Cellular/Molecular

Sex-Specific Mechanisms Underlie Long-Term Potentiation at Hippocampus→Medium Spiny Neuron Synapses in the Medial Shell of the Nucleus Accumbens

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Sex differences have complicated our understanding of the neurobiological basis of many behaviors that are key for survival. As such, continued elucidation of the similarities and differences between sexes is necessary to gain insight into brain function and vulnerability. The connection between the hippocampus (Hipp) and nucleus accumbens (NAc) is a crucial site where modulation of neuronal activity mediates reward-related behavior. Our previous work demonstrated that long-term potentiation (LTP) of Hipp→NAc synapses is rewarding, and mice can establish learned associations between LTP of these synapses and the contextual environment in which LTP occurred. Here, we investigated sex differences in the mechanisms underlying Hipp→NAc LTP using whole-cell electrophysiology and pharmacology. We observed similarities in basal synaptic strength between males and females and found that LTP occurs postsynaptically with similar magnitudes in both sexes. However, key sex differences emerged as LTP in males required NMDA receptors (NMDAR), whereas LTP in females utilized an NMDAR-independent mechanism involving L-type voltage-gated Ca^{2+} channels (VGCCs) and estrogen receptor α (ERα). We also uncovered sex-similar features as LTP in both sexes depended on CaMKII activity and occurred independently of dopamine-1 receptor (D1R) activation. Our results have elucidated sex-specific molecular mechanisms for LTP in an integral pathway that mediates reward-related behaviors, emphasizing the importance of considering sex as a variable in mechanistic studies. Continued characterization of sex-specific mechanisms underlying plasticity will offer novel insight into the neurophysiological basis of behavior, with significant implications for understanding how diverse processes mediate behavior and contribute to vulnerability to developing psychiatric disorders.

Key words: **hippocampus; long-term potentiation; nucleus accumbens; plasticity; sex differences**

Significance Statement

Strengthening of hippocampus→nucleus accumbens (Hipp→NAc) synapses drives reward-related behaviors. Long-term potentiation (LTP) occurs with a similar magnitude in males and females, and both sexes have a predicted postsynaptic locus of plasticity. Despite these similarities, here we illustrate that sex-specific molecular mechanisms underlie LTP at Hipp→NAc synapses. Given the bidirectional relationship between Hipp→NAc synaptic strength in mediating reward-related behaviors, the use of distinct molecular mechanisms may explain sex differences observed in stress susceptibility or response to rewarding stimuli. Uncovering these latent sex differences offers a deeper understanding of the sex-specific function of this behaviorally relevant synapse with widespread implications for circuits that underlie learning and reward-related behavior.

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Introduction

Sex differences in reward-related behaviors are prevalent across a variety of species. For instance, humans and rodents show clear sex differences in sensitivity to rewarding stimuli and reward value (Yararbas et al., 2010; Warthen et al., 2011; Holly et al., 2012; Becker, 2016; Alarcón et al., 2017; Sinclair et al., 2017; Legget et al., 2018; Westbrook et al., 2018; Cullity et al., 2021; Aubry et al., 2022). There are also well-documented sex differences in related disorders like major depressive

disorder (Marcus et al., 2005; Brody et al., 2018; Huang et al., 2019) and depressive-like behaviors in rodents (Dalla et al., 2008; Trainor et al., 2011; Burke et al., 2016; Song et al., 2018; Baratta et al., 2019; Goodwill et al., 2019; L.-L. Liu et al., 2019; Williams et al., 2020; Pitzer et al., 2022), and males and females tend to respond differently to antidepressant treatment [reviewed in LeGates et al. (2019)]. This may be explained by clear sex differences in depression-related neuronal activity in humans and preclinical models (Bangasser and Cuarenta, 2021; X. Wang et al., 2023). However, the precise neuronal mechanisms underlying sex differences in behavior and circuit function remain unknown.

The nucleus accumbens (NAc) is a key node of the reward pathway that responds to rewarding stimuli (Richter et al., 2020), integrates information from various sources to mediate goal-directed behavior (Gruber et al., 2009; Francis and Lobo, 2017), and is altered in preclinical depression models (Wacker et al., 2009; Drysdale et al., 2017). The hippocampus (Hipp) provides crucial excitatory input to the NAc, which influences NAc activity and conveys spatial and contextual information to guide reward-related behavior (O'Donnell et al., 1999; Floresco et al., 2001; Belujon and Grace, 2008; Ito et al., 2008; Britt et al., 2012; Gill and Grace, 2013; Bagot et al., 2015; Okuyama et al., 2016; Oliva et al., 2016; Gauthier and Tank, 2018; LeGates et al., 2018; Sjulson et al., 2018; Trouche et al., 2019; Y. Zhou et al., 2019; Williams et al., 2020; Lind et al., 2023). Our previous work revealed that long-term potentiation (LTP) of Hipp→NAc synapses drives reward-related behaviors, while exposure to chronic stress reduced Hipp→NAc excitatory synaptic strength, abolished LTP, and produced a concomitant aberration in reward-related behaviors (LeGates et al., 2018). This is supported by data from human subjects showing that functional connectivity of Hipp→striatal pathways is correlated to fluctuations in positive affect due to experiential diversity (Heller et al., 2020). These findings demonstrate a key bidirectional relationship between the strength of Hipp→NAc synapses and reward-related behaviors, highlighting the Hipp→NAc pathway as a crucial component of reward circuitry.

Given numerous examples of sex differences in reward behaviors that may be impacted by the Hipp→NAc pathway, we were interested in characterizing the molecular mechanisms underlying Hipp→NAc LTP in male and female mice. We previously found that LTP at Hipp→NAc medium spiny neuron (MSN) synapses in the medial shell of male mice requires NMDARs, postsynaptic Ca^{2+} influx, and CaMKII activity but occurs independently of D1R activation (LeGates et al., 2018). Here, we performed whole-cell electrophysiology and pharmacology to characterize the mechanisms underlying Hipp→NAc MSN plasticity in females, comparing them to mechanisms used in males. We found that high-frequency stimulation (HFS) of hippocampal axons induced LTP of similar magnitude in males and females. While LTP was supported by postsynaptic mechanisms in both sexes, we observed several key sex differences: LTP in males was NMDAR dependent while LTP in females occurred through an NMDAR-independent mechanism involving L-type VGCCs and ERα activity. LTP at Hipp→NAc synapses in both sexes required CaMKII activation and occurred independent of D1R activity suggesting important sex similarities exist as well. Taken together, these data reveal latent sex differences produce similar LTP at Hipp→NAc synapses, which may be a key factor contributing to sex differences in behavior and disorder.

Materials and Methods

Animals. Adult (8–10-week-old) male and female D1dra-tdTomato or C57BL/6J mice were bred in-house or purchased directly from Jackson Laboratories. The use of D1dra-tdTomato mice allowed us to identify dopamine-1-receptor and putative dopamine-2-receptor-expressing MSNs (D1-MSN and pD2-MSN): D1-MSNs expressed tdTomato while pD2-MSNs were unlabeled. D1dra-tdTomato mice were used for the experiments described in Figures 1 and 6 while C57BL/6J mice were used for the remaining experiments. Mice were housed with same-sex cage mates in a temperature- and humidity-controlled environment under a 12 h light/dark cycle (lights on at 07:00). We did not track estrous cycle in females. All experiments were performed in accordance with the regulations set forth by the Institutional Animal Care and Use Committee at the University of Maryland, Baltimore County.

Mouse brain slice preparation. Acute parasagittal slices (lateral 0.36–0.72) containing the fornix and nucleus accumbens were prepared for whole-cell patch-clamp electrophysiology. Animals were deeply anesthetized with isoflurane and decapitated, and brains were quickly dissected and submerged in ice-cold, bubbled (carbogen: 95% O_2/5% CO_2) *N*-methyl-D-glucamine (NMDG) recovery solution containing the following (in mM): 93 NMDG, 2.5 KCl, 1.2 NaH_2PO_4, 11 glucose, 25 $NaHCO_3$, 1.2 $MgCl_2$, and 2.4 $CaCl_2$, pH 7.3–7.4, osmolarity = 300–310 mOsm. Using a vibratome (VT1000S, Leica Microsystems), parasagittal slices (400 µm) were cut in cold, oxygenated NMDG. Slices were transferred to 32–34°C NMDG for 7–12 min to recover and were then transferred to room temperature artificial cerebrospinal fluid (aCSF) containing the following (in mM): 120 NaCl, 3 KCl, 1.0 NaH_2PO_4, 20 glucose, 25 $NaHCO_3$, 1.5 $MgCl_2{\cdot}7H_2O$, and 2.5 $CaCl_2$, pH 7.3–7.4. Slices were allowed to recover for 1 h at room temperature before beginning electrophysiological recordings.

