Brief Communication

β -Adrenoceptor activation enhances L-type calcium channel currents in anterior piriform cortex pyramidal cells of neonatal mice: implication for odor learning

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Early odor preference learning occurs in one-week-old rodents when a novel odor is paired with a tactile stimulation mimicking maternal care. β -Adrenoceptors and L-type calcium channels (LTCCs) in the anterior piriform cortex (aPC) are critically involved in this learning. However, whether β -adrenoceptors interact directly with LTCCs in aPC pyramidal cells is unknown. Here we show that pyramidal cells expressed significant LTCC currents that declined with age. β -Adrenoceptor activation via isoproterenol age-dependently enhanced LTCC currents. Nifedipine-sensitive, isoproterenol enhancement of calcium currents was only observed in post-natal day 7–10 mice. aPC β -adrenoceptor activation induced early odor preference learning was blocked by nifedipine coinfusion.

L-type calcium channels (LTCCs) are expressed in the heart (Hess et al. 1986) and brain (Hell et al. 1993). In neurons, LTCC-mediated calcium influx is critical for long-term potentiation (Grover and Teyler 1990; Kapur et al. 1998; Weisskopf et al. 1999; Moosmang et al. 2005), the putative cellular mechanism for learning. Blockade of LTCC leads to deficits in different learning paradigms including passive avoidance learning (Lashgari et al. 2006), spatial memory (Moosmang et al. 2005), fear extinction (Davis and Bauer 2012), and olfactory associative learning (Zhang et al. 2010; Jerome et al. 2012). Up-regulation of LTCC Cav1.2 subunit activity by β -adrenoceptor signaling plays an important role in regulating Ca^{2+} influx into myocytes (Reuter 1983; Yue et al. 1990) and neurons (Gray and Johnston 1987; Kavalali et al. 1997; Hoogland and Saggau 2004). However, few studies have looked at the functional role of β -adrenoceptor modulation of LTCCs in learning.

Early odor preference learning is a type of classical conditioning in which a tactile stimulus mimicking maternal care (e.g., brush stroking) serves as the unconditioned stimulus (US), and a novel odor serves as the conditioned stimulus (CS). The pairing of the US and CS lead to an approach response to the CS odor, lasting hours to days depending on the training paradigms (Yuan et al. 2014). Tactile stimulation triggers norepinephrine release onto the olfactory bulb and anterior piriform cortex (aPC) and activates the cAMP/PKA pathway via β -adrenoceptors (McLean et al. 1999; Grimes et al. 2012; Morrison et al. 2013; Ghosh et al. 2015). Early odor preference learning occurs in a sensitive post-natal period and terminates around post-natal day (PD) 10 (Sullivan et al. 2000) when a tactile stimulus no longer triggers sufficient norepinephrine release (Nakamura et al. 1987). NMDA receptors (NMDARs) and LTCCs activated upon exposure to an odor critically mediate calcium-dependent kinase activities (Jerome et al. 2012; Lethbridge et al. 2012; Morrison et al. 2013). The convergence of the US and CS pathways leads to CREB phosphorylation and CREB-dependent transcription critical for odor learning (McLean et al. 1999; Yuan et al. 2003, 2014). Here we investigated whether β -adrenoceptors directly modulate LTCCs in aPC pyrami-

dal cells as seen in heart (Yue et al. 1990) and hippocampal neurons (Gray and Johnston 1987; Kavalali et al. 1997; Hoogland and Saggau 2004). We compared the proportions of the LTCC currents and β -adrenoceptor modulations in pups within and beyond the sensitive period. The interaction of β -adrenoceptors and LTCCs in early odor preference learning was studied with pharmacological manipulations in the aPC during training.

All experimental procedures were approved by the Animal Care Committee at Memorial University and adhered to Canadian Council on Animal Care guidelines. C57B1/6J mice (Charles River) were bred on site. Dams were maintained under a 12-h light–dark cycle with ad libitum food and water. Day of birth was considered PD0.

