Brief Communication

Olfactory bulb α_2 -adrenoceptor activation promotes rat pup odor-preference learning via a cAMP-independent mechanism

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In this study, three lines of evidence suggest a role for α_2 -adrenoreceptors in rat pup odor-preference learning: olfactory bulb infusions of the α_2 -antagonist, yohimbine, prevents learning; the α_2 -agonist, clonidine, paired with odor, induces learning; and subthreshold clonidine paired with subthreshold β -adrenoceptor activation also recruits learning. Increased mitral cell layer pCREB occurs with clonidine-infusion, but cAMP is not increased. Similar results using a GABA_A-antagonist suggest that disinhibition may support clonidine-induced learning. We suggest that norepinephrine can act through multiple bulbar adrenoceptor subtypes to induce odor learning and that cAMP-dependent, as well as cAMP-independent, signals may act as unconditioned stimuli.

Odor-preference learning in the week-old rat pup occurs when a novel odor (conditioned stimulus, CS) is paired with activation of the noradrenergic locus coeruleus. The locus coeruleus is activated by the range of stimuli that can induce odor-preference learning including stroking (Sullivan and Leon 1986; McLean et al. 1993) and feeding (Johanson and Teicher 1980; Kucharski and Hall 1987; Sullivan and Hall 1988), all of which serve as unconditioned stimuli (US). Even rough maternal handling mimicked by mild shocks will engage odor-preference learning (Camp and Rudy 1988; Sullivan et al. 2000a). Odor-preference learning enables rat pups to locate the dam at a period when visual and auditory input is minimal. Odor paired with the activation of β -adrenoceptors in the olfactory bulb is sufficient to induce odor learning, while a bulbar β -adrenoceptor antagonist prevents odor-preference learning (Sullivan et al. 2000b). Thus, the olfactory bulb appears to be the critical site for the CS-US pairing, and the likely location of the odor memory.

However, in addition to β -adrenoceptors, which induce odor learning via activation of the cAMP/PKA/CREB cascade (McLean et al. 1999; Yuan et al. 2003a,b; Cui et al. 2007; Grimes et al. 2012), there are bulbar α -adrenoceptors likely to be engaged by norepinephrine (NE) release. Recently, studies of α_2 -adrenoceptor activation in the olfactory bulb in vitro have revealed receptor effects that could promote odor learning (Nai et al. 2010; Pandipati et al. 2010). In particular, the α_2 -adrenoceptor agonist, clonidine, has been shown to decrease granule cell excitability (Nai et al. 2010), releasing the odor-encoding mitral cells from tonic inhibition, and to promote olfactory bulb synchrony at γ EEG frequencies (Pandipati et al. 2010). These studies predict a role for α_2 -adrenoceptor activation in odor-preference learning.

The present experiments assess the role of bulbar α_2 -adrenoceptors in rat pup odor-preference learning.

In all experiments, drugs were infused into the olfactory bulbs on postnatal day (PND) 6. Day of birth was considered PND 0. Sprague-Dawley rat pups of both sexes were used and litters were culled to 12 pups on PND 1. Dams were maintained un-

der a 12-h reverse light/dark cycle at 22°C in polycarbonate cages with ad libitum access to food and water. All procedures were approved by the Institutional Animal Care Committee at Memorial University of Newfoundland and followed the Canadian Council on Animal Care guidelines.

Details of infusion methods have been reported previously (Lethbridge et al. 2012). Briefly, PND 5 rat pups were anesthetized via hypothermia and two customized guide cannulae (27-gauge, 2.5 mm apart, anchored by dental acrylic and extending ~1 mm beyond the acrylic) were implanted into the center of the olfactory bulb and fixed to the skull with dental acrylic. Infusion cannulae made from 30-gauge stainless-steel tubing were inserted into PE20 polypropylene tubing attached to a 10- μ L microsyringe and placed in a multisyringe pump.