Whole-cell recordings. We performed whole-cell patch-clamp recordings using an Axopatch 200B amplifier (Axon Instruments, Molecular Devices) and a Digidata 1550B digitizer (Axon Instruments). Slices were placed in a submersion-type recording chamber and superfused with room temperature aCSF (flow rate, 0.5–1 ml/min). Patch pipettes (4–8 MΩ) were made from borosilicate glass (World Precision Instruments) using a Sutter Instruments P-97 model puller. Cells were visualized using a 60× water immersion objective (Nikon Eclipse FN-1). D1R-MSNs were identified by the expression of tdTomato while putative D2R-MSNs were cells with a similar morphology that lacked expression of tdTomato.

All recordings were performed in voltage-clamp conditions from MSNs in the NAc medial shell. A bipolar stimulating electrode (FHC) was placed in the fornix to electrically stimulate hippocampal axons and record evoked excitatory postsynaptic currents (EPSCs). For local stimulation experiments (Fig. 6*c*,*d*), a bipolar stimulating electrode (FHC) was placed in the NAc to nonspecifically stimulate all inputs to NAc MSNs. For LTP experiments, patch pipettes were filled with a solution containing the following (in mM): 130 K-gluconate, 5 KCl, 2 $MgCl_6$-H_2O, 10 HEPES, 4 Mg-ATP, 0.3 Na_2-GTP, 10 Na_2-phosphocreatine, and 1 EGTA, pH 7.3–7.4; osmolarity = 285–295 mOsm. EPSCs were recorded from paired pulses (100 ms apart) performed every 10 s. Paired pulse ratio (PPR) was calculated by dividing EPSC2 by EPSC 1 (i.e. PPR = EPSC2/EPSC1). A 5 min baseline EPSC recording was obtained, then HFS (four trains of 100 Hz stimulation for 1 s with 15 s between trains while holding the cell at −40 mV) was used to induce LTP, followed by a 30 min recording of EPSCs. For experiments determining current–voltage (*I–V*) relationship, the patch pipette solution was composed of 135 mM CsCl, 2 mM $MgCl_6$-H_2O, 10 mM HEPES, 4 mM Mg-ATP, 0.3 mM Na_2-GTP, 10 mM Na_2-phosphocreatine, 1 mM EGTA, 5 mM QX-314, and 100 µM spermine, pH 7.3–7.4; osmolarity = 285–295 mOsm. EPSCs were collected from holding potentials ranging from −80 to +40 mV to create an *I–V* curve. For all pharmacological experiments, drugs [APV (Tocris, 50 µM), NASPM (Tocris, 20 µM), nimodipine (Tocris, 3 µM), KN-62 (Tocris, 3 µM), SCH23390 (Tocris, 3 µM), MPP dihydrochloride (Tocris, 3 µM)] were superfused over the slice for at least 15 min prior to recording. We used the following exclusion criteria to eliminate

unhealthy cells and unreliable recordings: (1) We only proceeded with experiments on cells with series resistances <10 MΩ, (2) cells were excluded if their series resistance changed by >20% (comparing the resistance at the beginning and end of the experiment), (3) cells in poor health or poor recording status were excluded (i.e., cell partially or fully sealed up, a decrease in holding current >100 pA that is consistent with the cell dying, an increase in jitter post-HFS, and/or an increase in response failure rate to >50%).

Quantification, statistical analysis, and reproducibility. A total of 223 cells were recorded from 194 mice for these experiments. Males and females were kept separate in our analyses. We found no statistically significant difference between D1R- and pD2R-MSNs, so they are plotted together unless otherwise indicated. Both the number of cells and number of mice is reported for each experiment. The sample size (n) per condition represents the number of cells unless otherwise indicated in the figure caption. For LTP experiments, the 5 min baseline and last 5 min of recording were used for statistical comparisons. Two-tailed, paired Wilcoxon tests were used to determine whether a group of cells had a significant increase above baseline, indicating LTP. Pairwise comparisons using the Mann–Whitney U test were used to assess experimental condition differences due to non-normal distributions of data. Significant pairwise comparisons were reported. A p value of <0.05 was considered statistically significant, where exact p values can be found in the figure captions. For statistical tests considering both sex and cell type, a two-way ANOVA was used. All statistical analyses were performed using GraphPad Prism 9/10 software. For box plots, the line in the middle of the box is plotted at the median. The box extends from the 25th to 75th percentiles. Whiskers represent minimum and maximum. Figures were created with BioRender.com.

Results

HFS induces Hipp→NAc MSN LTP of similar magnitude in males and females

We performed whole-cell patch-clamp electrophysiology while electrically stimulating the fornix to record Hipp-evoked EPSCs in MSNs in the medial shell of the NAc (Fig. 1*a*). Slices were taken from D1dra-tdTomato mice, allowing us to distinguish between dopamine-1- and putative dopamine-2-receptor-expressing MSNs (D1-MSN and pD2-MSN) based on expression of tdTomato. In response to high frequency stimulation (HFS), we observed LTP of similar magnitude in male and female mice, with no difference between D1- and pD2-MSNs (Fig. 1). Comparison of paired-pulse ratio (PPR) baseline and post-HFS 25–30 min values suggests that LTP involves postsynaptic mechanisms in both male and female mice (Fig. 1*c*,*e*). These results indicate that LTP occurs at Hipp→NAc MSN synapses similarly in males and females, with no difference in baseline EPSC amplitude (Fig. 1*b*), LTP magnitude (Fig. 1*c*–*f*), or predicted locus of plasticity mechanisms between the sexes (Fig. 1*c*,*e*). Since there was no difference between D1- and pD2-MSNs, cells were pooled for the remainder of the data shown.

NMDAR activity is required for male, but not female, Hipp→NAc MSN LTP

The prediction that both sexes use postsynaptic mechanisms for LTP suggests a rise in postsynaptic Ca^{2+} levels. At Hipp→NAc synapses in male mice, the proximate means of this Ca^{2+} is NMDARs (LeGates et al., 2018). We reproduced this result by repeating the experiment described above in the presence of 50 µM 2-aminophosphonovaleric acid (APV), an NMDAR antagonist (Fig. 2*a*,*b*). However, in slices taken from female mice, we found that APV was unable to block LTP (Fig. 2*c*,*d*), suggesting that while NMDARs are necessary for LTP at Hipp→NAc synapses in males, they are not required for LTP in females. We measured AMPA:NMDA ratio at Hipp→NAc synapses in male and female mice and found no sex difference in this ratio (Fig. 2*e*), suggesting that there is no difference in the relative strength of these synapses. The ability to collect