We used whole-cell patch clamp recording to study aPC pyramidal cell calcium currents. Mouse pups of either sex from P7–10 and P14 above (P14–20) age groups were anesthetized with isoflurane and decapitated. Brains were extracted quickly and put in ice cold high-sucrose solution containing (in mM): 83 NaCl, 2.5 KCl, 3.3 MgSO_4 , 1 NaH_2PO_4 , 26.2 NaHCO_3 , 22 glucose, 72 sucrose, 0.5 CaCl_2 , bubbled with 95% O_2 and 5% CO_2 . Para-sagittal slices of 300 μm thickness were cut in Leica vibratome (VT 1000P) and incubated in sucrose solution at 35°C for 30 min and then left at room temperature. Slices were transferred to a recording chamber perfused with warm (30°C–32°C) Barium artificial CSF (aCSF) containing (in mM): 110 NaCl, 2.5 KCl, 1.3 MgCl_2 , 1 NaH_2PO_4 , 26.2 NaHCO_3 , 22 glucose, 2.5 BaCl_2 , tetrodotoxin (0.5 μM ; Tocris) with a flow rate of 2–3 mL/min. Slices were viewed with Olympus BX51WI upright microscope in differential interference contrast. Whole-cell Ca^{2+} currents were recorded selectively from layer II pyramidal neurons with 3–6 M Ω glass micropipette pulled in a Flaming/Brown puller (P-97, Stutter Instrument Co.). To distinguish from semilunar cells, pyramidal cells were selected by somatic morphology under DIC (oval shaped vs. semilunar shaped), depth in the layer II (deeper vs.

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superficial) (Suzuki and Bekkers 2011). In a previous report (Ghosh et al. 2015), we used the same criterion of cell selection and posthoc biocytin reconstruction demonstrated that the majority of cells recorded were pyramidal cells. Intrapipette solution contained (in mM): 130 D-gluconic acid, 130 CsOH, 5 NaCl, 10 HEPES, 12 phosphocreatine, 3 MgATP, 0.2 NaGTP, and 0.2 EGTA. Cells included in the data set had an initial access resistance $<20\text{ M}\Omega$ with $<25\%$ change throughout the duration of recording.

Cells were held at -70 mV in voltage-clamp mode, and depolarizing currents were injected into the cell through a recording pipette for 150 msec during each step. Steps ranged from -60 to 10 mV with 5 mV increase in each step. It is been reported that nifedipine-sensitive LTCCs in the piriform cortex demonstrates slow kinetics and half activation $\sim 0\text{ mV}$ (Magistretti et al. 1999). Ca^{2+} current was measured during the 0 mV step at its steady state at 146 msec. Control traces were recorded 10 min after establishing the whole-cell configuration. Drugs (LTCC antagonist nifedipine, $10\text{ }\mu\text{M}$; β -adrenoceptor agonist isoproterenol, $10\text{ }\mu\text{M}$; PKA inhibitor H89, $10\text{ }\mu\text{M}$; Sigma) were added to the aCSF for 10 min and then washed with aCSF for 30 min. Cadmium chloride ($100\text{ }\mu\text{M}$, Sigma) was added to the bath at the end of the experiments. Leak subtraction was done by subtracting cadmium traces from corresponding control, drug, and wash traces as shown in example traces. Multiclamp 700B amplifier and pClamp10 software was used for data acquisition. Signals were filtered at 2 kHz and digitized at 10 kHz sampling frequency. Clampfit 10.6 was used for data analysis.