In the first experiment, on PND 6, peppermint odor was paired with mild electrical shock. Animals received bilateral intrabulbar infusions of saline or yohimbine (500 μ M, 1 μ L/bulb at 0.1 μ L/min) and were randomly assigned to one of three groups: (1) saline + shock, (2) saline + shock + odor, or (3) yohimbine + shock + odor. The training chamber included a grid assembly floor connected to a shock generator (Muromachi Kikai Co.). The paired group received 11 presentations of a 30-sec odor stimulus delivered by sliding an odorized bedding tray (0.3 mL peppermint extract/500 mL clean bedding) under the grid for 30 sec, ending with a 1-sec shock (0.5 mA). The intertrial interval was 2 min.

On PND 7, pups were tested for odor-preference memory in a stainless-steel test box placed on top of two bedding boxes separated by a 2-cm neutral zone. One box contained peppermint bedding while the other box contained clean, unscented bedding. Each pup underwent five 1-min trials during which it was placed in the neutral zone of the test box and allowed to move freely. The amount of time spent over peppermint bedding and unscented bedding over five trials was calculated. Values reported are the percentages of time spent over peppermint bedding divided by total time spent over both beddings. One-way ANOVAs and post-hoc Fisher tests were used to evaluate statistical significance with *P* set at <0.05. An intrabulbar infusion of 4% methylene blue dye was followed by dissection of the olfactory bulbs to check cannulae position. Pups with cannulae blockage during infusion, or misplaced cannulae, were excluded from analysis.

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Pairing peppermint odor with shock induced odor-preference learning, while the α_2 -adrenoceptor antagonist yohimbine prevented odor-preference learning ($F_{(2,33)} = 12.18$, $P < 0.001$) (Fig. 1A). Saline + shock + odor pups spent significantly more time ($56.05\% \pm 3.68$, $n = 12$) over peppermint than either the saline + shock group ($37.63\% \pm 4.04$, $n = 12$) or the yohimbine + shock + odor group ($33.86\% \pm 2.21$, $n = 12$). Blocking α_2 -adrenoceptors locally in the olfactory bulb prevented preference learning that was induced by pairing odor with electrical shock.

We next asked whether α_2 -adrenoceptor activation could act as a US for odor-preference learning. PND 6 rats were placed on peppermint bedding for 10 min and the α_2 -adrenoceptor agonist, clonidine (5, 50, or 500 μM) or saline, was infused into the olfactory bulb bilaterally at the rate of 0.1 $\mu\text{L}/\text{min}$. To control for the potential effect of clonidine on α_1 -adrenoceptors at the higher concentration, a group of animals with co-infusion of prazosin (10 μM , α_1 -adrenoceptor antagonist) and clonidine (500 μM) was included in the study. Clonidine dose-dependently induced odor-preference learning on PND 7 ($F_{(4,62)} = 4.77$, $P = 0.002$) (Fig. 1B). The 500 μM clonidine infusion group spent significantly more time on the peppermint side ($63.89\% \pm 3.03$, $n = 14$) than the saline group ($43.82\% \pm 2.97$, $n = 18$), the 5 μM clonidine group ($51.19\% \pm 2.25$, $n = 14$), or the 50 μM clonidine group ($52.48\% \pm 4.49$, $n = 16$). The coinfusion of 500 μM clonidine and 10 μM prazosin group ($57.8\% \pm 5.97$, $n = 5$) still showed a significant learning effect when compared with the saline group. This outcome suggests that clonidine-mediated α_2 -adrenoceptor activation can act as an US for odor-preference learning.

We then sought to clarify the cellular mechanisms of α_2 -adrenoceptor action during clonidine-induced learning. The evidence that clonidine reduces granule cell activity (Nai et al. 2010; Pandipati et al. 2010) predicts elevated mitral cell excitation during odor paired with clonidine. We performed pCREB immunohistochemistry as an index of mitral cell activation and to assess the role of CREB in the clonidine model. Unilateral bulbar infusions of either clonidine (500 μM) or the GABA_A receptor antagonist gabazine (100 μM , previously shown to induce odor-preference learning) (Lethbridge et al. 2012) were paired with odor. The remaining bulb was infused with saline as a control. Additional animals were given intrabulbar isoproterenol (50 μM) (Fig. 2A,B) or a systemic isoproterenol injection

