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Research Report

Role of olfactory bulb serotonin in olfactory learning in the greater short-nosed fruit bat, *Cynopterus sphinx* (Chiroptera: Pteropodidae)

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ABSTRACT

The role of olfactory bulb (OB) serotonin [5-hydroxytryptamine (5-HT)] in olfactory learning and memory was tested in the greater short-nosed fruit bat, *Cynopterus sphinx* (family Pteropodidae). Graded concentrations (25, 40, and 60 µg) of 5,7-dihydroxytryptamine (5,7-DHT) or saline were injected into the OB of bats one day before training to the novel odor. In a behavioral test, 5,7-DHT (60 µg) injected bats made significantly fewer feeding attempts and bouts when compared to saline-injected bats during learning and in the memory test. Subsequent biochemical analysis showed that 5-HT level was effectively depleted in the OB of 5,7-DHT injected bats. To test odor-induced 5-HT mediated changes in 5-HT receptors and second messenger cascade in the OB, we examined the expression of 5-HT receptors and mitogen-activated protein kinase (MAPK)/Erk cascade after training to the novel odor. We found that odor stimulation up-regulated the expression of 5-HT_{1A} receptor, *Erk1* and *Creb1* mRNA, and phosphorylation of ERK1 and CREB1. Odor stimulation failed to induce expression in 5-HT-depleted bats, which is similar to control bats and significantly low compared to saline-treated bats. Together these data revealed that the level of 5-HT in the OB may regulate olfactory learning and memory in *C. sphinx* through Erk and CREB.

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1. Introduction

Long-term potentiation (LTP) is an actively-dependent enhancement of synaptic transmission that can critically regulate long-term memory (LTM) formation (Martin et al., 2000). Formation of LTM, particularly the regulation of synaptic activity during learning and memory consolidation,

requires activation of gene transcription and *de novo* protein synthesis (Davis and Squire, 1984; Alberini et al., 1994; Bourchouladze et al., 1998; Guzowski et al., 2001; Bozon et al., 2002). Learning-evoked changes are accompanied by alterations in gene expression and they depend upon the elevation of cyclic adenosine monophosphate (cAMP), activation of protein kinase A (PKA), and mitogen-activated protein

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kinase (MAPK) (Romero et al., 1996; Selkirk et al., 1998; Stamford et al., 2000). Extracellular-regulated kinase (Erk) family of MAPKs is involved in common signaling pathway of learning and memory (reviewed in Sweatt, 2001; Thiels and Klann, 2001; Adams and Sweatt, 2002). Erk can phosphorylate transcriptional activator cAMP response element binding protein 1 (CREB1) and phosphorylation of CREB1 promotes induction of genes regulated by cAMP response elements (CREs) (Mohamed et al., 2005). CREB1 acts as a universal modulator in memory formation and plays a key role in synaptic plasticity process, which is needed for learning and formation of LTM (Balschun et al., 2003). Furthermore, the number of neurotransmitters and their receptors appear to influence synaptic plasticity and memory (Roberson et al., 1999).

Sensory input combined with appropriate levels of monoaminergic input initiate a cAMP cascade that ultimately contributes to long-term changes in cell function (Kandel, 2001). Serotonin [5-hydroxytryptamine (5-HT)]/norepinephrine (NE) interaction in the olfactory bulb (OB) elevates cAMP level and further phosphorylates CREB, leading to changes in protein synthesis (Yuan et al., 2003). 5-HT has been detected in primary olfactory centers of the brain of many species where the centrifugal systems innervating the main olfactory bulb (MOB) play a crucial role in modulating/processing of olfactory information in the OB (Moiseiwitsch and Lauder, 1995; Moriizumi et al., 1994; Whitaker-Azmitia et al., 1996; Gómez et al., 2005). The molecular and cellular mechanisms underlying storage of short- and long-term memory have been extensively linked to 5-HT and stimulation of its diverse receptors (Kandel, 2001; Barbas et al., 2003). Recent findings indicate that activation of brainstem serotonergic neurons regulate the amplitude of olfactory input (Petzold et al., 2009).

