdala

Katherine Louderback

Abstract

Stress has been associated with a number of adverse effects, including anxiety disorders and addiction. Glucocorticoids are released during stress and bind to glucocorticoid receptors (GRs) present in every cell of the body. Limbic areas, such as the hippocampus, express high levels of GR, and the receptors have been extensively examined within these regions for their ability to alter synaptic plasticity. GRs within one limbic region, the extended amygdala - consisting of the shell of the nucleus accumbens (NAc-Sh), the central nucleus of the amygdala (CeA), and the bed nucleus of the stria terminalis (BNST), have received relatively less attention. Given the prominent role of the extended amygdala in the integration of stress and reward circuitry, and the demonstrated capability of GRs to alter synaptic plasticity, it is somewhat surprising that GRs within the region have not been studied to a greater extent. This review will examine current literature of GR-mediated effects within the extended amygdala. In short, GR activation seems to increase excitability in the extended amygdala. GRs facilitate dopamine release in response to drugs of abuse and stress within the NAc-Sh, facilitate fear conditioning and anxiety within the CeA, and decrease anxiety and maintain excitability within the BNST. Activation of GRs within the extended amygdala plays a pivotal role in response to stress and reward, and disregulation of GRs within the region could lead to maladaptive responses that typify anxiety disorders and addiction.

Keywords

Stress
Anxiety
Addiction
Plasticity
Glucocorticoid Receptor
Extended Amygdala
Nucleus Accumbens
Central Nucleus of the Amygdala
Bed Nucleus of the Stria Terminalis

Introduction

Stress is prevalent in everyday life, and can be defined as "a condition or feeling experienced when a person perceives that demands exceed the personal and social resources the individual is able to mobilize"[1]. While surmounting stress experienced is crucial to survival, maladaptive responses to stress or prolonged stress can prove detrimental. Stress has been associated with anxiety disorders such as generalized anxiety disorder, post-traumatic stress disorder (PTSD), and panic disorder, as well as addiction. Indeed, stress is a commonly cited reason for relapse to drug use in addicts, and diagnosis of an anxiety disorder is significantly associated with drug use[2]. A deeper understanding of the effects of stress on anxiety and reward circuitry will prove invaluable for treating and preventing anxiety and addictive behaviors such as stress-induced reinstatement of drug seeking.

The HPA Axis and Glucocorticoid Release

Upon exposure to a stressful stimulus, the hypothalamic-pituitary-adrenal (HPA) axis is activated. Corticotropin releasing factor (CRF) is first released from the parvocellular neurons of the hypothalamus to the pituitary through the portal system, triggering the release of adrenocorticotropin (ACTH)[3]. ACTH then acts upon the adrenal cortex, leading to the release of glucocorticoids (cortisol in humans and corticosterone in rodents; CORT) into the blood stream. CORT binds to two receptor types, the mineralocorticoid receptor (MR) and the GR, which has about 10-fold lower affinity for CORT than MR[4]. While MRs are almost entirely occupied under basal conditions, the lower affinity GR is only activated when high circulating concentrations of CORT are present – such as during the circadian peak of CORT release and during stress – and acts as negative feedback to inhibit the HPA axis[4]. Interestingly, it has also been demonstrated that administration of drugs of abuse and drug withdrawal leads to an increase in plasma CORT levels in rodents[5-6] and humans[7-9] and subsequent activation of GRs. Thus, GRs may play a role in drug addiction and withdrawal, in addition to its role in the stress response.

Complete knockout of GR is lethal in mice, indicating that this receptor is necessary for survival[10]. Site-specific genetic or pharmacological alterations in GR function have proved more useful in assessing the receptors' roles. GRs are expressed ubiquitously within the brain[4,11], and show highest expression within a number of limbic regions, including the hippocampus, CeA, BNST.

Effects of Glucocorticoid Receptor Activation

The effects of GR activation are extensive, and involve two distinct mechanisms: the genomic pathway and the non-genomic pathway[12]. In the genomic pathway, GRs within the cytosol bind CORT that diffuses freely through the plasma membrane. Unbound GR is maintained in a protein heterocomplex in the cytoplasm[13-14]. The binding of ligand leads to the increased phosphorylation of GR[15]. This phosphorylation allows GR to form a dimer with other transcription factors (TFs) or another GR[16-17] and translocate to the nucleus[15]. GRs can function as a homodimer or with other TFs in order to trans-activate or trans-repress genes. Within the nucleus, the ligand-bound GR homodimer is able to bind glucocorticoid response elements (GREs) that are present upstream of the promoter of a number of genes[18-19] or the homodimer can bind another TF in order to enhance or inhibit its transcription effect[20]. In fact, transcription can be altered by GRs in an estimated 1-2% of all genes[21].