Figure 1. Olfactory bulb α_2 -adrenoceptors are critically involved in early odor-preference learning in rats. (A) Bulbar infusion of the α_2 -adrenoceptor antagonist yohimbine prevented odor-preference learning induced by odor + shock pairing. (PP) Peppermint. (B) Clonidine bulbar infusion dose-dependently induced odor-preference learning. Bars show the percentages of time spent on the peppermint side in a two-choice test box in different experimental groups. (**) $P < 0.01$; (*) $P < 0.05$. Error bars, mean $\pm$ SEM.

Figure 2. α_2 -adrenoceptor activation increases pCREB expression in mitral cells via a cAMP-independent pathway. (A) An example of mitral cell pCREB expression following bulbar infusion of the β -adrenoceptor agonist isoproterenol. (MC) Mitral cell layer. Scale bars, 500 μm and 100 μm . (B) Mitral cell cAMP activation in an alternate section from the same bulb induced by isoproterenol infusion. Scale bars, 500 μm and 100 μm . (C) Clonidine infusion increased mitral cell pCREB expression in the olfactory bulb. Clonidine was infused into the right olfactory bulb. Bars show the relative optical densities (RODs) of mitral cell pCREB in the lateral and medial regions of the two olfactory bulbs. (**) $P < 0.01$. (D) Gabazine infusion increased mitral cell pCREB expression in the olfactory bulb. Gabazine was infused into the right olfactory bulb. (*) $P < 0.05$. (E) Clonidine infusion did not change mitral cell cAMP expression in the olfactory bulb. (F) Gabazine infusion did not change mitral cell cAMP expression in the olfactory bulb. Error bars, mean $\pm$ SEM.

(2 mg/kg, data not shown) to confirm the β -adrenoceptor-associated increase in pCREB and cAMP patterns reported previously (Yuan et al. 2000, 2003a,b; Cui et al. 2007). At 5–10 min following the end of training, animals were anesthetized with chloral hydrate and perfused transcardially with ice-cold saline followed by ice-cold fixative (4% paraformaldehyde in 0.1 M phosphate buffer at pH 7.4). Brains were removed and post-fixed for 1 h in fixative and then immersed in 20% sucrose overnight at 4°C. They were stored in sucrose until cutting. Brains were quick-frozen on dry ice and 30- μm coronal sections cut in a

cryostat at -20°C . A pCREB antibody (1:100, Cell Signalling) was used to probe for CREB phosphorylation at Ser133. The antibody was dissolved in phosphate-buffered saline with 0.2% Triton-X-100, 0.02% sodium azide, and 2% normal goat serum and applied to sections overnight at 4°C in a humidified chamber. The next day, sections were incubated in a biotinylated secondary antibody (Vectastain Elite) followed by a diaminobenzidine tetrahydrochloride reaction. Sections were dehydrated and coverslipped with Permount.

Staining for pCREB was analyzed using a Bioquant image analysis system. Images of sections were captured with a CCD camera connected to a Leitz microscope. For each section analyzed, the optical density (OD) of the olfactory nerve layer was used as a measure of background OD. Regions of interest (ROIs) were selected using a hand tracing tool. The relative OD of each ROI was obtained using the following formula: (OD of ROI - OD of background)/OD of background. Image analysis was conducted on every third to fourth section across the rostrocaudal extent of the olfactory bulb measuring the mitral cell layer in both the lateral and medial regions. The relative ODs (RODs) of the lateral and medial measurements were compared among groups and the mean $\pm$ SEM are reported for each ROI. Paired *t*-tests were used to evaluate differences ($P < 0.05$).

