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The role of endogenous pituitary adenylyl cyclase activating polypeptide (PACAP) in nicotine self-administration, reward and aversion

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ABSTRACT

Pituitary adenylyl cyclase activating polypeptide (PACAP) and its receptors (PAC1, VPAC1, and VPAC2) are localized in brain regions implicated in stress response, reward seeking and aversive responses, raising the possibility that PACAP may be involved in motivational effects of nicotine. To test this hypothesis, we used two-bottle choice (TBC) and place conditioning paradigms and assessed if nicotine preference or conditioned place preference (CPP) or aversion (CPA) induced by nicotine would be altered in mice lacking PACAP compared to their wild-type controls. In the TBC paradigm, mice had access to two water bottles during the first week and then one of the water bottles was switched to nicotine solution (20, 40 and then 80 μg/mL). The volume of water and nicotine consumed was measured every day. In the place conditioning paradigm, mice were tested for baseline place preference on day 1, received conditioning with saline versus a low (0.25) or high (1 mg/kg) dose nicotine and, respectively, tested for CPP or CPA 24 h following the last conditioning. We discovered that mice lacking PACAP compared to their wild-type controls exhibited more preference for nicotine over water in the TBC paradigm, particularly at the two higher concentrations of nicotine. While the rewarding action of the low dose nicotine was not altered in mice lacking PACAP, the aversive effect of the high dose nicotine was blunted in these mice compared to their wild-type controls. The present results suggest that endogenous PACAP may play a functional role in nicotine preference and its aversive effect.

1. Introduction

Smoking tobacco not only affects the user but also others, such as second- and even third-hand bystanders. It has been reported that nearly fifty million people in the US continue to use one form of tobacco (Fiore et al., 2014). Chronic nicotine use can lead to addiction, which is characterized by compulsive use of nicotine despite negative consequences and high relapse rate. Indeed, while about 70% of smokers want to quit, only a small percentage (7%) of them succeed. This is even worse if smokers simultaneously use other drugs, such as alcohol (Carmody et al., 1985; DiFranza and Guerrera, 1990; Miller and Gold, 1998; Rimm et al., 1995), or suffer from mental illnesses (Mackowick et al., 2012a; Mackowick et al., 2012b; Picciotto et al., 2002; Picciotto and Zoli, 2002).

The socioeconomic burdens of tobacco use are also tremendously high. According to the previous Center for Disease Control estimates, annual productivity losses attributed to smoking were about $100 billion. In fact, it is predicted that decreases in the use of tobacco products may reduce the US economic burden by over $50 billion (McGinnis and Foege, 1999). Despite these alarming reports, a limited number of pharmacotherapeutic agents are available to treat this relapsing chronic brain disorder. In some cases, these medications are not effective or cause similar adverse effects as smoking tobacco.

Nicotine has both rewarding and aversive effects, which are known to play a major role in its addictive properties. While the rewarding action of nicotine contributes to the positive reinforcing actions of nicotine as well as in the initiation of addiction to nicotine, the aversive effect of nicotine hampers its initial intake/use [for a review, see (Fowler and Kenny, 2014)]. Notably, negative affective states developing following the cessation of nicotine serve as negative reinforcement and lead to craving and relapse. Thus, novel key mechanisms and pathways that facilitate the aversive effects of nicotine and/or reduce its rewarding and reinforcing actions or reduce the negative affective states associated with nicotine withdrawal need to be characterized because they can be potential targets for the development of pharmacotherapy to curb nicotine addiction and smoking cessation.