It has been demonstrated that CORT is also able to induce rapid effects within minutes, a time frame not compatible with transcriptional effects of GR, via a putative membrane-bound GR (mGR). For instance, injection of the specific GR agonist dexamethasone to the paraventricular nucleus of the hypothalamus (PVN) is able to inhibit ACTH release in response to restraint stress within minutes[22]. Dexamethasone conjugated to BSA, which is membrane impermeable, is able to recapitulate this effect, giving further evidence for a mGR. Some debate does exist over the involvement of the classical GR in these rapid effects of CORT and dexamethasone. A possible yet-undetermined G-protein coupled receptor (GPCR) has been implicated as pituitary cell lines were able bind CORT and dexamethasone at the membrane with no apparent affinity for the GR antagonist RU486[23]. The binding of ligand in this study was blocked by pertussis toxin, which uncouples G-proteins from their GPCR[23]. However, GR antagonism has been shown to inhibit some rapid effects of CORT or dexamethasone[24]. In addition, possible mechanisms have been identified that could localize the classical GR to the membrane – such as the presence of a conserved palmitoylation site that has been shown to link the estrogen receptor to the membrane[25-26] and direct binding of GRs to caveolin[27].

GR-mediated Alterations in Synaptic Plasticity

A predominant effect of mGR activation is the recruitment of the endocannabinoid (eCB) system. Through the activation of PLC, GRs induce the production and retrograde release of the eCB 2-arachidonoylglycerol (2-AG) from the postsynaptic bouton[28]. 2-AG binds to the cannabinoid receptor (CB1), leading to a decrease in presynaptic neurotransmitter release[29]. In this way, mGRs can inhibit excitatory transmission[22,24] or inhibit GABAergic projections to glutamatergic neurons, thus disinhibiting excitatory transmission[30,31].

GRs have been implicated in alterations to synaptic plasticity and excitability. The hippocampus, in particular, has been studied extensively due to long-established electrophysiological recording techniques and high expression of both GRs and MRs. GRs are generally thought to reduce neuronal excitability within the hippocampus. For instance, in the CA1 region, activation of GRs mediates impairments in NMDA-dependent long-term potentiation (LTP) through a slow genomic mechanism[32-33], as well as facilitates metabotropic glutamate receptor-dependent long term depression (LTD) by lowering the threshold for LTD induction[34].

The Extended Amygdala

Although the involvement of GRs in many limbic areas has been examined[21,35], one region that has received relatively less attention is the extended amygdala. The extended amygdala consists of the shell of the nucleus accumbens (NAc-Sh), the central nucleus of the amygdala (CeA), and the bed nucleus of the stria terminalis (BNST)[36-38]. This region is situated at the crossroads of stress and reward circuitry and has thus been heavily implicated in the negative affect associated with stress disorders and withdrawal from drugs of abuse[39-41]. While the involvement of noradrenergic[42] and CRF signaling[43] within the extended amygdala in anxiety and addiction behaviors has been studied extensively, the role of GRs within this region is less clear. GRs within the extended amygdala are poised to alter synaptic plasticity and behavioral responses to stress and drugs of abuse. Given the prominent role of this region in stress response and HPA axis modulation, the high expression of GRs, and the proven ability of GR to alter synaptic transmission, the paucity of literature examining GRs within the extended amygdala is somewhat surprising. This review will explore current literature of GR-mediated effects within the extended amygdala, particularly in the context of anxiety and addiction behavior.

Nucleus Accumbens

GR-mediated Effects on Excitability

Within the NAc-Sh, GR activation has been associated with an increase in neuronal excitability and extracellular dopamine (DA) levels. It has long been known that the

NAc-Sh is more responsive to glucocorticoids than the NAc core region[44]. Recently, Campioni, et al.[45] demonstrated that the activation of GR leads to increased neuronal excitability in the NAc-Sh. The AMPA/NMDA ratio was increased in the shell following a cold water forced swim stress, and this effect was postulated to be GR-mediated, as it was mirrored with CORT application and abolished by RU486. Increased AMPAR miniature excitatory postsynaptic current (mEPSC) amplitude and reduced rectification of AMPA currents suggested that the increase in excitability was primarily due to an increase in the number of functional GluR2-containing AMPA receptors (AMPARs) present at the postsynaptic membrane[45]. In accordance, it has been demonstrated using cell culture models that long-term corticosterone application facilitates the lateral diffusion of AMPARs though a GR-mediated mechanism that can be blocked with a GR antagonist[46]. Because GR-facilitated integration of AMPARs to the post synaptic membrane is delayed and can be blocked by the protein synthesis inhibitor cycloheximide, it has been suggested that this effect is mediated through the genomic pathway[47]. The observation of increased AMPAR mEPSC amplitude in the NAc is mirrored by earlier work in the CA1 region of the hippocampus in which CORT or a selective GR agonist was able to enhance amplitude – but not frequency – of AMPAR mEPSCs[48]. The enhanced excitability within the NAc in response to GR activation could play a role in the increased drive to obtain a drug of abuse or in the ability of stress to evoke compulsive behaviors in addicted individuals.

