Stress-Induced Changes in Nucleus Accumbens Glutamate Synaptic Plasticity

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Campioni MR, Xu M, McGehee DS. Stress-induced changes in nucleus accumbens glutamate synaptic plasticity. J Neurophysiol 101: 3192–3198, 2009. First published August 8, 2009; doi:10.1152/jn.91111.2008. Stress hormones released in the CNS following exposure to unavoidable, aversive stimuli have been shown to alter the physiology of neurons in multiple brain regions including hippocampus, amygdala, prefrontal cortex, and ventral tegmental area. The nucleus accumbens (NAc), a motor-limbic interface linked to motivation and reward, receives inputs from each of these stress-affected brain regions, raising the possibility that its function might also be altered in response to stress. To assess potential stress-induced plasticity in the NAc, we exposed adult mice to daily cold water forced swim for 2 consecutive days and conducted electrophysiological experiments assessing glutamate receptor function in brain slices taken 18–24 h following the second swim. We found that AMPA receptor (AMPAR)/N-methyl-D-aspartate receptor (NMDAR) ratios, a measure of synaptic strength, were increased in the NAc shell but not core medium spiny neurons (MSNs) in stressed animals relative to controls. This effect was blocked by preadministration of glucocorticoid receptor (GR) antagonist RU486, suggesting that the observed changes are dependent on corticosteroid signaling. The role of corticosterone (CORT) in the corticosteroid signaling. The role of corticosterone (CORT) in the mesocorticolimbic circuit is the activation of the hypothalamic-pituitary-adrenal (HPA) axis. Following exposure to aversive or threatening stimuli, a series of hormones are released, beginning with corticotrophin-releasing factor (CRF) from the paraventricular nucleus of the hypothalamus, adrenocorticotropic hormone from the anterior pituitary, and glucocorticoids (GCs) from the adrenal cortex (McEwen et al. 1986). These hormones affect physiology throughout the organism, including the CNS (Sousa et al. 2000).

Institutional Animal Care and Use Committee and conform to methods described in the authors’ Animal Care and Use protocols.

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Animals and in vivo manipulations

Eight- to 10-wk-old C57BL/6J mice (20–25 g, Jackson Labs, Ben Harbor, ME) were acclimated to their home cage for >7 days before testing. For 2 days preceding brain slice electrophysiology, all animals were singly housed. Animals were stressed using once daily forced swim for 5 min in 4–6°C water for 2 consecutive days. One exposure to this stressor increases AMPA receptor (AMPA/R) N-methyl-D-aspartate receptor (NMDAR) ratios in VTA DA neurons (Saal et al. 2003). The effects of GR receptor blockade were tested by intraperitoneal administration of GR antagonist RU486 (40 mg/kg in DMSO; Tocris, Ellisville, MO) 30 min before cold water stress. The half-life of RU486 is 25–28 h, so the dose administered on day 2 was reduced to 25 mg/kg. The effects of CORT were assessed using once daily intraperitoneal injection of vehicle (50% DMSO, 50% saline) or 10 or 25 mg/kg CORT (Sigma, St. Louis, MO). Animals were killed, and brains slices were prepared 18–24 h following the final injection or swim.

Slice preparation

Chemicals were obtained from Sigma, unless otherwise specified. Animals were anesthetized using inhaled isofluorane and rapidly decapitated into ice cold sucrose-artificial cerebrospinal fluid (ACSF) with 1 mM ascorbic acid (in mM: 252 sucrose, 2.5 KCl, 1 MgCl2, 2.5 CaCl2, 20 glucose, and 25 NaHCO3). Sagittal slices (250 μM) were taken at the level of the NAc (3–4 slices per animal), transferred to a perfusion chamber with normal ACSF (sucrose replaced with 125 mM NaCl, 2.5 KCl, 1 MgCl2, 2.5 CaCl2, 20 glucose, 1 NaH2PO4, and 25 NaHCO3), saturated with 95% O2/5% CO2. The perfusion of normal ACSF (in mM: 125 NaCl, 2.5 KCl, 1 MgCl2, 2.5 CaCl2, 20 glucose, 1 NaH2PO4, and 25 NaHCO3) was used at the level of the NAc (3–4 slices per animal), transferred to a perfusion chamber with normal ACSF (sucrose replaced with 125 mM NaCl), containing 1 mM ascorbic acid, heated to 32°C, to a perfusion chamber with normal ACSF (sucrose replaced with 125 mM NaCl, 2.5 KCl, 1 MgCl2, 2.5 CaCl2, 20 glucose, and 25 NaHCO3). Sagittal slices (250 μM) were taken at the level of the NAc (3–4 slices per animal), transferred to a perfusion chamber with normal ACSF (sucrose replaced with 125 mM NaCl), containing 1 mM ascorbic acid, heated to 32°C, and perfused at 20 ml/min. Slices were equilibrated for 30 min to 1 h before electrophysiology. All solutions were saturated with 95% O2/5% CO2.