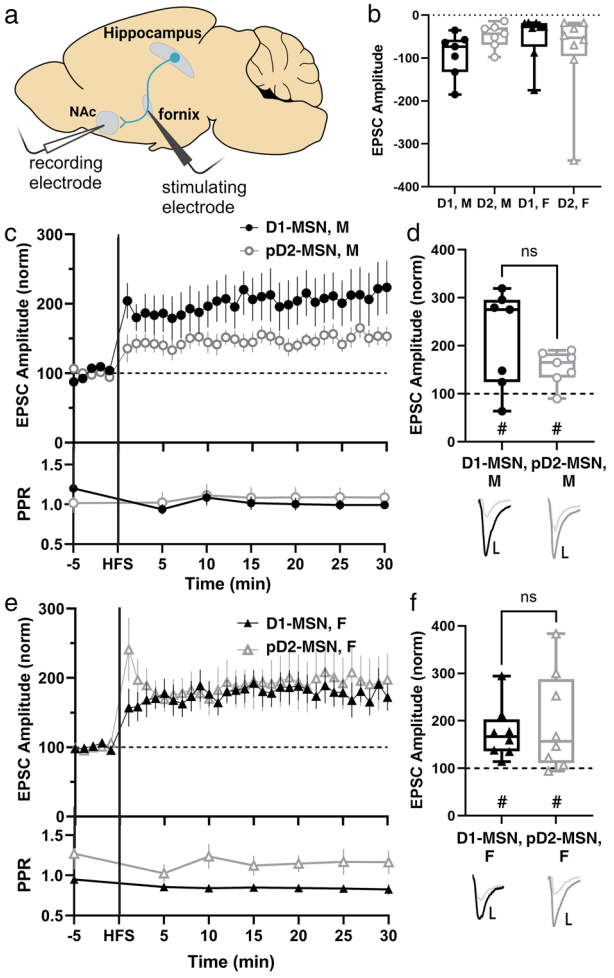

Figure 1. Both sexes display a similar magnitude of LTP and a predicted postsynaptic locus of plasticity. ***a***, Recording strategy with stimulating electrode placed in the fornix and recording electrode in the NAc medial shell to record Hipp-evoked EPSCs from MSNs. The shown parasagittal section represents a slice from lateral +0.48. ***b***, Comparison of baseline, non-normalized EPSC amplitudes in male and female D1- and pD2-MSNs reveals no difference among sex or cell subtype (M D1-MSN $n = 7$ cells from 6 mice, M pD2-MSN $n = 7$ cells from 7 mice, F D1-MSN $n = 8$ cells from 7 mice, D2-MSN $n = 8$ cells from 8 mice; two-way ANOVA, ns $p = 0.5191$). ***c***, Hippocampal-evoked EPSC amplitudes and PPR from D1- and pD2-MSNs in males. Data represent 1 min bins (means of all cells in each condition ± SEM; comparison of baseline PPR to 25–30 min PPR: M D1 $n = 7$ cells from 6 mice, $p = 0.0781$, two-tailed paired Wilcoxon test; M pD2 $n = 7$ cells from 7 mice, $p > 0.9999$, two-tailed paired Wilcoxon test). ***d***, Summary EPSC data from 25 to 30 min post-HFS revealing similar magnitudes of LTP (M D1-MSN $n = 7$ cells from 6 mice, $^{\#}p = 0.0469$, two-tailed paired Wilcoxon test; M pD2-MSN $n = 7$ cells from 7 mice, $^{\#}p = 0.0312$, two-tailed paired Wilcoxon test; $p = 0.3829$, Mann–Whitney U test). Representative traces with scale bars, 40 pA/10 ms. ***e***, Hippocampal-evoked EPSC amplitudes and PPR from D1- and pD2-MSNs in females. Data represent 1 min bins (means of all cells in each condition ± SEM; comparison of baseline PPR to 25–30 min PPR: F D1 $n = 7$ cells from 6 mice, $p = 0.5781$, two-tailed paired Wilcoxon test; M pD2 $n = 8$ cells from 8 mice, $p = 0.3125$, two-tailed paired Wilcoxon test). ***f***, Summary EPSC data from 25 to 30 min post-HFS revealing similar magnitudes of LTP (F D1-MSN $n = 8$ cells from 7 mice, $^{\#}p = 0.0078$, two-tailed paired Wilcoxon test; F pD2-MSN $n = 8$ cells from 8 mice, $^{\#}p = 0.0156$, two-tailed paired Wilcoxon test; $p = 0.9591$, Mann–Whitney U test). Comparison of LTP magnitude between male and female D1- and pD2-MSNs reveal no significant difference (two-way ANOVA, ns $p = 0.6067$). Representative traces with scale bars, 40 pA/10 ms. *Differences between treatment and control by two-tailed Mann–Whitney U test. $^{\#}$Significant increase in EPSC amplitude above baseline revealed by two-tailed paired Wilcoxon test.

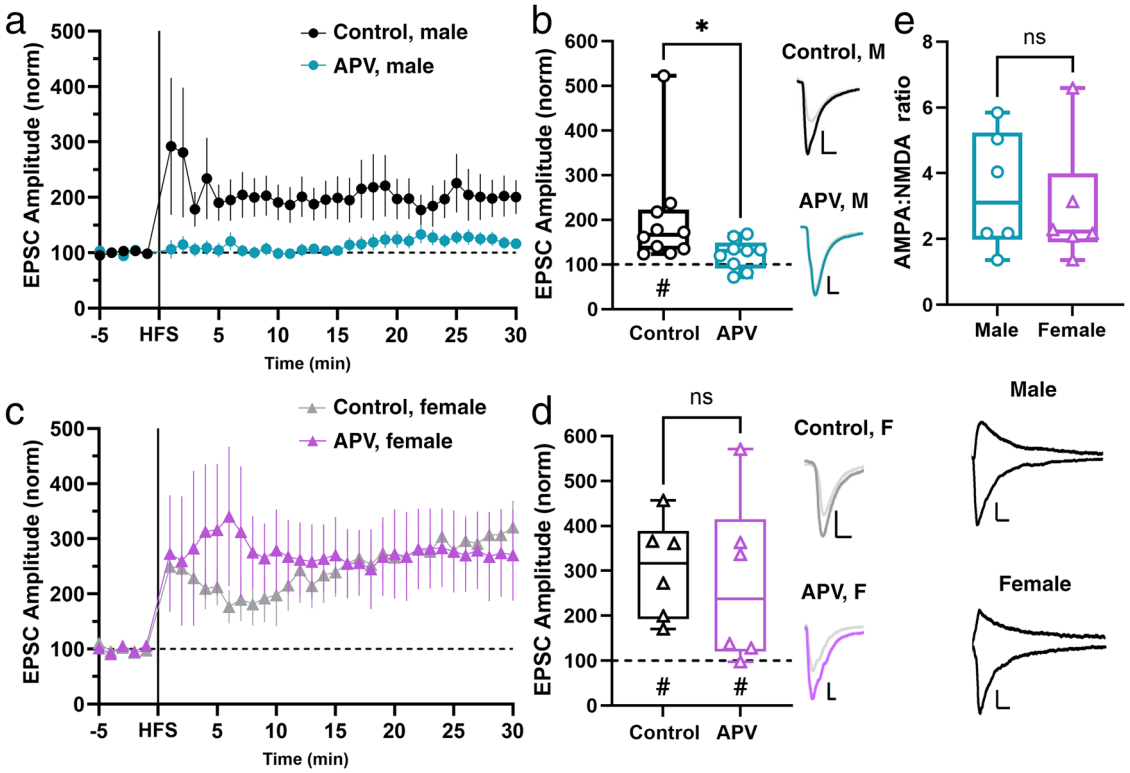

Figure 2. LTP is NMDAR independent at Hipp→NAc synapses in females. ***a***, Comparison of LTP in the presence and absence of NMDAR antagonist, APV, in males. Data represent 1 min bins (means of all cells in each condition ± SEM). ***b***, Summary EPSC data from 25 to 30 min post-HFS showing abolishment of LTP in APV condition (Ctrl M $n = 10$ cells from 9 mice, $^{\#}p = 0.0248$, two-tailed paired Wilcoxon test; APV M $n = 9$ cells from 8 mice, $p = 0.0750$, two-tailed paired Wilcoxon test; $^{*}p = 0.0172$, Mann–Whitney U test). Statistical difference is not driven by the control cell with large magnitude LTP (exclusion of this cell results in $^{*}p = 0.0315$, Mann–Whitney *U* test). Representative trace with scale bars, 20 pA/10 ms. ***c***, Comparison of LTP in the presence and absence of NMDAR antagonist, APV, in female mice. Data represent 1 min bins (means of all cells in each condition ± SEM). ***d***, Summary EPSC data from 25 to 30 min post-HFS showing similar LTP magnitude in control and APV conditions (Ctrl F $n = 6$ cells from 6 mice, $^{\#}p = 0.0312$, two-tailed paired Wilcoxon test; APV F $n = 7$ cells from 5 mice, $^{\#}p = 0.0312$, two-tailed paired Wilcoxon test; $p = 0.4248$, Mann–Whitney *U* test). Representative trace with scale bars, 20 pA/10 ms. ***e***, AMPA:NMDA ratio comparison in male and female mice reveals no sex differences in basal Hipp→NAc synaptic properties (male $n = 6$ cells from 4 mice; female $n = 6$ cells from 3 mice; $p = 0.7338$, Mann–Whitney *U* test). Representative trace with scale bars, 20 pA/50 ms. *Differences between treatment and control by two-tailed Mann–Whitney *U* test. $^{\#}$Significant increase in EPSC amplitude above baseline revealed by two-tailed paired Wilcoxon test.