GR Involvement in NAc Dopaminergic Signaling

Dopaminergic projections from the ventral tegmental area (VTA) to the NAc are crucial in the reward system[49], and it has been demonstrated that stressors are capable of initiating relapse to drug seeking in humans[50-51] and rodents[52-53]. Thus, the effect of stress on dopamine release within the NAc is an active area of research. Indeed, footshock stress is capable of increasing extracellular DA levels within the NAc shell in the rat, with no change in the NAc core[54]. This effect appears to be mediated through stress-induced CORT release, as adrenalectomy selectively lowers extracellular DA in the shell but not the core[44]. The DA spike observed in the NAc-Sh following stress or the administration of various drugs of abuse may be due in part to the activation of GRs. The hyperlocomotion and increase in extracellular NAc DA following systemic morphine administration can be attenuated by i.c.v. treatment with RU486[55]. In fact, direct infusion of RU486 to the NAc is capable of preventing conditioned place preference to morphine in rodents[56]. It has also been found that mice lacking GRs in D1 dopamine receptor-containing (dopaminoceptive) neurons showed decreased DA release in the NAc following cocaine administration[57]. These studies suggest that GRs have a central role in the release of DA within the NAc following drug administration.

The rise in extracellular DA within the NAc following stress or administration of drugs of abuse could be partially due to GRs in the VTA. Acute stress has been demonstrated to increase the AMPA/NMDA ratio in DA neurons within the VTA to a greater extent than acute administration of drugs of abuse[58], and this effect is blocked completely by RU486. Morphine, cocaine, nicotine, and forced swim stress impair the ability of GABAergic synapses to induce LTP onto VTA DA neurons. This leads to a disinhibition of these projections to the NAc, and increased DA release within the NAc[59]. The stress-induced impairment of GABAergic LTP is believed to be GR-mediated as it was attenuated by RU486. Further, direct infusion of CORT to the VTA is sufficient to induce NAc DA release, and this is effectively blocked by coapplication of RU486[60]. Because exposure to a stressor is capable of initiating DA release within the NAc through a GR-dependent mechanism, and because drugs of abuse have been demonstrated to induce a similar DA spike within the NAc, GRs within the NAc and regions projecting to the NAc are crucial for drug-seeking behaviors such as stress-induced reinstatement. Elevation in NAc DA following exposure to drugs of abuse is a key component in the early rewarding stages of drug addiction[39], thus xposure to a stressor after a long period of drug abstinence would cause a GR-mediated DA spike within the NAc that may be reminiscent of the rewarding effects of such early drug use. This could lead a previously addicted individual to return to their drug of choice in order to mediate the rewarding effects while simultaneously blocking the negative affect caused by the stressor.

Central Nucleus of the Amygdala

Regulation of the HPA Axis and GR Pharmacology:The CeA is well situated to contribute to the HPA axis response to a stressor. Electrical stimulation of the CeA leads to an HPA response with increased serum CORT[61]. Stimulation of GABAergic projections from the CeA to the BNST quiets BNST GABAergic projections to the PVN, thus leading to a disinhibition of the HPA response[62]. The CeA in particular has been implicated in the response to an acute stressor, and has been argued to mediate stimulus-specific fear-like behavior associated with such a stressor[63-64]. Indeed, ablation of the CeA completely eliminates cue-induced potentiation

of startle response to a footshock[65].

The CeA contains the densest expression of GR within the amygdala[11], potentially implicating GRs in the fear response mediated by the CeA. This has led some to examine the effects of GRs within the CeA on fear- and anxiety-like responses in rodents. Selective pharmacologic activation of GRs within the CeA elevates GR expression levels, increases anxiety-like behavior in the elevated plus maze (EPM), and increases the plasma CORT in response to the stress of exposure to the EPM[66]. Conversely, increased anxiety-like behavior on the EPM following implantation of a CORT pellet into the CeA can be blocked with co-administration of the GR antagonist RU486 into the CeA[67].