Electrophysiology

Cells were visualized with a fixed-stage upright microscope (Zeiss, Oberkochen, Germany) using infrared-differential interference contrast microscopy. During recording, slices received constant bath perfusion of normal ACSF (in mM: 125 NaCl, 2.5 KCl, 1 MgCl2, 2.5 CaCl2, 20 glucose, and 25 NaHCO3). Sagittal slices (250 μM) were taken at the level of the NAc (3–4 slices per animal), transferred to a perfusion chamber with normal ACSF (sucrose replaced with 125 mM NaCl), containing 1 mM ascorbic acid, heated to 32°C, and perfused at 20 ml/min. Slices were equilibrated for 30 min to 1 h before electrophysiology. All solutions were saturated with 95% O2/5% CO2.

To examine the effects of stress on glutamatergic transmission in the NAc, we exposed adult male C57BL/6J mice to 5-min cold water forced swim for 2 consecutive days. Eighteen to 24 h following the second swim, animals were killed for electrophysiology. Sagittal brain slices at the level of the NAc were taken and used for whole cell patch-clamp recordings.

Cold water stress enhances synaptic strength in NAc shell MSNs

The status of the glutamatergic inputs to NAc neurons was assayed by measuring the ratio of the AMPAR component of the synaptic currents to the NMDAR component (Fig. 1A). To measure the AMPAR currents, cells were held at −70 mV, and EPSCs were evoked using a bipolar stimulating electrode and five additional EPSCs were evoked. Evoked EPSC data were analyzed off-line, using Clampex 8.2 (Molecular Devices). AMPAR values for a cell were calculated by averaging the current traces recorded at −70 mV and measuring the amplitude and timing of the averaged peak. The +40-mV traces were also averaged, and the NMDAR current was determined by sampling a 10-ms window 40 ms after the peak AMPAR current, when the AMPA current has decayed. To assess AMPAR EPSC I-V properties, recordings were made with 0.1 mM spermine (Tocris) in the internal solution and NMDAR antagonist 50 μM d-AP5 (Tocris) in the external solution. EPSCs were evoked at multiple holding potentials (−70, −40, 0, 20, 40, and 60 mV). Rectification index values were obtained using by dividing the average peak current evoked at −70 mV by the average peak current elicited at +40 mV. The effects of stress on AMPAR subunit composition were assessed using 100–200 μM of GluR2-lacking AMPAR antagonist 1-naphthylacetyl spermine trihydrochloride (Naspm). The contribution of GluR2-lacking AMPARs was calculated by dividing the amplitude of the evoked EPSC measured following 8–10 min of Naspm application by the EPSC value obtained before drug wash in.

For analysis of miniature excitatory postsynaptic currents (mEPSCs), the internal solution contained (in mM) 142 K-glucuronate, 1 KCl, 10 HEPES, 5 ATP, and 0.1 GTP; pH 7.4; mOsm 315–325, with 1 μM TTX in the bath (Alomone, Jerusalem, Israel). To analyze dual component (AMPA and NMDA) mEPSCs, slices were perfused in a Mg2+-free external solution. Cells were held at −70 mV, and mEPSCs were recorded for 2 min, after which 50 μM d-AP5 was applied for 8–10 min, and then recorded again for 2 min (Kourrich et al. 2007). Average mEPSCs in the presence and absence of d-AP5 were subtracted to estimate average NMDA mEPSC amplitudes. All mEPSC data were analyzed using Minianalysis software (Synaptosoft, Decatur, GA); mEPSCs were defined as inward currents with amplitudes >5 times RMS noise.