NMDAR-mediated currents also shows that females have NMDARs present at Hipp→NAc synapses, suggesting that the lack of requirement for NMDARs in female LTP is not explained by a lack of NMDARs in the synapse. These experiments reveal the surprising sex-specific use of an NMDAR-independent pathway for LTP at Hipp→NAc synapses in females.

L-type VGCC is required for Hipp→NAc MSN LTP in females

There are various NMDAR-independent mechanisms that have been shown to underlie postsynaptically expressed LTP which involve Ca^{2+}-permeable AMPA receptors (CP-AMPAR), mobilization of intracellular Ca^{2+} stores, or VGCCs (Nanou and Catterall, 2018; Park et al., 2018; Padamsey et al., 2019; Alkadhi, 2021). To begin to understand which mechanisms may underlie LTP at Hipp→NAc synapses, we modified our LTP induction protocol to deliver HFS while holding the cell at −70 mV rather than the depolarized (−40 mV) potential we typically use. This modification effectively prevents the activation of any voltage-dependent processes during LTP induction. We found that delivering HFS in the absence of simultaneous depolarization prevented LTP induction (Fig. 3*a–c*), implicating the involvement of a voltage-dependent means of external Ca^{2+} in LTP at female Hipp→NAc synapses.

From here, we wanted to determine which type of voltage-gated channel was necessary for LTP at female Hipp→NAc synapses. L-type VGCCs have been implicated in postsynaptic forms of LTP in the amygdala and CA1 region of the hippocampus (Huber et al., 1995; Weisskopf et al., 1999) and are expressed postsynaptically within the NAc, allowing for voltage-dependent influx of Ca^{2+} into MSNs. Therefore, we hypothesized that L-type VGCCs mediate LTP at Hipp→NAc synapses in females. We tested this idea by pretreating slices with the L-type VGCC antagonist nimodipine (10 μM). Bath application of nimodipine was sufficient to block LTP in female mice (Fig. 3*d*,*e*), suggesting that L-type VGCCs are required for LTP at Hipp→NAc synapses in females. In contrast, inhibition of L-type VGCCs was not sufficient to block LTP in males, although LTP magnitude was reduced in the presence of nimodipine (Fig. 3*f*,*g*). Together, with our recordings in the presence of APV, this demonstrates that males and females utilize distinct sources of postsynaptic Ca^{2+} to mediate LTP at Hipp→NAc synapses, where males rely primarily on NMDARs with some contribution from L-type VGCCs while females utilize an NMDAR-independent mechanism that requires L-type VGCCs.

CP-AMPAR are not involved in Hipp→NAc MSN LTP

Given the role of CP-AMPARs in sex-specific mechanisms of synaptic potentiation in hippocampal CA1 neurons (Jain and Woolley, 2023), their contributions to multiple forms of NAc plasticity and behaviors that occur in response to drug exposure (Guire et al., 2008; Mameli et al., 2009; McCutcheon et al., 2011; Wolf and Tseng, 2012; Terrier et al., 2016; Carr, 2020; Park et al.,