Genetic Deletion of GRs within the CeA

The development of a transgenic "floxed" mouse harboring loxP sites around exons 1 and 2 of the GR gene, NR3C1, has been an invaluable resource for determining region-specific involvement of GRs within the brain as the mouse exhibits a loss of GR expression in regions exposed to Cre-recombinase[68]. Lentivirally-mediated delivery of Cre-recombinase has allowed precise site-specific deletion of GR in this mouse line, and was recently utilized in order to examine the effect of GR deletion within the CeA (CeAGRKO) on anxiety- and fear-related behaviors[69-70]. The resulting 65% deletion of GRs within CeA neurons did not lead to alterations in locomotor activity or circulating plasma levels of CORT, and the apparent incongruity with the pharmacological HPA data described above may be attributable to the incomplete GR deletion observed in the present study. In accordance with the CeA's role in fear-like behavior, CeAGRKO mice exhibited impairment in both cue and contextual fear conditioning when compared to mice injected with lentiviral GFP[69]. Interestingly, the effect of GRs specifically within the CeA on fear-conditioning was further confirmed by mice with forebrain GR knockout (FBGRKO). These animals lack GRs in the cortex, hippocampus, BLA, and striatum but do not show GR disruption in the CeA or PVN[71]. FBGRKO mice do not demonstrate impairments in fear conditioning, indicating that the fear-like CeAGRKO phenotype is region-specific. Further, it was demonstrated that adrenalectomized mice show impairments in contextual fear conditioning, but have intact cue fear conditioning[72]. Thus, there may be mechanisms in place within other brain areas to account for global brain reductions in CORT signaling, as specific impairment of CeA GRs leads to a more robust fear conditioning phenotype than adrenalectomy. Thus, GRs within the CeA are capable of inducing HPA axis activation in response to an acutely stressful stimulus, which defies the classical role of GRs in the negative feedback of the HPA axis upon activation. Thus, elevated GR activation within this region could be postulated to cause chronically elevated CORT levels and future anxiety related disorders.

Bed Nucleus of the Stria Terminalis

Despite direct projections to the PVN and heavy GR expression, the roles of GRs within the BNST are very poorly understood. Dunn[73] demonstrated that electrical stimulation of the lateral aspect of the BNST decreased plasma CORT levels, presumably through activation of GABAergic projections to the PVN. Adrenalectomy decreases expression of CRF mRNA within the dorsolateral aspect of the BNST (dlBNST) and the CeA while increasing extracellular norepinephrine and DA in the dlBNST[74]. Our group has recently shown that chronic stress or systemic CORT administration increases anxiety-like behavior in mice and blunts LTP within the dlBNST[75]. It has long been known that chronic treatment with CORT downregulates GR function within the brain[76], leading to impaired negative feedback of the HPA axis. Thus, the inhibitory effect of CORT treatment on BNST plasticity may represent decreased GR function and reflect a role of GRs in the maintenance of excitability within the region. In support of this hypothesis, specific deletion of BNST GRs using the floxed GR mice described above exacerbated anxiety-like behavior in response to chronic stress as well decreasing locomotion in a stressful situation (EPM), mimicking the effects of chronic CORT administration described above (unpublished data). An important future study will examine alterations in excitability within the BNST of these mice, as well as the consequence of pharmacological manipulation of GRs on BNST excitability. We hypothesize that one role of GRs within the BNST is to maintain excitability in order to inhibit the HPA axis in response to a stressor. Thus, chronic stress exposure could downregulate GRs within the region and lead to hyperactivity of the HPA axis and associated conditions, such as anxiety-related disorders and addiction.

Conclusions

While GRs have been postulated to reduce excitability in other limbic regions such as the hippocampus[32-34], emerging literature seems to indicate that GRs in the extended amygdala strengthen excitability. GRs in this region likely mediate appropriate response to stressful events in healthy individuals, but dysregulation of GRs, through drug addiction or chronic stress for example, may trigger the development of maladaptive behaviors. . For instance, GR-mediated enhancement of glutamate response and extracel-

lular dopamine in the NAc might contribute to the salience of natural rewards under normal circumstances, but may lead to stress-induced relapse to addiction in individuals with altered extended amygdala circuitry as a result of previous drug use. Activation of CeA GRs causes anxiety-like responses and CORT release[66-67], whereas selective deletion of CeA GRs appears to alleviate fear-like behavior[69]. Thus, CeA GRs likely initiate an HPA response to a frightening stimulus by strengthening GABAergic projections to the BNST and disinbibiting the PVN. However, an individual with unusually high GR tone within the CeA would likely have a lowered threshold for fear-like responses and may be susceptible to anxiety disorders and addiction. Finally, GRs within the BNST may maintain excitability in order to inhibit the HPA axis following exposure to a stressor. However, in an individual that has undergone chronic stress, BNST GRs could be downregulated, and the ability of the BNST to inhibit the HPA axis would be impaired. This could result in anxiety disorders or stress-induced relapse to drug seeking, a behavior that is dependent upon the BNST[41]. GRs within the extended amygdala are important in mediating anxiety- or addiction-like responses to stress. Extensive further study of the effects of GRs within the region on plasticity and anxiety- and addiction-like behaviors will prove crucial to complete understanding of such maladaptive responses to stress.