Statistical analysis

A 4 × 1 ANOVA was used to evaluate main effects of treatment in AMPAR/NMDAR ratio datasets. Fisher’s protected least significant difference (PLSD) post hoc tests were used to assess effects between treatment groups. Cumulative probability distributions were analyzed using the Kolmogorov-Smirnov (K-S) test. Student’s unpaired t-test were used to assess group differences in mEPSC amplitude, mEPSC frequency, rectification index, Naspm block, and subtracted NMDA current datasets. Any individual measurements that fell beyond 2 SD from the group mean were identified as outliers and removed from the analyses. All statistical tests were performed using Systat software (SPSS, Chicago, IL). Data were averaged by animal and represented as group means ± SE.
placed rostral to the NAc. Cells were depolarized to +40 mV, and EPSCs were evoked again. NMDAR current was defined by a 10-ms window in the EPSC recorded at +40 mV starting 40 ms after the AMPAR peak measured at −70 mV. The timing of the 10-ms window coincides with a near total decay of AMPA-mediated EPSCs, providing an uncontaminated measurement of NMDAR EPSCs. The ratio of the AMPA peak at −70 mV, and the calculated NMDA value from the +40 mV trace was used to evaluate stress-induced changes in synaptic strength in NAc MSNs.

Cold water stress induced an increase in AMPAR/NMDAR ratios measured in the NAc shell (Fig. 1B; *P < 0.02; control, 3.42 ± 0.23, n = 17 cells, 6 mice; stress, 4.64 ± 0.35, n = 16 cells, 6 mice). This is consistent with stress-induced long-term potentiation (LTP) of the excitatory synaptic inputs to these cells. Administration of the GR antagonist, RU486 (40 mg/kg), 30 min before the forced swim completely blocked the stress effects (RU486 + stress, 2.55 ± 0.20, n = 15 cells, 5 mice), suggesting that GC signaling is essential for the observed stress-induced plasticity. Treatment with RU486 alone did not affect synaptic strength in NAc shell MSNs (RU486, 3.367 ± 0.54, n = 15 cells, 5 mice). Interestingly, there was a trend toward a decrease in AMPAR/NMDAR ratio when comparing the RU486 plus stress group to either controls (*P < 0.1) or to animals receiving RU486 alone (*P < 0.13). This raises the possibility that, in the absence of GR activation, stress might decrease synaptic efficacy in NAc shell MSNs. In contrast to the shell, we saw no stress-induced changes in synaptic strength when recording from neurons in the NAc core (Fig. 1C; control, 3.58 ± 0.18, n = 18 cells, 6 mice; stress, 3.13 ± 0.44, n = 15 cells, 5 mice; RU486, 3.01 ± 0.32, n = 15 cells, 5 mice; RU486 + stress, 2.729 ± 0.24, n = 14 cells, 6 mice). The subregion specificity of this change was not surprising, given previous studies that showed stress and GC-mediated increases in NAc dopamine overflow only in the NAc shell (Barrot et al. 2000; Kalivas and Duffy 1995).

Exogenous corticosterone enhances synaptic strength in NAc shell MSNs

Given that GR activation is apparently necessary for stress-induced enhancement of corticocumbens synaptic strength, we tested the effect of exogenous CORT administration on AMPAR/NMDAR ratios in NAc shell MSNs. Mice were given intraperitoneal injections of vehicle (DMSO and sterile saline), 10 mg/kg CORT, or 25 mg/kg CORT once daily for 2 consecutive days. Eighteen to 24 h following the second injection, animals were killed for electrophysiology as described above. These experiments showed an inverted U-shaped relationship between synaptic strength and CORT dose. Specifically, mice that received 10 mg/kg CORT showed increased AMPAR/NMDAR ratios in NAc shell MSNs compared with those recorded in vehicle-injected controls (Fig. 2; *P < 0.003; vehicle, 2.83 ± 0.21, n = 14 cells, 5 mice; 10 mg/kg CORT, 5.04 ± 0.62, n = 15 cells, 5 mice) and 25 mg/kg CORT-treated animals (P < 0.035; 25 mg/kg CORT, 3.65 ± 0.24, n = 14 cells, 5 mice). AMPAR/NMDAR ratios recorded from animals given 25 mg/kg CORT were not significantly different from vehicle controls (Fig. 2; *P < 0.18). While the loss of CORT’s ability to enhance synaptic strength at the 25 mg/kg dose was...
unexpected, it parallels previous findings that show primed burst-induced hippocampal LTP is facilitated by low to intermediate CORT levels but not with higher concentrations (Diamond et al. 1992).