Figure 1 shows the whole-cell calcium currents and nifedipine-sensitive LTCCs in two age groups (P7–10 vs. $>\text{P14}$). Whole-cell Ca^{2+} currents were reduced in the presence of nifedipine, suggesting an LTCC-mediated component. The LTCC component was significantly bigger in P7–10 pups ($49.5\% \pm 4.09\%$ of the control, $n = 11$, example current traces in one animal are shown in Figure 1A upper panel and the I – V curve is shown in the lower panel) than in P14 above pups ($27.2\% \pm 6.05\%$, $n = 8$, $t = 3.18$, $P = 0.006$; examples are shown in Fig. 1B; the comparison of the two age groups is shown in Fig. 1C). The larger portion

of the LTCC current in P7–10 pups correlates with a highly plastic period in which LTCC-dependent early odor preference learning occurs (Jerome et al. 2012; Mukherjee and Yuan, 2016).

Figure 2A and B demonstrated effects of isoproterenol on the whole-cell calcium currents in the two age groups. β -Adrenoceptor activation by isoproterenol moderately increased whole-cell Ca^{2+} current in P7–10 mice ($115\% \pm 7\%$ normalized to the control, compared with the wash $101\% \pm 3\%$, $n = 8$, $t = 2.51$, $P = 0.04$, paired t -test; Fig. 2A). However, isoproterenol was ineffective in older pups ($96\% \pm 5\%$ normalized to the control, compared with the wash $94\% \pm 6\%$, $n = 7$, $t = 0.44$, $P = 0.68$, paired t -test; Fig. 2B). In subsequent experiments, we tested whether isoproterenol enhanced LTCCs in the younger age group. Nifedipine application prior to isoproterenol abolished the effect of isoproterenol on whole-cell Ca^{2+} currents in P7–10 pups (normalized to control, nifedipine: $52\% \pm 6\%$, nifedipine + isoproterenol: $53\% \pm 4\%$, $n = 5$, $t = 0.23$, $P = 0.83$, paired t -test; Fig. 2C). This result suggests that β -adrenoceptor activation enhances LTCC-mediated currents in young pups during the sensitive period. Finally, isoproterenol enhancement of whole-cell Ca^{2+} current was also dependent on the cAMP/PKA activation. PKA inhibitor H89 preincubation prevented isoproterenol mediated increase in Ca^{2+} currents (normalized to the control: $96\% \pm 3\%$ in H89, $91\% \pm 5\%$ in isoproterenol, $n = 5$, $t = 1.34$, $P = 0.25$, paired t -test; Fig. 2D).

We then investigated interaction of the β -adrenoceptors and LTCCs in learning during the sensitive period. Behavioral study was done at 27°C with previously established protocols (Morrison et al. 2013; Ghosh et al. 2015). Briefly, intracranial infusion surgery and odor training were carried out on P7 pups. Pups were anesthetized via hypothermia (under ice) and placed in a stereotaxic apparatus. After an incision of the skin, two small holes were drilled. Of note, $0.5\text{ }\mu\text{L}$ of drug (isoproterenol $500\text{ }\mu\text{M}$, dissolved in saline; nifedipine $100\text{ }\mu\text{M}$ dissolved in 1% ethanol + saline; isoproterenol + nifedipine; isoproterenol + H89 $100\text{ }\mu\text{M}$ dissolved in saline; isoproterenol + APV $100\text{ }\mu\text{M}$ dissolved in saline) or vehicle (1% ethanol + saline) was infused bilaterally in specific coordinates for aPC (1.8 mm anterior and 2 mm bilateral, 3.5 mm ventral with respect to the bregma) at the rate of $0.25\text{ }\mu\text{L}/\text{min}$ through cannulas attached to the infusion tubing. The infusion tubing was attached to a Hamilton syringe driven by a precision pump (Fusion 400, Chemyx Inc.). One minute after infusion, cannulas were gently withdrawn, skin was sutured, and pups were left for 30 min on warm bedding for recovery before odor training.