References

1. Fink G, (2010). Stress Science: Neuroendocrinology, 1st Ed. San Diego: Academic Press.
2. Sareen J, Chartie M, Paulus MP and Stein MB (2006). Illicit drug use and anxiety disorders: findings from two community surveys. Psychiatry research, 142(1): 11-17.
3. Harris GW (1948). Neural control of the Pituitary Gland. Physiological Reviews, 28(2): 139-179.
4. Reul JM and de Kloet ER (1985). Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. Endocrinology, 117(6): 2505-2511.
5. Ellis FW (1966). Effect of Ethanol on Plasma Corticosterone Levels. Journal of Pharmacology and Experimental Therapeutics. 153(1): 121-127.
6. Levy AD, Li Q, Kerr JE., Rittenhouse PA, Milonas G, Cabrera TM, Battaglia G, Alvarez Sanz MC and Van de Kar LD(1991). Cocaine-induced elevation of plasma adrenocorticotropin hormone and corticosterone is mediated by serotonergic neurons. The Journal of pharmacology and experimental therapeutics, 259(2): 495-500.
7. Mello NK and Mendelson JH (1997). Cocaine's Effects on Neuroendocrine Systems: Clinical and Preclinical Studies. Pharmacology Biochemistry and Behavior, 57(3): 571-599.
8. Adinoff B, Ruether K, Krebaum S, Iranmanesh A and Williams MJ (2003). Increased salivary cortisol concentrations during chronic alcohol intoxication in a naturalistic clinical sample of men. Alcoholism, clinical and experimental research, 27(9): 1420-1427.
9. Mendelson JH, Sholar MB, Goletiani N, Siegel AJ and Mello NK (2006). Effects of Low and High Nicotine Cigarette Smoking on Mood States and the HPA Axis in Men. Neuropsychopharmacology, 30(9): 1751-1763.
10. Cole TJ, Blendy JA, Monaghan AP., Krieglstein K, Schmid W, Aguzzi A, Fantuzzi G, Hummler E, Unsicker K and Schultz G (1995). Targeted disruption of the glucocorticoid receptor gene blocks adrenergic chromaffin cell development and severely retards lung maturation. Genes & Development, 9(13): 1608-1621.
11. Morimoto M, Morita N, Ozawa H and Yokoyama K (1996). Distribution of glucocorticoid receptor immunoreactivity and mRNA in the rat brain: an immunohistochemical and in situ hybridization study. Neuroscience Research, 26: 235-269.
12. Prager EM and Johnson LR (2009). Stress at the synapse: signal transduction mechanisms of adrenal steroids at neuronal membranes. Science signaling, 2(86): 1-10.
13. Smith DF and Toft DO (1993). Steroid receptors and their associated proteins. Molecular endocrinology, 7(1): 4-11.
14. Morishima Y, Murphy PJ, Li DP, Sanchez ER and Pratt WB (2000). Stepwise assembly of a glucocorticoid receptor.hsp90 heterocomplex resolves two sequential ATP-dependent events involving first hsp70 and then hsp90 in opening of the steroid binding pocket. The Journal of biological chemistry, 275(24): 18054-18060.
15. Wang Z, Frederick J and Garabedian MJ (2002). Deciphering the phosphorylation "code" of the glucocorticoid receptor in vivo. The Journal of biological chemistry, 277(29): 26573-26580.
16. Kassel O and Herrlich P (2007). Crosstalk between the glucocorticoid receptor and other transcription factors: molecular aspects. Molecular and cellular endocrinology, 275(1-2): 13-29.
17. Presman DM, Alvarez LD, Levi V, Eduardo S, Digman MA, Martí MA, Veleiro AS, Burton G and Pecci A (2010). Insights on glucocorticoid receptor activity modulation through the binding of rigid steroids. PloS one, 5(10): e13279
18. Chandler VL, Maler BA and Yamamoto KR (1983). DNA sequences bound specifically by glucocorticoid receptor in vitro render a heterologous promoter hormone responsive in vivo. Cell, 33(2): 489-499.
19. Becker PB, Gloss B, Schmid W, Strahle U and Schutz G (1986). In vivo protein-DNA interactions in a glucocorticoid response element require the presence of the hormone, Nature, 324: 686-688.
20. Schoneveld OJLM, Gaemers IC and Lamers WH (2004). Mechanisms of glucocorticoid signalling. Biochimica et biophysica acta, 1680(2): 114-128.
21. Joëls M, Krugers HJ, Lucassen PJ and Karst H (2009). Corticosteroid effects on cellular physiology of limbic cells. Brain research, 1293: 91-100.
22. Evanson NK, Tasker JG, Hill MN, Hillard CJ and Herman JP (2010). Fast feedback inhibition of the HPA axis by glucocorticoids is mediated by endocannabinoid signaling. Endocrinology, 151(10): 4811-4819.
23. Maier C, Rünzler D, Schindelar J, Grabner G, Waldhäusl W, Köhler G and Luger A (2005). G-protein-coupled glucocorticoid receptors on the pituitary cell membrane. Journal of cell science, 118: 3353-3361.
24. Karst H, Berger S, Erdmann G, Schütz G and Joëls M (2010). Metaplasticity of amygdalar responses to the stress hormone corticosterone. Proceedings of the National Academy of Sciences of the United States of America, 107(32): 14449-14454.