Cold water stress increases AMPA mEPSC amplitude in NAc shell MSNs

AMPAR/NMDAR ratios are a useful metric for assessing changes in synaptic strength, but the observed changes can result from alterations in AMPARs, NMDARs, or both. To identify any stress-induced changes in AMPA-mediated currents in the MSNs, mEPSCs were recorded in the presence of TTX (1 μM) at −70 mV (Fig. 3A). Cumulative probability plots (Fig. 3B) and frequency histograms (Fig. 3C) of AMPAR mEPSC amplitudes show a shift to larger events in the recordings from NAc shell MSNs of stressed animals relative to controls (K-S test; P < 0.022; control, n = 10 cells, 5 mice; stress n = 10 cells, 5 mice). Consistent with these findings, mean mEPSC amplitude was larger in stressed mice (Fig. 3C, inset; P < 0.02) Comparison of interevent interval distributions (Fig. 3, D and E) and mean mEPSC frequencies (Fig. 3E, inset) showed no differences between groups, suggesting that stress does not affect presynaptic release probability. These data support the hypothesis that stress enhances synaptic strength in NAc shell MSNs by increasing the number or function of AMPARs on the plasma membrane. Similar results have been previously reported in hippocampal slices, where exogenous CORT enhances mEPSC amplitude without affecting event frequency (Karst and Joels 2005).

Cold water stress reduces AMPA current rectification in NAc shell MSNs

Subunit composition determines the rectification and ion permeability characteristics of individual AMPARs (Burnashev et al. 1992; Verdoorn et al. 1991). Specifically, GluR2 subunits undergo a high efficacy posttranscriptional RNA editing process that leads to the replacement of an uncharged glutamine residue with a charged arginine residue in the second transmembrane segment of the protein (Sommer et al. 1991). AMPARs that contain edited GluR2 subunits have a linear I-V relationship and low permeability to divalent cations, whereas GluR2-lacking AMPARs show inward rectification and permeability to Ca²⁺ (Burnashev et al. 1992; Verdoorn et al. 1991). To assess if stress-induced enhancement of AMPA currents in NAc shell MSNs was accompanied by changes in rectification, we bath applied d-AP5 (50 μM) to block NMDARs, and voltage clamped the cells with spermine (0.1 mM) in the internal solution to limit possible dilution of
intracellular polyamines. EPSCs were evoked at holding potentials ranging from −70 to +40 mV (Fig. 4A). We calculated the ratio between the peak current at −70 and +40 mV to determine the AMPAR current rectification index. Using this method, we found that AMPAR currents in the NAc shell MSNs of stressed animals showed less rectification compared with controls (Fig. 4B; *P < 0.05; control, 3.14 ± 0.42, n = 14 cells, 5 mice; stress, 2.198 ± 0.14, n = 14 cells, 6 mice).

To further study the effects of stress on NAc shell MSN glutamate receptor subunit composition, we used Naspm, a blocker of GluR2-lacking AMPARs. Neurons were held at −70 mV, and EPSCs were evoked at 0.1 Hz. After recording stable baseline currents, 100–200 μM Naspm was applied to the slice for 8–10 min, and EPSCs were evoked again (Fig. 4C). Comparing the ratio of the evoked current amplitudes in the presence and absence of Naspm shows more GluR2-lacking receptors in control relative to stressed mice (Fig. 4D; *P < 0.01; control, 0.76 ± 0.03, n = 11 cells, 6 mice; stress, 0.89 ± 0.02, n = 8 cells, 5 mice). Together, these data suggest that following 2 consecutive days of cold water stress, there is a net increase in AMPARs that contain GluR2 subunits in NAc shell MSNs. Interestingly, this finding parallels data from a recent study showing that exposure of cultured hippocampal neurons to CORT leads to increased synaptic incorporation of GluR2-containing AMPARs via a GC-dependent mechanism (Groc et al. 2008).