Pups were placed on peppermint-scented bedding (0.3 mL peppermint extract in 500 mL bedding) for 10 min and were returned to the dam afterward. Twenty-four hours after the training, pups were placed in a two-choice testing apparatus consisting of a stainless steel box ($30 \times 20 \times 18\text{ cm}$) with mesh bottom kept over two training boxes—one with peppermint-scented bedding and the other with non-scented normal bedding. Time spent over either side was recorded in five 1-min trials with 1 min rest in between trials. Time spent over peppermint bedding was measured as percentage of total trial time. The aPC location was verified with methylene blue (2%) in the pilot experiments ($n = 6$), and infusion tracks were checked in pups following testing.

Previous research has shown that aPC adrenoceptors are critical for early odor preference learning in rodents (Morrison et al. 2013; Ghosh et al. 2015). Blocking β -adrenoceptors with propranolol systemic injection prevented odor preference learning in mice induced by pairing peppermint odor with stroking (Ghosh et al. 2015). In Figure 3, we show different behavioral outputs (percentage of time spent over peppermint-scented bedding during the testing) in pups with aPC drug or vehicle infusions. Training and testing schematic is shown in the upper panel of Figure

Figure 1. L-type calcium currents (LTCCs) in mouse pups of P7–11 and P14 above. (A) Example traces of whole-cell currents in a P10 mouse pup under control condition and during nifedipine (NIF) application (upper panel) and I – V relationship (lower panel). (B) Example traces of whole-cell currents in a P16 mouse pup under control condition and during nifedipine (NIF) application (upper panel) and I – V relationship (lower panel). Scale bars: 25 msec and 500 pA. Dotted lines indicate the time point for calcium current measurement. (C) Percentage of LTCC currents in P7–11 and P14 above mice. (*) $P < 0.05$.

Figure 2. Effects of β -adrenoceptor activation on whole-cell Ca^{2+} currents. (A) Example traces of whole-cell currents in a P10 mouse pup under control condition, during isoproterenol (ISO) application and wash (upper panel), I - V relationship (middle panel), and normalized current plots (lower panel). (B) Example traces of whole-cell currents in a P17 mouse pup under control condition, during isoproterenol (ISO) application and wash (upper panel), I - V relationship (middle panel), and normalized current plots (lower panel). (C) Example traces of whole-cell currents in a P9 mouse pup under control condition during nifedipine (NIF) and NIF + ISO applications (upper panel), I - V relationship (middle panel), and normalized current plots (lower panel). (D) Example traces of whole-cell currents in a P8 mouse pup under control condition during nifedipine (NIF) and NIF + ISO applications (upper panel), I - V relationship (middle panel), and normalized current plots (lower panel). (*) $P < 0.05$. Scale bars: 25 msec and 500 pA.

3A. Direct activation of β -adrenoceptors in the aPC induced odor preference learning when paired with odor alone. One-way ANOVA demonstrated significant group effects ($F_{(4,22)} = 11.82$, $P < 0.01$, Fig. 3A). Post hoc Fisher Test showed that the isoproterenol-infused group spent significantly more time in peppermint ($65.6\% \pm 1\%$, $n = 6$) compared with the saline infused group ($37.2\% \pm 2.6\%$, $n = 6$, $t = 5.50$, $P < 0.01$). The isoproterenol effect was reversed by co-infusion of H89 ($43.9\% \pm 2.6\%$, $n = 6$, $t = 4.21$, $P < 0.01$). Coinfusion of nifedipine prevented early odor preference learning (39.3 ± 3.21 , $n = 5$, $t = 7.8$, $P < 0.01$). These results suggest that LTCC-mediated calcium signaling is critical. β -Adrenoceptor augmentation of the LTCC currents likely promotes LTCC-mediated plasticity and learning through cAMP/PKA signaling (proposed pathways and interactions shown in Fig. 3B). β -Adrenoceptor-dependent LTCC activation at olfactory bulb synapses is also critical for odor associative learning (Zhang et al. 2010; Jerome et al. 2012). One caveat is that in vivo drug infusion affects more cell types than pyramidal cells in the aPC.