Pituitary adenylyl cyclase activating polypeptide (PACAP) is a 38 amino acid peptide and is a member of the secretin family with greater homology to the vasoactive intestinal polypeptide (VIP). PACAP and its receptors (PAC1, VPAC1, and VPAC2) are localized in brain regions

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implicated in stress response, motivated behaviors, reward seeking and drug addiction. Notably, they are found in the hypothalamus on arginine vasopressin (AVP)- and corticotropic releasing hormone (CRH)-containing neurons (Yu et al., 2008) as well as in brain regions involved in motivated behaviors [reviewed in (Vaudry et al., 2000)]. Importantly, PACAP has been shown to regulate the expression of CRH (Agarwal et al., 2005; Grinevich et al., 1997; Stroth and Eiden, 2010; Stroth et al., 2011a; Stroth et al., 2011b). Considering that the stress circuit has been implicated in the motivational effects of nicotine (al'Absi, 2006; Gentile et al., 2011; Lovallo, 2006; McKee et al., 2011; Van Waes et al., 2006; Wong et al., 2014), we hypothesized that the PACAP signaling is involved in these effects of nicotine. Interestingly, we have previously shown that nicotine activates the HPA axis, at least in part, via a CRH-mediated mechanism (Lutfy et al., 2012) and CRH has been reported to induce aversion (Cador et al., 1992) and taste aversion (Benoit et al., 2000). Thus, we tested the hypothesis that endogenous PACAP mediates the reinforcing and aversive effects of nicotine. To address this hypothesis, we used the place conditioning and TBC paradigms, which are widely used as animal models of drug reward and aversion (Bardo and Bevins, 2000; Tzschentke, 1998), and preference (Belknap et al., 1993; Frahm et al., 2011; Meliska et al., 1995a; Meliska et al., 1995b), respectively, and assessed the role of endogenous PACAP in these actions of nicotine.

2. Materials and methods

2.1. Animals

Female mice (3–5 months of age) lacking PACAP and their wild-type littermates/controls fully backcrossed on a C57BL/6 mouse strain were bred in house and used throughout. The original heterozygous breeding pairs were generously supplied by Dr. James Waschek (Los Angeles, CA) and these mice have been described previously (Colwell et al., 2004). Mice were placed 2–4 per cage with free access to food and water except during the conditioning as well as pre- and post-conditioning test periods. All experiments were approved by the Animal Care and Use Committee at Western University of Health Sciences (Pomona, CA) and were in accordance with the National Institute of Health guideline for the Use and Care of Laboratory Animals in Research. All experiments were conducted during the light phase except the two bottle-choice (TBC) paradigm which included drinking in both light and dark cycles.

2.2. Drugs

Nicotine bi-tartrate purchased from MP Biomedical (Solon, Ohio) and dissolved in normal saline or drinking water prior to use each day. The drug was injected subcutaneously or placed in the drinking water at the doses and concentrations described below. The concentrations and doses of nicotine were all as the salt form of the drug.

2.3. Two-bottle choice (TBC) paradigm

To determine the role of endogenous PACAP in nicotine preference, we used the TBC paradigm which is widely used to determine consummatory and reinforcing actions of nicotine, alcohol and natural reinforcers (Belknap et al., 1993; Frahm et al., 2011; Meliska et al., 1995a; Meliska et al., 1995b). We used the Volumetric Drinking Monitor (VDM; Columbus Instruments, Inc.) system and measured nicotine preference in mice lacking PACAP and their wild-type littermates/controls. Mice (n = 5–6 mice per genotype) were housed individually for a week while they had free access to laboratory chow and water via two sipper tubes each connected to a water bottle (500 mL). This was done to habituate the mice to the test condition and to determine preference for one water bottle over the other for each mouse. On day 8, one of the water bottles was replaced with a bottle containing nicotine (20 μg/mL). For the wild-type mice, the preferred water side was switched to nicotine solution to facilitate nicotine drinking. Considering that mice lacking PACAP did not exhibit preference for one side over the other, we selected the comparable water side to that of the wild-type mice and switched it to nicotine solution. On day 16 and then on day 27, the concentration of nicotine was increased to 40 and 80 μg/mL, respectively. The volume of water/water (days 1–7) and water/nicotine (days 8–15, 16–26 and 27–36 for the three concentrations of nicotine, respectively) consumed by each mouse was recorded daily. The experiment was repeated using two cohorts (n = 2–3 mice per genotype in each cohort). The concentration of nicotine was selected based on an earlier study which showed that mice consumed low concentration of nicotine (up to 50 μg/mL) when they had a choice between nicotine and water (Frahm et al., 2011).