Cold water stress does not alter NMDAR mEPSC amplitude in NAc shell MSNs

To evaluate potential changes in NMDAR function in NAc shell MSNs following cold water stress, we used a subtracted averages technique that has been used previously to assess NMDAR-mediated current amplitude (Kourrich et al. 2007; Thomas et al. 2001). Slices were bathed in an external solution containing TTX to block action potentials and zero external Mg²⁺ to unblock NMDARs. NAc shell MSNs were patched, and 2 min of mEPSC activity was recorded (Fig. 5A). Excitatory synaptic currents recorded under these conditions are mediated by both AMPARs and NMDARs. Competitive NMDAR antagonist D-AP5 (50 μM) was bath-applied for 8–10 min. Following blockade of NMDAR activity, another 2 min of mEPSCs were recorded (Fig. 5A). Events recorded before D-AP5 treatment were averaged for each cell, yielding an average dual-component mEPSC. By averaging the mEPSCs recorded after NMDAR block and subtracting this trace from the dual-component mEPSC trace obtained from the same cell, we generated a subtracted average NMDAR mEPSC (Fig. 5B). This subtracted trace represents the average contribution to NMDAR-mediated currents to mEPSCs recorded in the absence of extracellular Mg²⁺. Using this method, we observed no difference in NMDA current amplitude in control versus stressed mice (Fig. 5C; *P < 0.5; control, 3.492 ± 0.39 pA, n = 8 cells, 4 mice; stress, 3.80 ± 0.30 pA, n = 8 cells, 4 mice).
to have increased linearity in their I-V relationship and reduced Naspm sensitivity, relative to controls, implying that stress increased the number or function of GluR2-containing AMPARs in the NAc shell. Although our control I-V data differ somewhat from those reported in some previous studies (Conrad et al. 2008; Kourrich et al. 2007), there are important differences in species, animal age, and/or preparation that may account for this divergence. Notably, our experiments are done in adult animals, and recent publications have shown robust changes in EPSC properties in NAc MSNs during postnatal development (Kasanetz and Manzoni 2009; Zhang and Warren 2008). Together these data suggest that the observed change in the AMPAR/NMDAR ratio following stress was driven by increased number or function of synaptic AMPARs. Stress had no effect on NMDAR mEPSC amplitude in our experiments, suggesting that the shown changes in NAc shell MSN synaptic strength are driven primarily by enhancement of AMPA-mediated currents.

Previous studies have shown that stress can affect the physiology of the NAc. Acute restraint stress elevates c-Fos protein expression in numerous reward-related brain regions, including NAc shell and core (Perrotti et al. 2004). In the same study, chronic stress increased ΔFosB expression throughout the accumbens (Perrotti et al. 2004). These data have potential relevance to our study, because ΔFosB has been shown to increase GluR2 expression in the NAc (Kelz et al. 1999).

Our demonstration that cold water stress selectively enhances synaptic strength in the NAc shell is paralleled by data from previous studies showing shell-specific effects of stress and stress hormones. In rats, in vivo microdialysis has shown that DA levels are elevated in the NAc shell, but not the core, during the 20 min following foot shock stress (Kalivas and Duffy 1995). DA overflow into the NAc is also induced following administration of cocaine or morphine (Barrot et al. 1999). Adrenalectomy (ADX) selectively reduces the increase in NAc shell (Barrot et al. 2000). Stress differentially affects Fos-like immunoreactivity (Fos-LI) in the rat striatum, with NAc shell showing a larger increase than either NAc core or caudate-putamen (Barrot et al. 1999). Fos-LI is also elevated in rat NAc following an injection of cocaine, a DA reuptake inhibitor (Barrot et al. 1999). Although cocaine-induced Fos-LI is seen in both the shell and core, ADX selectively reduces the increase in NAc shell (Barrot et al. 2000). ADX, however, does not affect D1 receptor agonist-induced Fos-LI in the NAc shell (Barrot et al. 2000). Together, these data suggest that GC regulation of shell-projecting VTA DA neurons may contribute to the plasticity reported here.