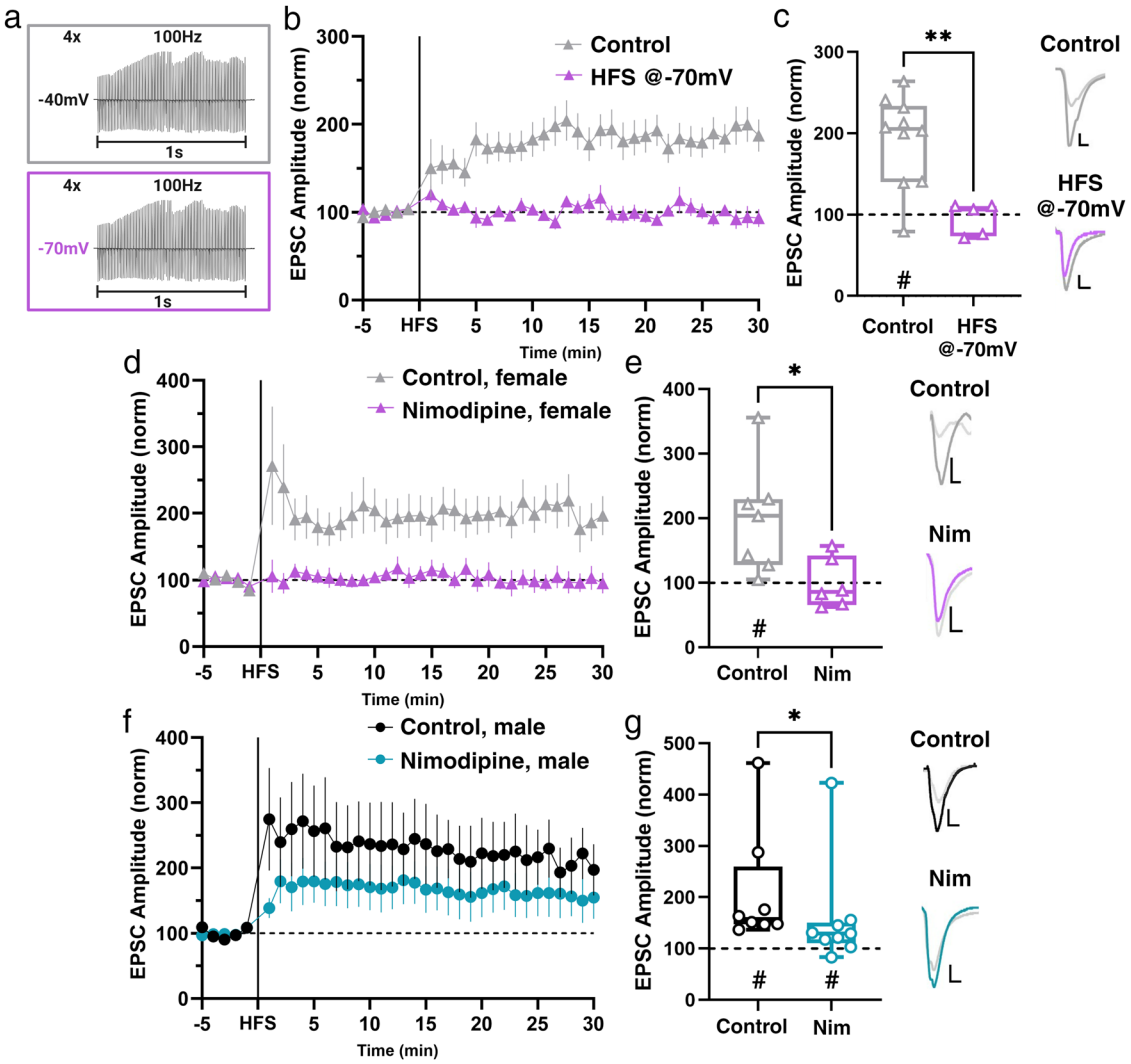

Figure 3. L-type VGCCs are required for LTP at Hipp→NAc synapses in females. ***a***, Control (depolarizing cell to −40 mV) and experimental (−70 mV) HFS protocols. ***b***, Comparison of LTP with control HFS and HFS at −70 mV protocols. Data represent 1 min bins (means of all cells in each condition ± SEM). ***c***, Summary EPSC data from 25 to 30 min post-HFS showing that HFS while holding the cell at −70 mV prevents LTP (control $n = 10$ cells from 9 mice, $^{\#}p = 0.0006$, two-tailed paired Wilcoxon test; HFS at −70 mV $n = 5$ cells from 5 mice, $p = 0.5998$, two-tailed paired Wilcoxon test; $^{*}p = 0.0047$, Mann–Whitney *U* test). Representative trace with scale bars, 20 pA/10 ms. ***d***, Comparison of LTP in the presence and absence of L-type VGCC antagonist, nimodipine (Nim), in female mice. Data represent 1 min bins (means of all cells in each condition ± SEM). ***e***, Summary EPSC data from 25 to 30 min post-HFS reveals that Nim prevents LTP (control $n = 7$ cells from 6 mice, $^{\#}p = 0.0223$, two-tailed paired Wilcoxon test; Nim $n = 6$ cells from 5 mice, $p = 0.9624$, two-tailed paired Wilcoxon test; $^{*}p = 0.0221$, Mann–Whitney *U* test). Representative trace with scale bars, 20 pA/10 ms. ***f***, Comparison of LTP in the presence and absence of L-type VGCC antagonist, nimodipine (Nim), in male mice. Data represent 1 min bins (means of all cells in each condition ± SEM). ***g***, Summary EPSC data from 25 to 30 min post-HFS reveals that Nim causes a decrease in the magnitude of LTP in males (control $n = 8$ cells from 7 mice, $^{\#}p = 0.0078$, two-tailed paired Wilcoxon test; Nim $n = 9$ cells from 8 mice, $^{\#}p = 0.0195$, two-tailed paired Wilcoxon test; $^{*}p = 0.0206$, Mann–Whitney *U* test). Representative trace with scale bars, 20 pA/10 ms. *Differences between treatment and control by two-tailed Mann–Whitney *U* test. $^{\#}$Significant increase in EPSC amplitude above baseline revealed by two-tailed paired Wilcoxon test.

2021), and presence at ventral subiculum→NAc synapses (Boxer et al., 2023), we sought to investigate their potential role in LTP at Hipp→NAc synapses in females. CP-AMPARs have unique electrophysiological properties and are inwardly rectifying, whereas Ca^{2+}-impermeable AMPARs display a linear current–voltage relationship (Cull-Candy et al., 2006; S. J. Liu and Zukin, 2007). This allows us to electrophysiologically determine the predominant population of AMPARs present at a particular synapse. We found that basal current–voltage relationships at Hipp→NAc MSN synapses were linear, demonstrating the absence of CP-AMPARs prior to HFS and precluding their involvement in LTP induction (Fig. 4*a*). Since CP-AMPARs can also be involved in LTP through preferential insertion following HFS (Whitehead et al., 2013), we aimed to determine whether they might instead play a role in LTP at Hipp→NAc synapses through this mechanism. We washed in 1-naphthylacetyl spermine (NASPM; 20 µM), a CP-AMPAR antagonist, 10 min after HFS, but found that NASPM wash-in had no effect on EPSC amplitude (Fig. 4*b*,*c*), suggesting that insertion of CP-AMPARs does not contribute to LTP at Hipp→NAc MSN synapses in female mice. Altogether, these results rule out the involvement of CP-AMPARs in LTP at Hipp→NAc MSN synapses in females which aligns with our previous observations in males (LeGates et al., 2018).

CaMKII is required for LTP in female mice

Despite males and females differing in their proximate means of postsynaptic Ca^{2+}, we hypothesized that similar, Ca^{2+}-dependent

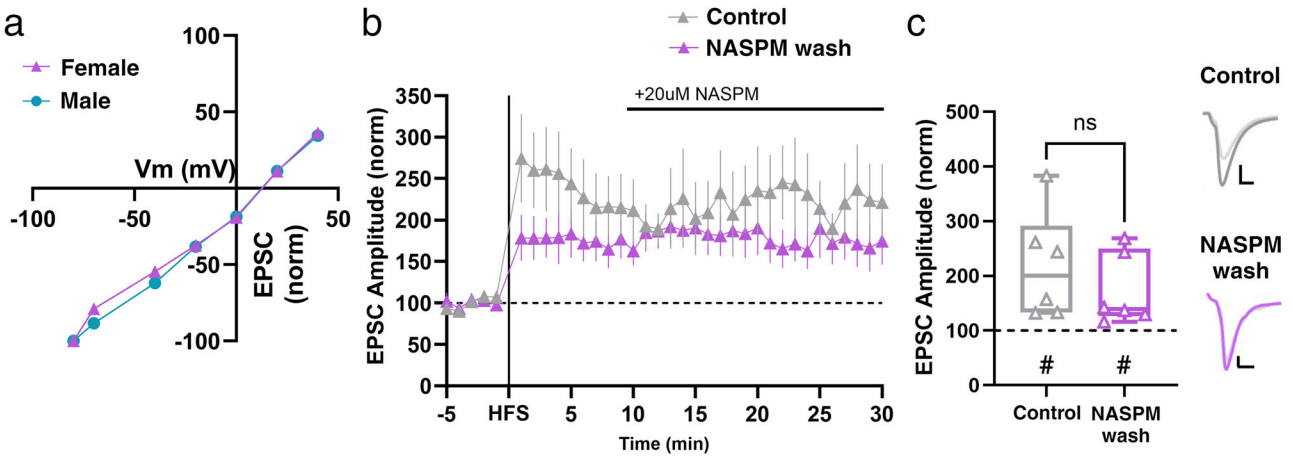

Figure 4. CP-AMPARs are not present at Hipp→NAc synapses and insertion of CP-AMPARs is not required for LTP in females. ***a***, Linear *I–V* relationship demonstrates AMPARs at Hipp→NAc synapses are Ca^{2+}-impermeable (male $n = 7$ cells from 4 mice; female $n = 9$ cells from 3 mice). ***b***, CP-AMPAR antagonist, NASPM, wash-on 10 min after HFS. Data represent 1 min bins (means of all cells in each condition ± SEM). ***c***, Summary EPSC data from 25 to 30 min post-HFS showing that NASPM wash has no effect on LTP (control $n = 6$ cells from 6 mice, $^{\#}p = 0.0156$, two-tailed paired Wilcoxon test; NASPM wash $n = 6$ cells from 6 mice, $^{\#}p = 0.0312$, two-tailed paired Wilcoxon test; $p = 0.3939$, Mann–Whitney *U* test). Representative trace with scale bars, 40 pA/10 ms. *Differences between treatment and control by two-tailed Mann–Whitney *U* test. $^{\#}$Significant increase in EPSC amplitude above baseline revealed by two-tailed paired Wilcoxon test.

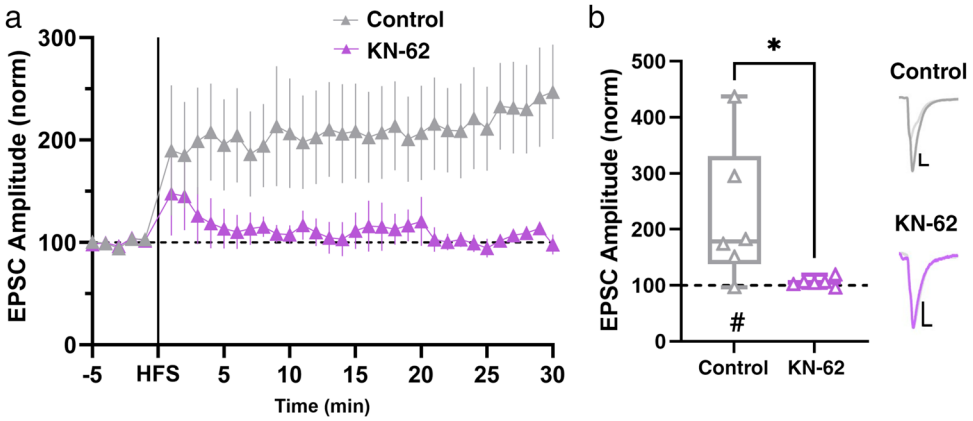

Figure 5. Downstream of Ca^{2+} influx, CAMKII activity is required for LTP in females. ***a***, Comparison of LTP in the presence and absence of CAMKII antagonist, KN-62. Data represent 1 min bins (means of all cells in each condition ± SEM). ***b***, Summary EPSC data from 25 to 30 min post-HFS showing that KN-62 prevents LTP (control $n = 6$ cells from 6 mice, $^{\#}p = 0.0312$, two-tailed paired Wilcoxon test; KN-62 $n = 6$ cells from 6 mice, $p = 0.1562$, two-tailed paired Wilcoxon test; $^{*}p = 0.0411$, Mann–Whitney *U* test). Representative trace with scale bars, 40 pA/10 ms. *Differences between treatment and control by two-tailed Mann–Whitney *U* test. $^{\#}$Significant increase in EPSC amplitude above baseline revealed by two-tailed paired Wilcoxon test.

molecular players may be recruited downstream of this Ca^{2+} to mediate LTP. In male mice, the postsynaptic rise in Ca^{2+} initiates activation of CaMKII to cause LTP (LeGates et al., 2018). To determine whether this is consistent for LTP at Hipp→NAc synapses in females, we applied a CaMKII inhibitor (KN-62, 3 μM) before recording from MSNs. We found that blocking CaMKII prevented LTP in female mice (Fig. 5), suggesting that CAMKII activity is required for LTP in both sexes.