2.4. Place conditioning paradigm

To examine the role of endogenous PACAP in the rewarding and aversive effects of nicotine, we used an unbiased place conditioning paradigm, which is widely used as an animal model of reward and aversion (Bardo and Bevins, 2000; Tzschentke, 1998). The description of the place conditioning apparatus is provided elsewhere by our research team (Nguyen et al., 2012; Tseng et al., 2013). Nicotine has both rewarding and aversive effects, while low doses of the drug induce place preference, the higher doses elicit place aversion (Castane et al., 2002; Grabus et al., 2006). To test the role of PACAP in the rewarding action of nicotine, mice lacking PACAP and their wild-type control (n = 15–17 mice per genotype) were tested for baseline preference toward the conditioning chambers on day 1. On day 2, mice were injected with either saline or a low dose of nicotine (0.25 mg/kg) and confined for 15 min to vehicle-paired or drug-paired chamber, respectively. In the afternoon on that day, animals received the alternate treatment and were confined to the opposite chamber for 15 min. This twice-daily conditioning lasted for 3 days. Mice were then tested for postconditioning place preference on day 5. On each test day, mice were placed in the neutral chamber, allowed to explore the conditioning chambers and the amount of time that mice spent in each chamber was recorded for 15 min.

To assess the role of endogenous PACAP in the aversive effects of nicotine, mice lacking PACAP and their wild-type littermates/controls (n = 7 mice per genotype) were tested for basal preference toward the conditioning chambers on day 1, as described above. The conditioning procedure was the same, as described above except a higher dose of nicotine (1 mg/kg) was used and mice received conditioning for 6 rather than 3 days because the 3-day conditioning paradigm that induced CPP was not enough to induce a significant CPA. The selection of nicotine dose was based on previous studies (Castane et al., 2002; Grabus et al., 2006).

2.5. Data analysis

Data represent mean ± standard error of the mean (S.E.M.) of the volume of water and nicotine consumed (mL) or the amount of time (sec) that mice spent in the conditioning chambers on pre- and post-conditioning test days. Data were analyzed using two- or three-way repeated measures analysis of variance (ANOVA) followed by the Fisher's LSD *post-hoc* test to reveal significant differences between groups. A $P < 0.05$ was considered statistically significant.

3. Results

3.1. TBC paradigm

Fig. 1 shows the volume of water and different concentrations of nicotine consumed by wild-type mice. To promote nicotine consumption in wild-type mice, the bottle on the preferred water side (Fig. 1,