The NAc is essential for the expression of addiction-like behaviors in animal models. Moreover, perturbations to an animal’s stress state or GC levels can affect drug self-administration, locomotor sensitization to psychostimulants, and reinstatement of drug seeking (Marinelli and Piazza 2002). Our data are interesting in the context of drug addiction, because withdrawal from cocaine induces similar synaptic changes to those we reported following cold water stress (Kourrich et al. 2007). In mouse brain slices taken after 2 wk of withdrawal from a sensitizing regimen of cocaine, AMPAR currents are enhanced at PFC-NAc shell synapses (Kourrich et al. 2007). Similarly, rats sensitized to cocaine have increased surface expression of AMPARs, 21 days after the final drug injection (Boudreau and Wolf 2005; Boudreau et al. 2007). Interestingly, viral-mediated gene transfer experiments in mouse have shown that increased expression of Glur2 in NAc

**DISCUSSION**

These data indicate that stress enhances synaptic strength in the NAc shell, a structure thought to be involved in motivation and reward. Enhancement of AMPAR-mediated excitatory drive to MSNs in the accumbens might contribute to the effects of stress on reward-related behaviors. We observed an increase in AMPAR/NMDAR ratios in NAc shell MSNs, but not core MSNs following 2 days of cold water stress. This increase was blocked by intraperitoneal preadministration of GR antagonist RU486, implicating GC signaling as a necessary component in the demonstrated change. Furthermore, CORT was shown to be sufficient to enhance corticoaccumbens synaptic strength because intraperitoneal injections of exogenous CORT also increased AMPAR/NMDAR ratios in NAc shell MSNs. We showed that the stress-induced change in AMPAR/NMDAR ratio was accompanied by increased AMPAR mEPSC amplitude without a corresponding change in mEPSC frequency. Additionally, AMPAR EPSCs from stressed animals were shown

**FIG. 5.** Stress has no effect on NMDAR mEPSCs. A: example of averaged mEPSCs from NAc shell MSNs, recorded in 0 Mg^{2+} external solution, before and after d-AP5 (50 μM). Scale bar: 10 pA, 100 ms. B: example of averaged mEPSCs before (black) and after (dark gray) d-AP5 in a representative MSN, with the subtracted average NMDAR mEPSC (light gray). C: average of subtracted average NMDAR mEPSC amplitudes showing no difference between control and stressed mice (P < 0.5).

Together with the observed increase in AMPAR mEPSC amplitude, these data suggest that the stress-induced changes in AMPAR/NMDAR ratios in NAc shell MSNs are driven by enhanced AMPAR number and/or function.
enhances the rewarding effects of cocaine (Kelz et al. 1999). The ability of both stress and cocaine withdrawal to increase AMPAR-mediated transmission in the NAc is paralleled by the ability of both stress and extended withdrawal to enhance reinstatement of drug seeking (Shaham et al. 2003). Additionally, intra-NAc infusions of AMPA induce reinstatement in animals that have undergone extinction training from drug self-administration, further suggesting that NAc AMPARs are critical for reinstatement (Suto et al. 2004). Therefore we hypothesize that GR activation and withdrawal might similarly contribute to the motivational effects of psychostimulants and reinstatement of drug seeking via enhanced AMPAR-mediated neurotransmission in NAc shell MSNs.

This study showed that cold water stress can enhance synaptic strength in NAc shell MSNs via a GR-dependent mechanism. Although it is well-established that stress and GCs alter DA transmission and fos expression in the NAc (Barrot et al. 1999, 2000; Kalivas and Duffy 1995; Perrotti et al. 2004), this is the first demonstration of stress-induced changes to NAc shell AMPAR function. Here, we showed a novel cellular substrate linking stress and reward. Better understanding of the neuroadaptations following exposure to environmental stressors will hopefully advance our understanding of the mechanisms underlying stress and reward-related pathways.

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