25. Pedram A, Razandi M, Sainson RCA, Kim JK, Hughes CC and Levin ER (2007). A conserved mechanism for steroid receptor translocation to the plasma membrane. The Journal of biological chemistry, 282(31): 22278-22288.
26. Groeneweg FL, Karst H, de Kloet ER and Joëls M (2011). Rapid non-genomic effects of corticosteroids and their role in the central stress response. The Journal of endocrinology, 209(2): 153-167.
27. Matthews L, Berry A, Ohanian V, Ohanian J, Garside H and Ray D (2008). Caveolin mediates rapid glucocorticoid effects and couples glucocorticoid action to the antiproliferative program. Molecular endocrinology, 22(6): 1320-1330.
28. Di S, Malcher-Lopes R, Halmos KC and Tasker JG (2003). Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. The Journal of Neuroscience 23(12): 4850-4857.
29. Kano M, Ohno-shosaku T, Hashimotodani Y and Uchigashima M (2009). Endocannabinoid-Mediated Control of Synaptic Transmission. Physiological Reviews, 89: 309-380.
30. Patel S, Kingsley PJ, Mackie K, Marnett LJ and Winder DG (2009). Repeated Homotypic Stress Elevates 2-Arachidonoylglycerol Levels and Enhances Short-Term Endocannabinoid Signaling at Inhibitory Synapses in Basolateral Amygdala. Neuropsychopharmacology, 34(13): 2699-2709.
31. Hill MN, McLaughlin RJ, Pan B, Fitzgerald ML, Roberts CJ, Lee TTY, Karatsoreos IN, Mackie K, Viau V, Pickel VM, McEwen BS, Liu Q, Gorzalka BB and Hillard CJ (2011). Recruitment of Prefrontal Cortical Endocannabinoid Signaling by Glucocorticoids Contributes to Termination of the Stress Response. Journal of Neuroscience, 31(29): 10506-10515.
32. Krugers HJ, Alfarez DN, Karst H, Parashkouhi K, van Gemert N and Joëls M (2005). Corticosterone shifts different forms of synaptic potentiation in opposite directions. Hippocampus, 15(6): 697-703.
33. Wiegert O, Pu Z, Shor S, Joëls M and Krugers H (2005). Glucocorticoid receptor activation selectively hampers N-methyl-D-aspartate receptor dependent hippocampal synaptic plasticity in vitro. Neuroscience, 135(2): 403-411.
34. Chaouloff F, Hémar A and Manzoni O (2008). Local facilitation of hippocampal metabotropic glutamate receptor-dependent long-term depression by corticosterone and dexamethasone. Psychoneuroendocrinology, 33(5): 686-691.
35. Sousa N, Cerqueira JJ and Almeida OFX (2008). Corticosteroid receptors and neuroplasticity. Brain research reviews, 57(2): 561-570.
36. Alheid G and Heimer L (1988). New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: The striatopallidal, amygdaloid, and corticopetal components of substantia innominata. Neuroscience, 27(1): 1-39.
37. Cassell MD, Freedman LJ and Shi C (1999). The intrinsic organization of the central extended amygdala. Annals of the New York Academy of Sciences, 877: 217-241.
38. Alheid GF (2003). Extended Amygdala and Basal Forebrain. Annals of the New York Academy of Sciences, 985: 185-205.
39. Koob GF and Volkow ND (2010). Neurocircuitry of addiction. Neuropsychopharmacology, 35(1): 217-238.
40. Yamada H and Bruijnzeel AW (2011). Stimulation of α2-adrenergic receptors in the central nucleus of the amygdala attenuates stress-induced reinstatement of nicotine seeking in rats. Neuropharmacology, 60(2-3): 303-311.