Unilateral clonidine infusion significantly increased mitral cell layer pCREB expression in the lateral (ROD clonidine: 0.059 ± 0.012 vs. saline: 0.041 ± 0.010 , $n = 6$), but not medial (ROD clonidine: 0.040 ± 0.012 vs. saline: 0.036 ± 0.010 , $n = 6$), regions of the olfactory bulb (Fig. 2C). Gabazine infusion increased mitral cell layer pCREB expression in both the lateral (gabazine: 0.082 ± 0.017 vs. saline: 0.050 ± 0.011 , $n = 7$) and the medial (gabazine: 0.079 ± 0.019 vs. saline: 0.055 ± 0.015 , $n = 7$) regions of the olfactory bulb (Fig. 2D). These results suggest that α_2 -adrenoceptor-mediated disinhibition synergizes with odor input to activate pCREB in odor-encoding mitral cells in the peppermint presentation region (Lethbridge et al. 2012), while gabazine disinhibition is strong enough to directly activate mitral cell pCREB more globally.

The activation of pCREB by clonidine and gabazine learning doses paired with odor 5–10 min post-training is consistent with a role for an α_2 -adrenoceptor-mediated disinhibition in learning and parallels the pCREB increases reported with an isoproterenol US (Yuan et al. 2000) and verified in examples for the present experiments (Fig. 2A).

Using alternate sections from a subset of the infused bulbs, we asked whether increases in cAMP occurred 5- to 10-min post-training as reported earlier for β -adrenoceptor-mediated learning (Fig. 2B; Yuan et al. 2003b; Cui et al. 2007). The procedures for cAMP staining and analysis were the same as those used for pCREB immunocytochemistry except that a cAMP antibody (1/2000, Genscript) was used.

Neither unilateral clonidine nor gabazine infusion changed mitral cell cAMP expression in either the lateral (clonidine: 0.055 ± 0.016 vs. saline: 0.059 ± 0.016 , $n = 6$; gabazine: 0.086 ± 0.022 vs. saline: 0.078 ± 0.012 , $n = 4$) or the medial (clonidine: 0.061 ± 0.016 vs. saline: 0.074 ± 0.025 , $n = 4$; gabazine: 0.113 ± 0.025 vs. saline: 0.108 ± 0.014 , $n = 4$) regions of the olfactory bulb (Fig. 2E,F).

The optical density of pCREB and cAMP staining did not vary among conditions in the granule cell layer in contrast to what we found for the mitral cell layer (data not shown). This result and the observation that the pCREB-reactive nuclei in the mitral cell layer were, in general, equal to or larger than $10\ \mu\text{m}$ in diameter (in contrast to $\sim 5\text{--}7\ \mu\text{m}$ in the granule cell layer) (see Fig. 2A, lower panel) suggest that changes in pCREB optical density in the mitral cell layer are due to changes in mitral cell reactivity rather than to changes in granule cell pCREB. However, using antibodies

to positively identify cell types should be considered in future studies to further strengthen this inference.

Finally, we probed the interaction between α_2 - and β -adrenoceptor activation during early odor-preference learning. We asked whether clonidine infusion would enable learning in animals that receive subthreshold doses of isoproterenol during training. We first replicated the reported inverted U-curve effect of isoproterenol (Sullivan et al. 1991) by giving PND 6 pups subcutaneous injections of saline or various doses of isoproterenol (1, 1.5, 2, 6 mg/kg, made in saline). Thirty minutes after injection, pups were removed from the dam and individually placed on unscented clean bedding for a 10-min habituation period and then transferred to peppermint bedding for a 10-min odor exposure.

Odor-preference testing the next day showed that only the moderate dose of isoproterenol, 2 mg/kg, induced learning ($F_{(4,43)} = 2.94$, $P = 0.031$) (Fig. 3A). Post-hoc tests showed significant differences between the 2 mg/kg group ($56.64\% \pm 4.48$, $n = 9$) and all lower dose groups: saline ($34.61\% \pm 3.73$, $n = 13$), 1 mg/kg isoproterenol ($35.81\% \pm 4.53$, $n = 9$), and 1.5 mg/kg isoproterenol ($40.24\% \pm 9.10$, $n = 8$).