Detailed characterizations of whole-cell calcium currents in the piriform cortex have revealed diverse kinetics of the calcium currents among pyramidal cells (Magistretti et al. 1999; Suzuki and Bekkers 2006), similar to what we have observed in this study. These studies demonstrate various calcium channels in piriform cortex neurons including at least L-, N-, and T-type channels recorded at the soma. In this study, we focused on the nifedipine-sensitive LTCCs and its regulation by β -adrenoceptor activations given their roles in odor learning. LTCCs contribute to $\sim 50\%$ of the total voltage-gated Ca^{2+} current in pyramidal cells in the hip-

pocampus and visual cortex (Mintz et al. 1992). Their roles in plasticity and learning are proposed to be bridging neuronal excitation to transcription of Ca^{2+} -regulated genes (Bading et al. 1993; Impey et al. 1996; Deisseroth et al. 1998; Dolmetsch et al. 2001). In the hippocampus, LTCCs mediate protein synthesis sensitive, NMDAR-independent late phase LTP and spatial learning (Grover and Teyler 1990; Moosmang et al. 2005). However, in the aPC, we have shown that LTCC activation is dependent on NMDAR activation and both channels play critical but distinct roles in the early odor preference learning (Mukherjee and Yuan 2016). Here either D-APV or nifedipine blocked isoproterenol induced learning (Fig. 3A), consistent with the learning requirement on both NMDARs and LTCCs. Between the two isoforms $\text{CaV}1.2$ and $\text{CaV}1.3$, $\text{CaV}1.2$ has been identified as a major player since $\text{CaV}1.2$ knock out (Moosmang et al. 2005) but not $\text{CaV}1.3$ knockout (Clark et al. 2003) mice have deficiency in synaptic plasticity or learning. $\text{CaV}1.2$ channels contain PKA binding site (Davare et al. 2001). PKA activation by cAMP enhances LTCC current in the hippocampus (Kavalali et al. 1997; Hoogland and Saggau 2004), likely through phosphorylation of LTCCs. Our result showing PKA-dependent enhancement of calcium currents by β -adrenoceptors in neonatal aPC is consistent with these reports.

An intriguing result from this study is the age-dependent changes of both LTCC component and β -adrenoceptor modulation. LTCC component in the aPC pyramidal cell is larger ($\sim 50\%$) in the sensitive period mice (P7–10)

Figure 3. The interaction of β -adrenoceptors and LTCCs in early odor preference learning in mice. (A) Percentage of time spent over peppermint-scented bedding in vehicle, ISO or NIF + ISO infused groups. (**) $P < 0.01$. (B) A proposed model for β -adrenoceptor interaction with LTCCs in anterior piriform cortex of pyramidal neurons. β -adrenoceptor activation serves as unconditioned stimulus to activate cAMP/PKA pathway. PKA translocates to the nucleus to phosphorylate CREB, and phosphorylates LTCCs in the membrane to enhance LTCC-mediated calcium signaling, which converges with cAMP/PKA pathway on CREB phosphorylation.

compared with those beyond the sensitive period (~27%, P14–20). A reduced proportion of LTCC currents parallel age-dependent down-regulation of NMDARs (Franks and Isaacson 2005) that has been attributed to reduced plasticity in older rats in the aPC (Poo and Isaacson 2011). Altered adrenoceptor expressions and functions with age can also contribute to changes in plasticity (Pandipati and Schoppa 2012; Ghosh et al. 2015). For example, we have shown previously that β -adrenoceptor activation enhances excitatory inputs and reduces inhibitory inputs in the aPC only in mice within the sensitive period (Ghosh et al. 2015). Here we provide further evidence for postsynaptic correlates of β -adrenoceptor roles in synaptic plasticity and odor learning through LTCCs. The lack of modulation of LTCCs by β -adrenoceptors in older mice may relate to reduced expression of either LTCCs or β -adrenoceptors with age.

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