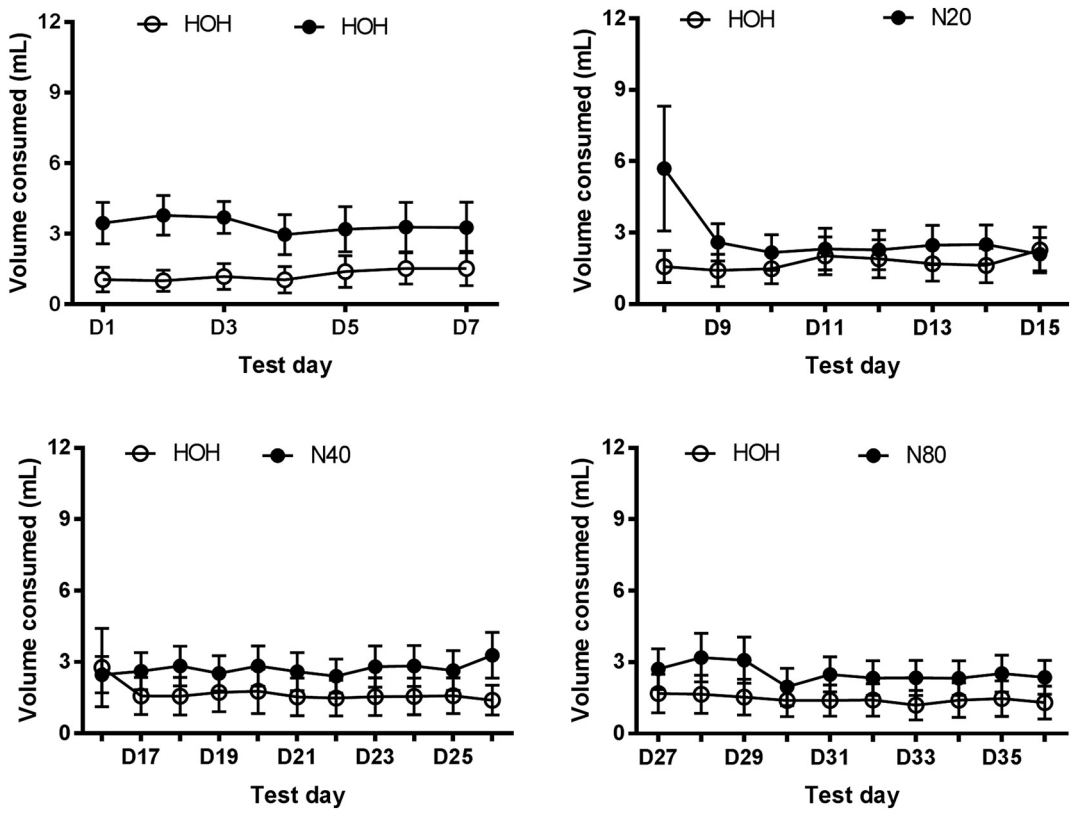

Fig. 1. Wild-type mice did not show preference for any concentration of nicotine. Data are mean ± S.E.M. of volume intake in wild-type mice (n = 6) from the two water bottles on days 1–7 (upper left panel) or water vs. 20 μg/mL (N20; upper right panel), 40 μg/mL; (N40, lower left panel) and 80 μg/mL (N80; lower right panel) of nicotine on days 8–15, 16–26 or 27–36, respectively.