We next tested whether coapplication of clonidine infused bilaterally as described earlier would left-shift the isoproterenol dose curve. A saline infusion-only group was included as a negative control. Co-application of the previously suboptimal 50 μM clonidine enabled odor-preference learning when combined with the previously suboptimal 1.5 mg/kg dose of isoproterenol ($F_{(5,46)} = 2.78$, $P = 0.028$) (Fig. 3B). The 1.5 mg/kg group ($53.77\% \pm 3.61$, $n = 9$) spent significantly more time over the peppermint bedding than the 2 mg/kg group ($31.75\% \pm 3.69$, $n = 7$) and the saline infusion group ($38.84\% \pm 2.09$, $n = 13$), which did not differ. These results reveal additive effects of α_2 - and β -adrenoceptor activation in the formation of early odor-preference learning.

Taken together, our pattern of results is consistent with a critical role for the α_2 -adrenoceptor in early odor-preference learning and supports the prediction from recent *in vitro* studies demonstrating an α_2 -adrenoceptor-mediated disinhibition of mitral cells from granule cells (Pandipati et al. 2010), which would enhance mitral cell excitation and facilitate recruitment of NMDA-mediated plasticity. These effects together with β -adrenoceptor-mediated effects on mitral cells (Hayar et al. 2001; Yuan et al. 2003b; Yuan 2009; Lethbridge et al. 2012), as well as behavioral evidence (Harley et al. 2006) that systemic α_1 -adrenoceptor

Figure 3. α_2 -adrenoceptor coactivation enables odor learning with suboptimal doses of isoproterenol. (A) Isoproterenol dose dependently induced early odor-preference learning in an inverted U-curve fashion. (B) Addition of subthreshold 50 μM clonidine enabled odor-preference learning with a subthreshold 1.5-mg/kg dose of isoproterenol. (**) $P < 0.01$; (*) $P < 0.05$. Error bars, mean $\pm$ SEM.

activation serves as a US for odor-preference in rat pups, argue that US-associated NE release in the olfactory bulb acts through multiple adrenoceptors to promote optimal plasticity-inducing activation of the odor-encoding mitral cells. Memory for the conditioning odor is likely to be represented as a stronger, sharper, and more synchronized mitral cell output from the olfactory bulb. An increased output synchrony has recently been shown to indicate encoded reward (Doucette et al. 2011). γ frequency enhancement by the α_2 -adrenoceptor may confer the reward signature in odor preference learning.

It is not known at this point how the varying forms of adrenoceptor plasticity promotion interact intracellularly. Although the role of disinhibition is well understood, the specific route to CREB phosphorylation in the absence of a cAMP increase in mitral cells remains to be elucidated. The ability to combine subthreshold α_2 - and subthreshold β -adrenoceptor activation to induce odor learning suggests a converging intracellular interaction. It will be interesting to examine cAMP changes in the additive model in future experiments.

The amount of NE released as a function of the US is also of considerable interest. Milk infusion (Kucharski and Hall 1987) and mild shock (Moriceau et al. 2009) produce longer-lasting memories than those induced by stroking or isoproterenol. We predict that the concentration of NE released in the vicinity of the bulbar adrenoceptors determines memory duration by acting through multiple concentration-sensitive receptor subtypes. The inverted U curve associated with β -adrenoceptor activation is well characterized (Sullivan et al. 1991; Langdon et al. 1997; Yuan et al. 2000). Additionally, at the granule cell-to-mitral cell synapse, NE has differing effects depending on both concentration and developmental stage (Nai et al. 2009; Pandipati et al. 2010). Under natural conditions, NE concentrations likely will favor complex interactions of excitation and inhibition, fine-tuning odor encoding at more than one level.

Finally, whether early odor-preference memory is restricted to the olfactory bulb after initial encoding is unknown. Some evidence suggests stronger memories come to be shared with downstream sites such as the piriform cortex (Kucharski and Hall 1987). For this to occur, changes in output synchrony such as those associated with α_2 -adrenoceptor activation may be even more important than changes in the strength of olfactory nerve-to-mitral cell firing (Lethbridge et al. 2012).

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