41. Briand LA, Vassoler FM, Pierce RC, Valentino RJ and Blendy JA (2010). Ventral tegmental afferents in stress-induced reinstatement: the role of cAMP response element-binding protein. The Journal of neuroscience, 30(48): 16149-16159.
42. Smith RJ and Aston-Jones G (2008). Noradrenergic transmission in the extended amygdala: role in increased drug-seeking and relapse during protracted drug abstinence. Brain structure & function, 213(1-2), 43-61.
43. Koob GF (2010). The role of CRF and CRF-related peptides in the dark side of addiction. Brain research, 1314: 3-14.
44. Barrot M, Marinelli M, Abrous DN, Rougé-Pont F, Le Moal M and Piazza PV (2000). The dopaminergic hyper-responsiveness of the shell of the nucleus accumbens is hormone-dependent. The European journal of neuroscience, 12(3): 973-979.
45. Campioni MR, Xu M and McGehee DS (2009). Stress-induced changes in nucleus accumbens glutamate synaptic plasticity. Journal of neurophysiology, 101(6): 3192-3198. The authors demonstrated the ability of stress and pharmacological GR activation to increase NAc-SH excitability through enhanced AMPA/NMDA ratio, mediated by recruitment of GluR2-containing AMPA receptors to the postsynaptic membrane.
46. Groc L, Choquet D and Chaouloff F (2008). The stress hormone corticosterone conditions AMPAR surface trafficking and synaptic potentiation. Nature neuroscience, 11(8), 868-870.
47. Martin S, Henley JM, Holman D, Zhou M, Wiegert O, van Spronsen M, Joels M, Hoogenraad CC and Krugers HJ (2009). Corticosterone alters AMPAR mobility and facilitates bidirectional synaptic plasticity. PloS one, 4(3): e4714.
48. Karst H and Joëls M (2005). Corticosterone slowly enhances miniature excitatory postsynaptic current amplitude in mice CA1 hippocampal cells. Journal of neurophysiology, 94(5): 3479-34786.
49. Willuhn I, Wanat MJ, Clark JJ and Phillips PEM (2010). Dopamine Signaling in the Nucleus Accumbens of Animals Self-Administering Drugs of Abuse. Current Topics of Behavioral Neuroscience, 3: 29-71.
50. Kosten TR, Rounsaville BJ and Kleber HD (1986). A 2.5 Year Follow-up of Depression, Life Crises, and Treatment Effects on Abstinence Among Opioid Addicts. Arch Gen Psychiatry, 43: 733-738.
51. Brown SA, Vik PV, Patterson TL, Grant I and Schuckit MA (1995). Stress, Vulnerability and Adult Alcohol Relapse. JSAD. 56(5): 538-545.
52. Erb S, Shaham Y and Stewart J (1996). Stress reinstates cocaine-seeking behavior after prolonged extinction and a drug-free period. Psychopharmacology, 128(4): 408-412.
53. Shaham Y and Stewart J (1995). Stress reinstates heroin-seeking in drug-free animals: an effect mimicking heroin, not withdrawal. Psychopharmacology, 119(3): 334-341.
54. Kalivas PW and Duffy P (1995). Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress. Brain research, 675(1-2): 325-328.
55. Marinelli M, Aouizerate B, Barrot M, Le Moal M and Piazza PV (1998). Dopamine-dependent responses to morphine depend on glucocorticoid receptors. Proceedings of the National Academy of Sciences of the United States of America, 95(13): 7742-7747.
56. Dong Z, Han H, Wang M, Xu L, Hao W and Cao J (2006). Morphine Conditioned Place Preference Depends on Glucocorticoid Receptors in Both Hippocampus and Nucleus Accumbens. Hippocampus, 16: 809-813.