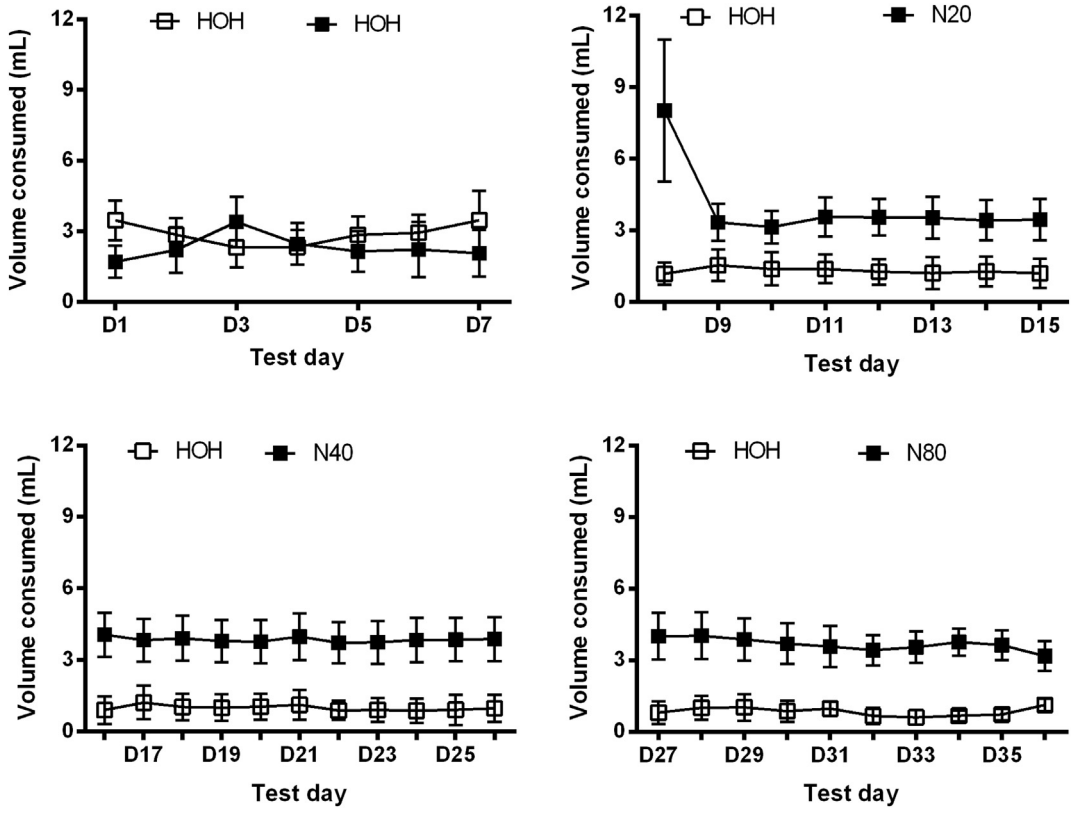

Fig. 2. Mice lacking PACAP consumed more nicotine than water. Data are mean ± S.E.M. of volume intake mice lacking PACAP (n = 5) from the two water bottles on days 1–7 (upper left panel), water/nicotine (20 μg/mL; N20) on days 8–15 (upper right panel), water/nicotine (40 μg/mL; N40) on days 16–26 (lower left panel) and water/nicotine (80 μg/mL; N80) on days 27–36 (lower right panel).

upper right panel) was replaced with the lowest concentration of nicotine (20 μg/mL) on day 8. This pattern of preferred drinking remained the same when the preferred water bottle was switched with the lowest nicotine concentration (20 μg/mL; Nic20) on day 8 (Fig. 1, upper right panel). However, mice rapidly reduced their preference for nicotine and no longer had preference for nicotine over water when the concentration of nicotine was increased to 40 μg/mL (Nic40) and 80 μg/mL (Fig. 1; lower panels). In contrast, nicotine intake remained higher in PACAP knockout mice regardless of the concentration of nicotine (Fig. 2). Interestingly, although these mice had comparable preference for the two water bottles during the initial week when only water was available (Fig. 2, upper left panel), they started to consume more nicotine and less water when one of the water bottles was switched to the lowest nicotine concentration (20 μg/mL; Nic20) (Fig. 2, upper right panel). This pattern of increased nicotine intake was also observed when the concentration of nicotine was increased to 40 μg/mL (Nic40) and 80 μg/mL (Fig. 2, lower left and right panels). In order to assess if there was any difference in preference for nicotine between wild-type and knockout mice, we normalized the volume of nicotine consumption on each day as the percent of their respective volume of water consumption on the last day of week 1 in mice of both genotypes (Fig. 3). Two-way ANOVA revealed a significant interaction between genotype and volume consumed ($F_{33,297} = 3.11$; $P < 0.001$). The *post-hoc* test yielded a significant increase in nicotine preference in mice lacking PACAP compared to their wild-type controls, suggesting that the nicotine preference was enhanced in the absence of PACAP signaling.