Specialized frugivory appears to be associated with increased relative brain volume suggesting that these two traits evolve together (Ratcliffe, 2009). Compared to other mammals, including insectivorous bats, frugivorous bats also have a relatively large hippocampus and well developed spatial memory (Hutchison et al., 2003; Schnitzler et al., 2003). Fruit and nectar feeding bats may use spatial memory to locate their previously experienced food sources (Wilson and McNaughton, 1993; Fleming and Eby, 2003; Thiele and Winter, 2005; Winter and Stich, 2005), and concentration of volatile compounds originated from the fruits/flowers may serve as a signal for the bats to assess ripeness and palatability (Luft et al., 2003; Sánchez et al., 2006; Hodgkinson et al., 2007). Laska (1990) observed olfactory preference of *Carollia* spp. in captivity, and reported that odor is more important than the form and texture of fruit. Experiments with wild and captive bats have demonstrated that sulphur-containing perfume attracts the flower visiting bat *Glossophaga soricina* (von Helversen et al., 2000). The greater short-nosed fruit bat *Cynopterus sphinx* feeds on variety of fruits, flowers and leaves (Bhat, 1994). Radio-tracking revealed that, after leaving the day roost, *C. sphinx* immediately visits the previously visited fruit tree, then starts searching for food sources in the vicinity (Marimuthu et al., 1998). *C. sphinx* always carries its young while foraging and late postnatal young accompany their mothers on foraging flights (Elangovan et al., 2003; Gopukumar et al., 2003). These precedents suggest that *C. sphinx* may have learned the location of food patches and odor of palatable fruits, flowers and

leaves. Moreover, it possibly uses spatial-temporal memory to locate the previously visited foraging area and then use the olfactory cue to find food sources.

We used *C. sphinx* as a model to understand the role of 5-HT in olfactory learning and memory in fruit bat. We tested the individuals' learning ability and retention of memory to the novel odor after depletion of 5-HT in the OB. We show here that olfactory learning, possibly mediated by odor stimuli combined with at least 50% of normal 5-HT levels in the OB, activates the 5-HT_{1A} receptor and enhances induction of *Erk1*, CREB1 transcription and its phosphorylation.

2. Results

2.1. Behavioral response to the novel odor

In captivity, *C. sphinx* actively foraged from 20:00 to 22:00 h and 01:00 to 02:00 h. Each bat was trained individually and its learning performance to the novel odor was compared on a day-to-day basis. Both saline and 5,7-dihydroxytryptamine (5,7-DHT)-treated bats responded positively to the novel odor but the latter reacted slowly (Fig. 1). Post hoc comparisons revealed significant differences in overall performance of 5,7-DHT (25, 40, 60 µg)-treated compared to saline-treated bats ($F_{3,101}=12.69$, $p<0.01$). The out-flying of the former group compared to the latter group did not vary significantly at any concentration of 5,7-DHT (25 µg: $F_{1,55}=0.52$, $p=0.82$; 40 µg: $F_{1,55}=0.78$, $p=0.39$; 60 µg: $F_{1,55}=3.94$, $p=0.60$). The lowest concentration of 5,7-DHT (25 µg)-treated bats showed attempts to feed ($F_{1,55}=0.03$, $p=0.86$), and feeding bouts ($F_{1,55}=9.83$, $p=0.63$) similar to those of saline-treated bats. However, the higher concentrations of 5,7-DHT-treated bats caused significantly fewer attempts to feed (40 µg: $F_{1,55}=0.58$, $p<0.05$; 60 µg: $F_{1,55}=5.96$, $p<0.05$) and feeding bouts (40 µg: $F_{1,55}=30.54$, $p<0.001$; 60 µg: $F_{1,55}=72.96$, $p<0.001$) than in saline-treated bats. Therefore, when 5-HT in the OB is depleted with 5,7-DHT, bats failed to respond to the novel odor (Fig. 2A). Interestingly, saline and 5,7-DHT-treated bats did not make a feeding attempt or bout to the fresh apple piece without cinnamon powder.

The odor which had been experienced by the animals was provided to test their retention of memory. The lowest concentration of 5,7-DHT (25 µg) did not significantly affect

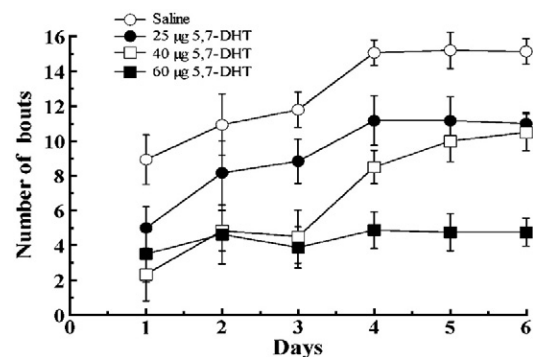


Fig. 1 – The mean number (\pm SEM) of feeding bouts of *C. sphinx* during exposure to the novel odor.

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