Female Hipp→NAc MSN LTP occurs independently of dopamine

Dopamine is a well-known modulator of reward-related behaviors and plays a crucial role in regulating excitatory synapses within the NAc (Speranza et al., 2021). Many characterized forms of LTP at excitatory synapses within the NAc require D1R activity (Floresco et al., 2001; Goto and Grace, 2005; Hernandez et al., 2005; Mameli and Lüscher, 2011; Du Hoffmann and Nicola, 2014; Pignatelli and Bonci, 2015; Madadi Asl et al., 2018; Yu et al., 2022), but at Hipp→NAc synapses, HFS-induced LTP in males is unaffected by dopamine receptor blockade, demonstrating that LTP at these synapses in males occurs independent of dopamine receptor signaling (LeGates et al., 2018). To test whether this was also true at Hipp→NAc synapses in females, we blocked D1R activity with SCH 23390 (3 μM) and found that pretreatment of slices with SCH 23390 had no impact on Hipp→NAc MSN LTP in female mice (Fig. 6*a–c*). In separate slices, we used local stimulation to elicit EPSCs that were not pathway specific and found that HFS induces LTP that was blocked by pretreatment with SCH 23390 (Fig. 6*d*,*e*). Together, these results support previous findings on the importance of D1Rs in excitatory synaptic plasticity broadly in the NAc and highlight a key distinction at Hipp→NAc synapses where LTP occurs independent of dopamine receptor signaling in male and female mice.

Estrogen receptor activity is required for female Hipp→NAc MSN LTP

Estrogen can alter excitatory synapse function and plasticity (described in detail by Frick et al., 2015; Oberlander and Woolley, 2017; Jain and Woolley, 2023) and can regulate Ca^{2+}

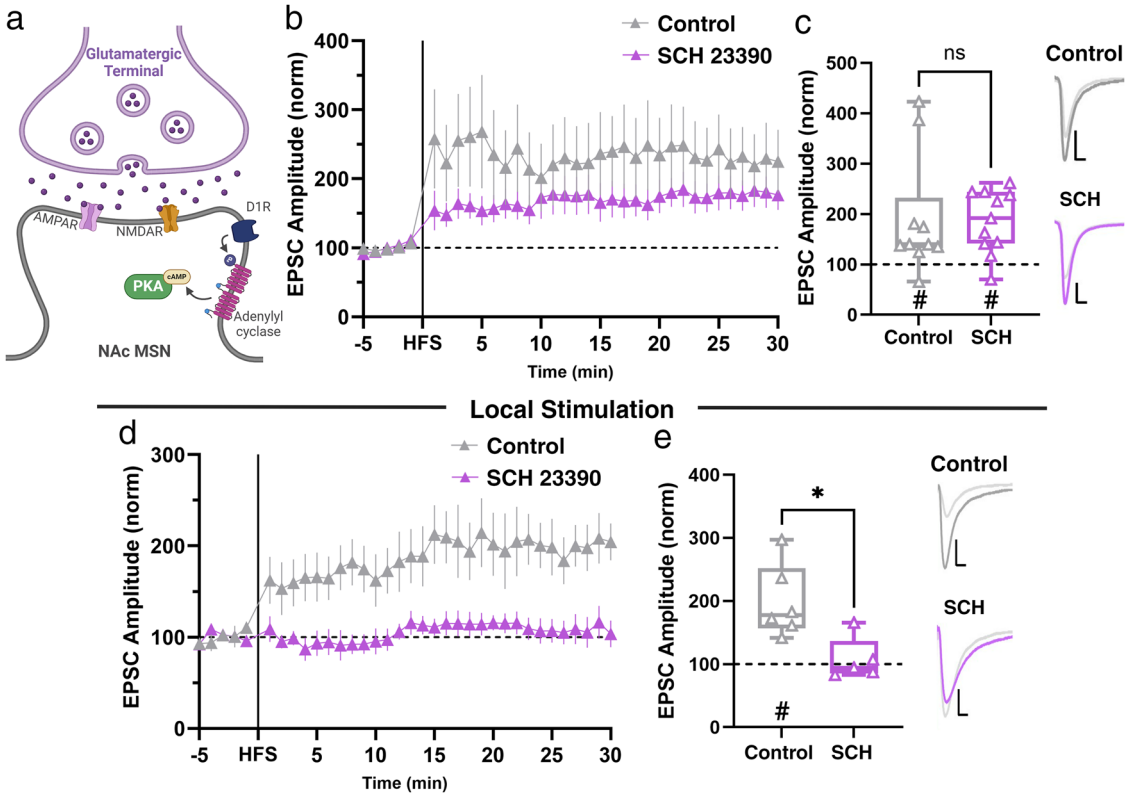

Figure 6. Dopamine receptor activity is not required for Hipp→NAc LTP in females. ***a***, Schematic of D1R downstream signaling that can contribute to LTP. ***b***, Comparison of LTP in the presence and absence of D1R antagonist, SCH23390 (SCH). Data represent 1 min bins (means of all cells in each condition ± SEM). ***c***, Summary EPSC data from 25 to 30 min post-HFS showing that SCH does not prevent LTP (control $n = 10$ cells from 10 mice, $^{\#}p = 0.0020$, two-tailed paired Wilcoxon test; SCH $n = 11$ cells from 9 mice, $^{\#}p = 0.0020$, two-tailed paired Wilcoxon test; $p = 0.3867$, Mann–Whitney *U* test). Representative trace with scale bars, 40 pA/10 ms. ***d***, Comparison of LTP induced by local stimulation of NAc in the presence and absence of SCH. Data represent 1 min bins (means of all cells in each condition ± SEM). ***e***, Summary EPSC data from 25 to 30 min post-HFS showing that LTP induced by local stimulation is prevented by application of SCH (control $n = 6$ cells from 5 mice, $^{\#}p = 0.0312$, two-tailed paired Wilcoxon test; SCH $n = 5$ cells from 4 mice, $p = 0.8125$, two-tailed paired Wilcoxon test; $^{*}p = 0.0173$, Mann–Whitney *U* test). Representative trace with scale bars, 40 pA/10 ms. *Differences between treatment and control by two-tailed Mann–Whitney *U* test. $^{\#}$Significant increase in EPSC amplitude above baseline revealed by two-tailed paired Wilcoxon test.

influx via L-type VGCCs in the striatum (Mermelstein et al., 1996; Sarkar et al., 2008). Additionally, while the mechanism underlying LTP at hippocampal CA1 is similar in male and females, females have an additional requirement of membrane-localized estrogen receptor-α (ERα) activation (X. Wang et al., 2018; Gall et al., 2023). Within the NAc, ERα is expressed primarily at the membrane in adult mice (Almey et al., 2022) and has been shown to interact with GPCRs to promote other forms of plasticity (Krentzel and Meitzen, 2018; Tonn Eisinger et al., 2018). Since ERα is moderately expressed in the NAc (Mitra et al., 2003) and has the potential to alter postsynaptic Ca^{2+} influx, we postulated that ERα is required for LTP at Hipp→NAc synapses in females. We used bath application of the ERα antagonist, MPP dihydrochloride (3 μM), to test the involvement of ERα in LTP at Hipp→NAc synapses. We found that pretreating slices with MPP prevented LTP in female mice but not male mice (Fig. 7), demonstrating the sex-specific requirement of ERα activation for LTP.