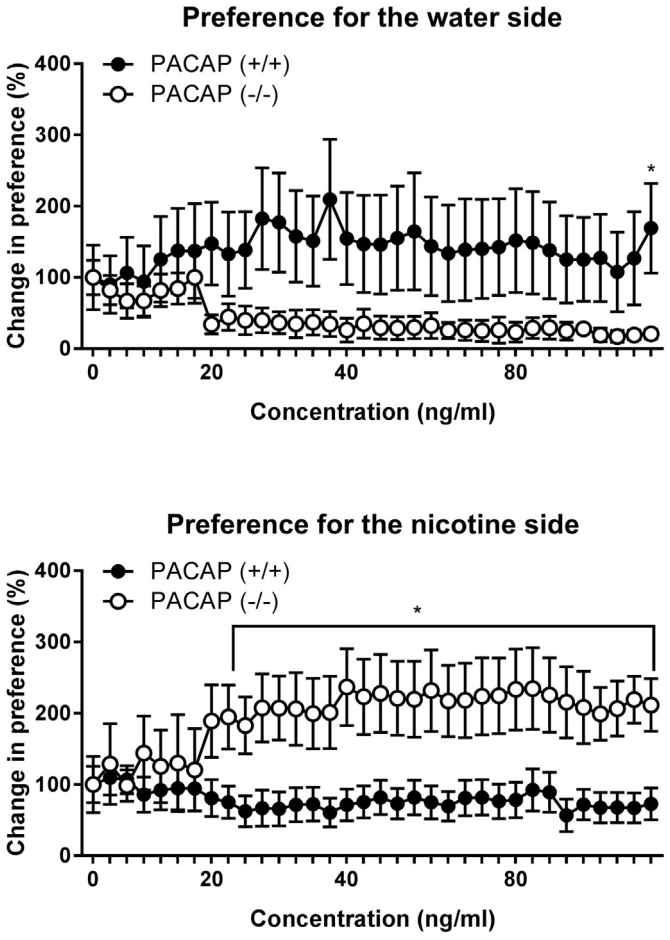

Fig. 3. Mice lacking PACAP exhibited a greater preference for nicotine compared to their wild-type controls. Data are mean ± S.E.M. of the percent change in preference for water (upper panel) and nicotine (lower panel) calculated as the percent of the volume intake on day 7 in mice of the two genotypes (n = 5–6 per genotype). *P < 0.05 vs. its respective wild-type controls.

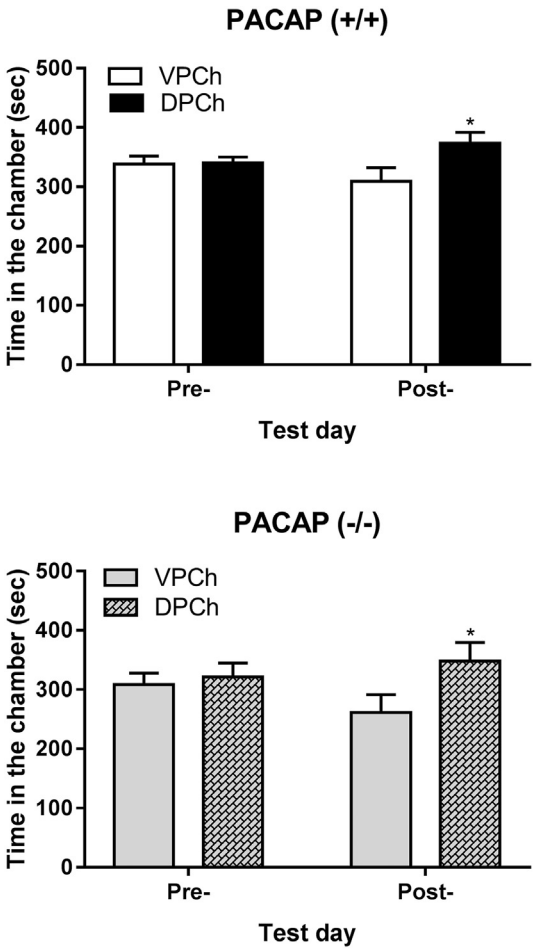

Fig. 4. Nicotine induced CPP was comparable between mice lacking PACAP and their wild-type controls. Data are mean ± S.E.M. of the amount of time that mice (n = 15–17 per genotype) spent in the vehicle-paired (VPCh) or drug-paired chamber (DPCh) before (Pre-) and after (Post-) conditioning test days in wild-type (upper panel) and PACAP knockout mice (lower panel). *P < 0.05 vs. VPCh.

3.2. Place conditioning paradigm

Considering that mice lacking PACAP consumed more nicotine than their wild-type controls, we examined if this response was due to increased nicotine reward in these mice. Fig. 4 shows the amount of time that wild-type (upper panel) and knockout (lower panel) mice spent in the nicotine-paired versus saline-paired chamber on the pre- and postconditioning test day. Three-way repeated measures ANOVA revealed a significant effect of time in the CPP chambers ($F_{1,1} = 10.75$; $P < 0.01$) and a significant interaction between the amount of time that mice spent in the CPP chamber and test day ($F_{1,1} = 8.23$; $P < 0.01$). However, there was no significant effect of genotype ($F_{1,1} = 3.07$; $P = 0.08$), genotype X time in the CPP chamber ($F_{1,1} = 0.38$; $P > 0.05$) or test day X genotype X time in the CPP chamber ($F_{1,1} = 0.05$; $P > 0.05$), showing that nicotine induced a comparable CPP in mice of both genotypes. This result suggests that the rewarding action of nicotine was not altered in the absence of PACAP.