This article demonstrates the essential role of NAc GRs in addiction-like drug-seeking behavior in rodents. Systemic administration of the GR antagonist RU486, as well as cannula delivered RU486 directly into the NAc or the hippocampus, blocked morphine conditioned place preference - a highly utilized model of drug-seeking - in rats.

57. Barik J, Parnaudeau S, Saint Amaux AL, Guiard BP, Golib Dzib JF, Bocquet O, Bailly A, Benecke A and Tronche F (2010). Glucocorticoid receptors in dopaminoceptive neurons, key for cocaine, are dispensable for molecular and behavioral morphine responses. Biological psychiatry, 68(3): 231-239.

58. Saal D, Dong Y, Bonci A and Malenka RC (2003). Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. Neuron, 37(4): 577-582.

59. Niehaus JL, Murali M and Kauer JA (2010). Drugs of abuse and stress impair LTP at inhibitory synapses in the ventral tegmental area. The European journal of neuroscience, 32(1): 108-117.

60. Tye SJ, Miller AD and 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(11): 982-990

61. Weidenfeld J, Itzik A and Feldman S (1997). Effect of glucocorticoids on the adrenocortical axis responses to electrical stimulation of the amygdala and the ventral noradrenergic bundle. Brain research, 754(1-2): 187-194.

62. Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC and Cullinan WE (2003). Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo–pituitary–adrenocortical responsiveness. Frontiers in Neuroendocrinology, 24(3): 151-180.

63. Davis M and Shi C (1999). The extended amygdala: are the central nucleus of the amygdala and the bed nucleus of the stria terminalis differentially involved in fear versus anxiety? Annals of the New York Academy of Sciences, 877: 281-291.

64. Walker DL, Miles LA and Davis M (2009). Selective participation of the bed nucleus of the stria terminalis and CRF in sustained anxiety-like versus phasic fear-like responses. Progress in neuro-psychopharmacology & biological psychiatry, 33(8): 1291-1308.

65. Hitchcock J and Davis M (1986). Lesions of the amygdala, but not of the cerebellum or red nucleus, block conditioned fear as measured with the potentiated startle paradigm. Behavioral neuroscience, 100(1): 11-22.

66. Weiser MJ, Foradori CD and Handa RJ (2010). Estrogen receptor beta activation prevents glucocorticoid receptor-dependent effects of the central nucleus of the amygdala on behavior and neuroendocrine function. Brain research, 1336: 78-88.

67. Myers B and Greenwood-Van Meerveld B (2007). Corticosteroid receptor-mediated mechanisms in the amygdala regulate anxiety and colonic sensitivity. American journal of physiology. Gastrointestinal and liver physiology, 292(6): G1622-G1629.

68. Brewer JA, Khor B, Vogt SK, Muglia LM, Fujiwara H, Haegele KE, Sleckman BP and Muglia LJ (2003). T-cell glucocorticoid receptor is required to suppress COX-2-mediated lethal immune activation. Nature medicine, 9(10): 1318-1322.

69. Kolber BJ, Roberts MS, Howell MP, Wozniak DF, Sands MS and Muglia LJ (2008). Central amygdala glucocorticoid receptor action promotes fear-associated CRH activation and conditioning. Proceedings of the National Academy of Sciences of the United States of America, 105(33): 12004-12009.

The authors lentivirally administered Cre-recombinase into the CeA of mice harboring loxP sites around the GR gene in order to selectively delete GRs from the region, and saw impairments in context- and cue-conditioned fear behavior and reduced CRF expression in response to stress, demonstrating the involvement of GRs in these effects.

70. Arnett MG, Kolber BJ, Boyle MP and Muglia LJ (2011). Behavioral insights from mouse models of forebrain--and amygdala-specific glucocorticoid receptor genetic disruption. Molecular and cellular endocrinology, 336(1-2): 2-5.

71. Boyle MP, Brewer JA, Funatsu M, Wozniak DF, Tsien JZ, Izumi Y and Muglia LJ (2005). Acquired deficit of forebrain glucocorticoid receptor produces depression-like changes in adrenal axis regulation and behavior. Proceedings of the National Academy of Sciences of the United States of America, 102(2): 473-478.

72. Pugh CR, Tremblay D, Fleshner M and Rudy JW (1997). A selective role for corticosterone in contextual-fear conditioning. Behavioral neuroscience, 111(3): 503-511.

73. Dunn JD (1987). Plasma corticosterone responses to electrical stimulation of the bed nucleus of the stria terminalis. Brain research, 407(2): 327-331.

74. Santibañez M, Gysling K and Forray MI (2005). Adrenalectomy decreases corticotropin-releasing hormone gene expression and increases noradrenaline and dopamine extracellular levels in the rat lateral bed nucleus of the stria terminalis. Journal of neuroscience research, 81(1): 140-152.

75. Conrad KL, Louderback KM, Gessner CP and Winder DG (2011). Stress-induced alterations in anxiety-like behavior and adaptations in plasticity in the bed nucleus of the stria terminalis. Physiology & behavior, 104(2): 248-256.

Our paper demonstrates possible involvement of GRs in synaptic plasticity within the dlBNST as chronic stress-mediated anxiety-like behavior and blunting of LTP within the dlBNST was mirrored with chronic CORT administration.

76. Spencer RL, Miller AH, Stein M and McEwen BS (1991). Corticosterone regulation of type I and type II adrenal steroid receptors in brain, pituitary, and immune tissue. Brain research, 549(2): 236-246.

Further Information

Danny Winder Lab Website: http://www.mc.vanderbilt.edu/root/vumc.php?site=winder