Discussion

Our data reveal key sex-specific and sex-similar molecular mechanisms underlying LTP at Hipp→NAc synapses (Fig. 8). Males and females displayed LTP of similar magnitude that relies on common mechanisms like postsynaptic Ca^{2+} influx and CaMKII activity. However, key differences emerged when we investigated the proximate means of postsynaptic Ca^{2+}; NMDARs are required for LTP at Hipp→NAc synapses in males, while L-type VGCCs are required in females. Furthermore, we identified a requirement for ERα in females that was not observed in males. Together, our results highlight the discovery of latent sex differences in the molecular mechanisms underlying LTP at Hipp→NAc synapses. Given the important role for these synapses in mediating reward-related behaviors, the identified sex differences have major implications for uncovering the neurobiological basis of sex variation in motivated behaviors and related psychiatric disorders.

Similarities in synaptic strength and LTP magnitude across sex and cell subtype

A wealth of evidence has established clear sex differences in excitatory circuitry throughout the brain (McLaughlin et al., 2009; McEwen, 2010; Duarte-Guterman et al., 2015; Cao et al., 2018; Bangasser and Cuarenta, 2021; Johnson et al., 2023). This includes the NAc core where it is related to sex differences in cocaine-induced behaviors and synaptic plasticity (Forlano and Woolley, 2010; Wissman et al., 2011, 2012; Catalfio et al., 2023; Knouse et al., 2023; Lewitus and Blackwell, 2023). Our investigation of Hipp→NAc shell synapses revealed no differences in AMPA:NMDA ratio, AMPA subunit composition (CP-AMPA vs AMPA), or LTP magnitude across sex or MSN subtype demonstrating similarities between sexes and subtypes in basal synaptic

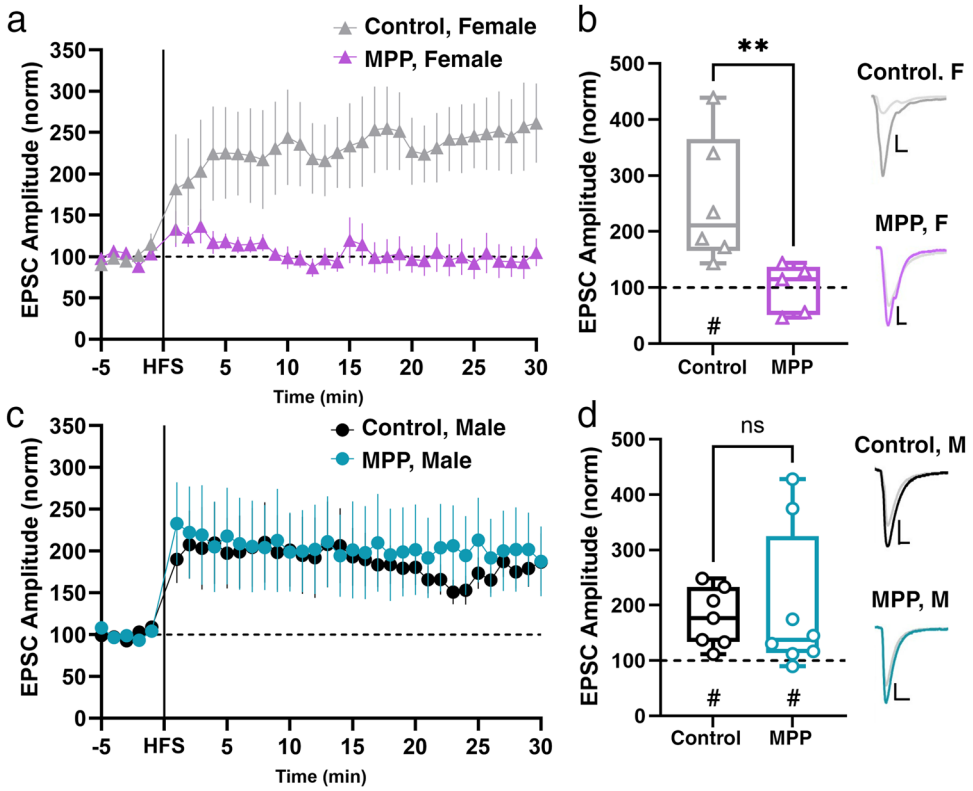

Figure 7. Sex-specific requirement for ERα activity for Hipp→NAc LTP. ***a***, Comparison of LTP in the presence and absence of an ERα antagonist, MPP dihydrochloride (MPP) in female mice. Data represent 1 min bins (means of all cells in each condition ± SEM). ***b***, Summary EPSC data from 25 to 30 min post-HFS showing that ERα inhibition prevents LTP in female mice (Ctrl F $n = 6$ cells from 6 mice, $^{\#}p = 0.0312$, two-tailed paired Wilcoxon test; MPP F $n = 5$ cells from 5 mice, $p = 0.8125$, two-tailed paired Wilcoxon test; $^{**}p = 0.0087$, Mann–Whitney *U* test). Representative trace with scale bars, 20 pA/10 ms. ***c***, Comparison of LTP in the presence and absence of an ERα antagonist, MPP dihydrochloride (MPP) in male mice. Data represent 1 min bins (means of all cells in each condition ± SEM). ***d***, Summary EPSC data from 25 to 30 min post-HFS showing that ERα inhibition has no effect on LTP in male mice (Ctrl M $n = 7$ cells from 7 mice, $^{\#}p = 0.0156$, two-tailed paired Wilcoxon test; MPP M $n = 8$ cells from 8 mice, $^{\#}p = 0.0391$, two-tailed paired Wilcoxon test; $p = 0.6126$, Mann–Whitney *U* test). Representative trace with scale bars, 20 pA/10 ms. *Differences between treatment and control by two-tailed Mann–Whitney *U* test. $^{\#}$Significant increase in EPSC amplitude above baseline revealed by two-tailed paired Wilcoxon test.

strength and activity-dependent plasticity. We also noted that a small subset of cells across our study displayed HFS-induced long-term depression (LTD). Given its infrequency, we did not investigate this further, but HFS-induced LTD has been observed within the nucleus accumbens (Kombian and Malenka, 1994; Chergui, 2011) and at Hipp→NAc synapses in a rodent model of schizophrenia (Belujon et al., 2014) making it an interesting avenue of future research.

Sex differences in excitatory synaptic plasticity mechanisms

Despite similarities in LTP magnitude and the locus of plasticity, our experiments demonstrate latent sex differences underlie LTP at Hipp→NAc synapses. Hipp→NAc LTP in males requires NMDARs while L-type VGCCs facilitate typical LTP magnitude (Figs. 2, 3). In contrast, LTP in females occurs independent of NMDARs and instead relies on L-type VGCC (Fig. 3). This key difference in the type of calcium channel involved is a particularly unique finding as numerous studies have shown that other excitatory synapses onto MSNs primarily use NMDAR-dependent forms of plasticity (Floresco et al., 2001; Thomas and Malenka, 2003; Popescu et al., 2007; Vega-Villar et al., 2019), and to our knowledge, this is the first description of latent sex differences composed of NMDAR-dependent and NMDAR-independent mechanisms.

L-type VGCCs and NMDARs, which are both critical in long-lasting synaptic plasticity, are both voltage-dependent channels that facilitate Ca^{2+} influx to bind calmodulin, leading to Ca^{2+}-dependent activation of CaMKII that is required for Hipp→NAc LTP in both sexes (Ataman et al., 2007; Berger and Bartsch, 2014; LeGates et al., 2018; Fig. 5). Despite these similarities, NMDARs and L-type VGCCs are differentially regulated, and their dysregulation is implicated in different behaviors and diseases (Q. Zhou and Sheng, 2013; Ortner and Striessnig, 2015; Myers et al., 2019; Laryushkin et al., 2021; Mielnik et al., 2021; Sanderson et al., 2022). For example, deletion of L-type VGCCs impairs learning and memory in females (Zanos et al., 2015; Klomp et al., 2022). Moreover, *Cacna1c*, which encodes the $Ca_v1.2$ subunit of the L-type VGCC, is associated with genetic risk for multiple mood disorders (Sklar et al., 2008; Bigos et al., 2010; Dedic et al., 2018; Moon et al., 2018; Jiang et al., 2023) and shows sex-specific interactions influencing depression (Dao et al., 2010). Since Hipp→NAc communication is a key mediator of reward-related behaviors, elucidation of sex-specific mechanisms underlying LTP may offer essential insight into sex differences in behavior and pathophysiology.