Given that nicotine-induced CPP was not altered in mice lacking PACAP, we then tested if the increased preference for nicotine over the water was due to decreased nicotine-induced aversion in these mice compared to their wild-type controls. Fig. 5 depicts the amount of time that mice of the two genotypes spent in the nicotine- versus saline-

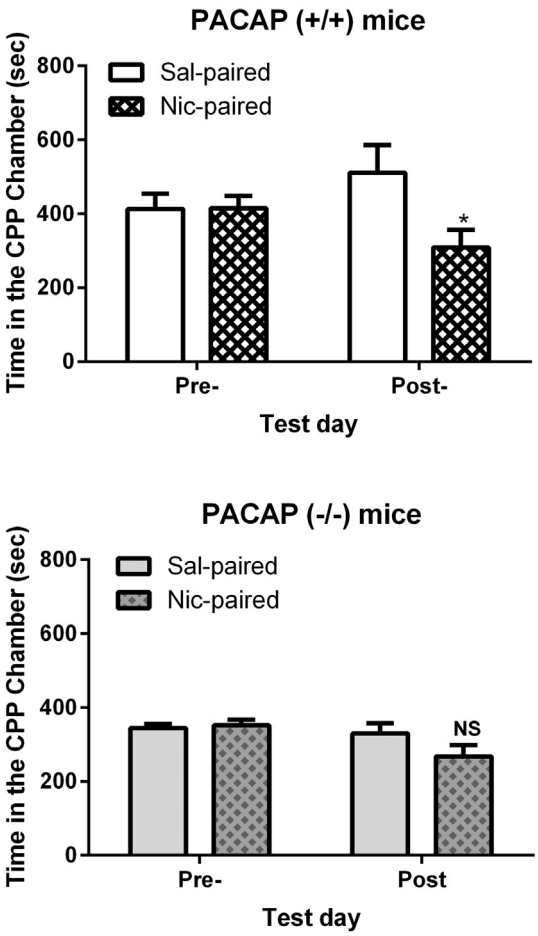

Fig. 5. Conditioned place aversion was blunted in mice lacking PACAP compared to their wild-type controls. Data are mean ± S.E.M. of the amount of time that mice (n = 7 mice per genotype) spent in the saline-paired or nicotine-paired chamber before (Pre-) and after (Post-) conditioning test days in wild-type (upper panel) and PACAP knockout mice (lower panel). *P < 0.05 vs. Sal-paired on the postconditioning test day.

paired chamber on pre- and post-conditioning test days. Three-way repeated measures ANOVA revealed a significant effect of genotype ($F_{1,1} = 9.83$; $P < 0.01$), a significant amount of time that mice spent in the CPP chambers ($F_{1,1} = 5.08$; $P < 0.03$) and a significant interaction between the amount of time in the CPP chambers and test days ($F_{1,1} = 5.87$; $P < 0.02$). Subsequent analyses showed that wild-type mice spent a significantly lesser amount of time in the nicotine- compared to the saline-paired chamber following but not prior to conditioning (Fig. 5, upper panel). This result indicates that nicotine administration induced aversion in wild-type mice. On the other hand, this response was blunted in mice lacking PACAP (Fig. 5, lower panel), suggesting that endogenous PACAP is involved in the aversive effect of nicotine.

4. Discussion

The main findings of the present study were that mice lacking PACAP and their wild-type controls exhibited a comparable CPP although knockout mice preferred nicotine over water in the TBC paradigm and expressed blunted nicotine-induced aversion compared to their wild-type controls. Taken together, the present data suggest that endogenous PACAP may mediate nicotine preference and aversion.