Hormones regulate Hipp→NAc synapses

Estrogen and testosterone are important regulators of synaptic transmission and plasticity in both sexes (Barth et al., 2015; W. Wang et al., 2016; Lu et al., 2019; Williams et al., 2020; Chen et al., 2022). We did not track estrous cycle in our experiments but observed variability in LTP magnitude in females,

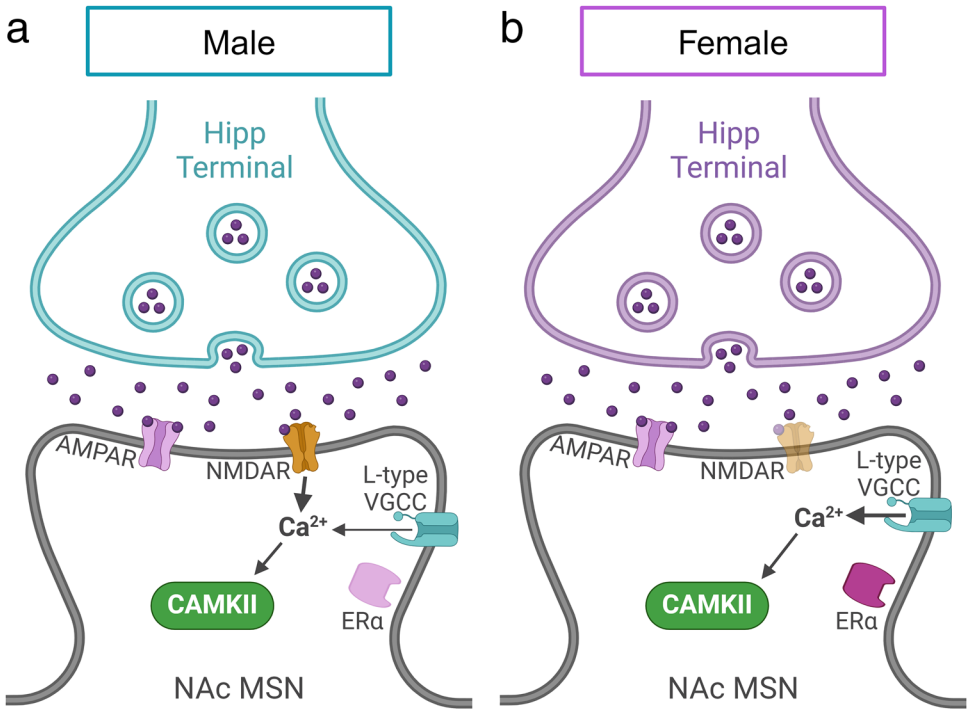

Figure 8. Comparison of sex-specific mechanisms involved in Hipp→NAc LTP. ***a***, LTP at Hipp→NAc synapses in males requires NMDAR-mediated Ca^{2+} influx and CAMKII activation but does not require ERα or D1R activity. ***b***, In females, LTP at Hipp→NAc synapses occurs with a mechanism involving L-type VGCCs instead of NMDARs for Ca^{2+} influx, CAMKII, and ERα activity but does not require D1R activity.

which may suggest a role for the estrous cycle in modulating plasticity at Hipp→NAc synapses. Additionally, the bimodal distribution of our data obtained in the presence of NMDAR antagonism may indicate estrous cycle-dependent differences in LTP mechanisms. To our knowledge, there are no descriptions of shifts in LTP mechanisms across the estrous cycle (e.g., NMDA-dependent to -independent), though there is evidence indicating estrous cycle-dependent changes in hippocampal LTP magnitude as well as expression and posttranslational modifications of key synaptic proteins including NMDARs (Warren et al., 1995; Good et al., 1999; Bi et al., 2001; Diao et al., 2007; Smith et al., 2009; Waters et al., 2009; Tada et al., 2015; Iqbal et al., 2020). Given the behavioral role for Hipp→NAc synapses in mediating learning and motivation, determining how the estrogen impacts plasticity of these synapses will provide key insight into the synaptic basis for sex-different and estrous cycle-dependent alterations in behavior.

A key distinction we observed was in the sex-specific requirement of ERα in LTP in females (Fig. 7). This is congruent with observations in the hippocampus demonstrating sex differences in the requirement of estrogen receptors for LTP in CA1 (Vierk et al., 2012; W. Wang et al., 2018) and may stem from differences in expression or function. Membrane-localized ERα (mERα) is prevalent in the hippocampus and NAc where nuclear ERα is less abundant (Mitra et al., 2003; Vasudevan and Pfaff, 2007; Schultz et al., 2009; Grove-Strawser et al., 2010; Stanić et al., 2014; Krentzel and Meitzen, 2018; Krentzel et al., 2020; Almey et al., 2022), and females express higher levels of synapse-localized ERα (W. Wang et al., 2018). mERα influences dendritic structure and synaptic function (P. Micevych and Christensen, 2012; W. Wang et al., 2018; Mazid et al., 2023), and in the NAc, where dendritic spine density is modulated by estradiol, mERα can rapidly modulate mEPSCs (Staffend et al., 2011; Peterson et al., 2015; Proaño et al., 2018, 2020; Krentzel et al., 2019; Beeson and Meitzen, 2023; Miller et al., 2023). mERα can functionally couple with mGluRs (P. E. Micevych and Mermelstein, 2008; Grove-Strawser et al., 2010; Tonn Eisinger et al., 2018) to influence L-type VGCCs (Subbamanda and Bhargava, 2022), supporting the idea that estradiol can have rapid, transcriptionally independent effects on excitatory synapses. Alternatively, our observed sex-specific effect of ERα antagonism could be due to sex-specific functions of ERα activation, which has been reported in brain regions with no sex differences in ERα expression (Oberlander and Woolley, 2017; Krentzel and Meitzen, 2018). Further studies are necessary to identify the source of the sex-specific requirement for ERα in LTP at Hipp→NAc synapses.

D1R is not required for LTP at Hipp→NAc synapses

Dopamine is a critical regulator of the reward system and typically an important factor in LTP within the NAc (Floresco et al., 2001; Jay et al., 2004; Goto and Grace, 2005; Mameli and Lüscher, 2011; Pignatelli and Bonci, 2015; Madadi Asl et al., 2018; Speranza et al., 2021; Yu et al., 2022). While D1R is required for LTP at many excitatory synapses in the NAc, our results (Fig. 6) and previous work (LeGates et al., 2018) show that D1R activation is not required for LTP at Hipp→NAc synapses, a finding observed elsewhere in the striatum and in hedonic reward learning behaviors (Pennartz et al., 1993; Berridge and Robinson, 1998; Cannon and Palmiter, 2003). Our findings do not preclude the possibility that dopamine can influence plasticity in this pathway. In fact, others have shown dopamine-dependent modulation of LTP magnitude even when not required for induction (Otani et al., 2003; FitzGerald et al., 2015; Palacios-Filardo and Mellor, 2019). Further examination is required to fully understand dopamine-dependent effects on Hipp→NAc synaptic plasticity.

Implications of latent sex differences in LTP at Hipp→NAc synapses

The modulation of Hipp→NAc synaptic transmission is a critical contributor to reward-related behaviors, and these synapses are altered in response to stress and cocaine (LeGates et al., 2018; Sjulson et al., 2018; Williams et al., 2020). As such, the sex differences in LTP mechanisms at Hipp→NAc synapses holds significant implications for stress- and reward-related behavior and physiology. Recent studies support the idea of sex-specific LTP mechanisms underlying sex differences in spatial learning and memory (Monfort et al., 2015; Sneider et al., 2015; Safari et al., 2021; Gall et al., 2023), so the use of distinct mechanisms for Hipp→NAc LTP may explain some sex-dependent behavioral changes that occur in response to stress and mood disorders (Seney and Sibille, 2014; Wei et al., 2014; Hodes et al., 2015; Brancato et al., 2017; Salk et al., 2017; Huang et al., 2019; Williams et al., 2020). Together, our findings highlight sex-specific mechanisms underlying plasticity in a reward pathway that redefines our knowledge about LTP and offers potential molecular targets for therapeutics to treat conditions linked to aberrant reward processing and stress.

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