PACAP and its receptors are found in the hypothalamus, habenula, VTA and NAc [(Condro et al., 2016), for a review, see (Vaudry et al., 2000)], brain regions implicated in the reinforcing and aversive effects of nicotine [reviewed in (Fowler and Kenny, 2014)], raising the possibility that PACAP and its receptors may be involved in the motivational effects of nicotine and possibly in the neurobiology of nicotine addiction. To test this possibility, we first determined the role of endogenous PACAP in nicotine preference using the TBC paradigm. In our hand, wild-type mice did not exhibit preference for nicotine over water at any nicotine concentration even though the drug was made available on the water-preferred side. In contrast, mice lacking PACAP exhibited preference for nicotine, as they consumed more nicotine than water at all concentrations of nicotine, suggesting that PACAP plays a functional role in nicotine preference.

Previous studies have implicated PACAP in consummatory behaviors in mice (Morley et al., 1992), rats (Chance et al., 1995), chicks (Tachibana et al., 2003), and goldfish (Matsuda et al., 2005). Furthermore, central administration of PACAP regulates basal motor activity in mice (Fujii et al., 2007; Marquez et al., 2009; Tanaka et al., 2006). In addition, mice lacking PACAP (Marquez et al., 2009) or PAC1 receptor (Otto et al., 2001) exhibit greater exploratory behaviors than wild-type controls, showing that PACAP is involved in the regulation of locomotion. However, our results cannot be explained by these changes in mice lacking PACAP because consumption of water was not increased in these mice. Thus, we hypothesized that the rewarding action of nicotine may have been enhanced in these mice, leading to greater nicotine consumption in the absence of PACAP signaling. Interestingly, high levels of PACAP (Ghatei et al., 1993; Palkovits et al., 1995) and high affinity PACAP binding sites (Masuo et al., 1992) are present in the VTA and NAc. Importantly, PACAP has been shown to enhance tyrosine hydroxylase activity in the NAc (Moser et al., 1999). Thus, we determined if nicotine-induced CPP would be altered in mice lacking PACAP compared to their wild-type controls. Our results demonstrated that mice of both genotypes exhibited a comparable CPP, suggesting that the rewarding action of nicotine was not altered in the absence of PACAP.

Considering that PACAP increases the expression of CRH (Agarwal et al., 2005; Grinevich et al., 1997; Stroth and Eiden, 2010; Stroth et al., 2011a; Stroth et al., 2011b), and that CRH induces conditioned place aversion (Cador et al., 1992) and taste aversion (Benoit et al., 2000), we then tested if the aversive effect of nicotine would be altered in the absence of PACAP. Our rationale was that nicotine consumption was enhanced in the absence of PACAP because the aversive effect of nicotine may have been reduced in the absence of PACAP. Consistent with this notion, we discovered that the aversive effect of nicotine was reduced in mice lacking PACAP compared to their wild-type controls. However, considering that the flavor of nicotine in the drinking water was not blocked, it may be that taste aversion is altered in these mice. Interestingly, mice lacking PACAP exhibited a greater preference for alcohol but not sucrose or quinine (Tanaka et al., 2010). One caveat of the present study is that we did not measure nicotine blood levels in these mice. However, if differences in plasma nicotine levels had been the reason for the behavioral differences observed in mice lacking PACAP compared to their wild-type controls, we would have expected to see differences between mice of the two genotypes in all paradigms. Nevertheless, further research is needed to fully characterize the role of PACAP in these effects of nicotine. Also, given that we used only adult female mice, future studies are needed to assess if there is any sex- or age-related differences in the action of PACAP in regulating the motivational effects of nicotine.

In summary, we discovered that nicotine preference was increased in mice lacking PACAP, a response that may be linked to decreased nicotine-induced aversion but not reward. One implication of this result could be that endogenous PACAP and related agonists could provide protection against nicotine consumption and possibly nicotine addiction, as these drugs may facilitate nicotine-induced aversion, a response that may deter nicotine use. However, further research is needed to test this intriguing possibility.

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Conflict of interest

The authors declare no conflict of interest.

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