Neuroscience Letters xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Chronic nicotine exposure inhibits estrogen-mediated synaptic functions in hippocampus of female rats

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ARTICLE INFO

Article history:
Received 20 December 2011
Received in revised form 24 March 2012
Accepted 5 April 2012

Keywords:
Hippocampus
Long-term potentiation
Paired-pulse modulation
Cyclic-AMP response element binding
Estrogen receptors

ABSTRACT

Nicotine, the addictive agent in cigarettes, reduces circulating estradiol-17β (E_2) and inhibits E_2-mediated intracellular signaling in hippocampus of female rats. In hippocampus, E_2-signaling regulates synaptic plasticity by phosphorylation of the N-methyl-D-aspartic acid receptor subunit NR2B and cyclic-AMP response element binding protein (pCREB). Therefore, we hypothesized that chronic nicotine exposure induces synaptic dysfunction in hippocampus of female rats. Female rats were exposed to nicotine or saline for 16 days followed by electrophysiological analysis of hippocampus. Briefly, population measurements of excitatory post-synaptic field potentials (fEPSPs) were recorded from stratum radiatum of the CA1 hippocampal slice subfield. A strict software-controlled protocol was used which recorded 30 min of baseline data (stimulation rate of 1/min), a paired-pulse stimulation sequence followed by tetanic stimulation, and 1 h of post-tetanus recording. EPSP amplitude and the initial EPSP slope were measured off-line. We then investigated by Western blot analysis the effects of nicotine on hippocampal estrogen receptor-beta (ER-β), NR2B and pCREB. The results demonstrated significantly decreased post-tetanic potentiation and paired-pulse facilitation at the 40, and 80 ms interval in nicotine-exposed rats compared to the saline group. Western blot analysis revealed that nicotine decreased protein levels of ER-β, NR2B, and pCREB. We also confirmed the role of E_2 in regulating NR2B and pCREB phosphorylation by performing Western blots in hippocapmal tissue obtained from E_2-treated ovariectomized rats. In conclusion, chronic nicotine exposure attenuates short-term synaptic plasticity, and the observed synaptic defects might be a consequence of loss of estradiol-17β-signaling. However, determining the exact molecular mechanisms of chronic nicotine exposure on synaptic plasticity specific to the female brain require further investigation.

1. Introduction

Cigarette smoking is an important risk factor for cerebral ischemia in women [4]. Nicotine is the main addictive and toxic agent in tobacco smoke; however, the extent to which nicotine itself is involved in the pathogenesis of smoking-related cerebral ischemia is not known. Nicotine addiction produces diverse physiological effects common to both sexes owing to activation of nicotinic acetylcholine receptors [15]. In addition to these effects, in women nicotine reduces circulating female sex hormone–estrogen levels and leads to early onset of menopause [16,24]. In laboratory studies on female rats, we confirmed later epidemiological findings that chronic nicotine exposure reduced circulating 17β-estradiol (E_2; a potent estrogen) levels [29].

Circulating estrogen is proven to protect women against ischemic brain damage during their pre-menopausal life and is lost after reproductive senescence [7,23]. Exogenous administration of estrogen to ovariectomized rats has been demonstrated to improve neuronal survival after ischemia, attributing to estrogen a key role in protection against brain injury [2,18,19,32]. In this context, we recently demonstrated that chronic nicotine exposure abrogates the endogenous or exogenous estrogen-conferred protection of hippocampus against cerebral ischemia in normally cycling or ovariectomized female rats, respectively [27]. Hippocampus is the most vulnerable region of brain following cerebral ischemia, and studies from various labs including ours have demonstrated that E_2-mediated post-ischemic neuroprotection requires activation of the cyclic-AMP response element binding protein (CREB) pathway [17,18,30]. Phosphorylated CREB (pCREB) maintains synaptic plasticity via regulation of short-term (measured by paired-pulse facilitation; PPF) and long-term potentiations (LTP; a cellular

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0304-3940/$ – see front matter © 2012 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.neulet.2012.04.015

correlate of learning and memory) in the hippocampus [3]. It has been shown that loss of synaptic function leads to neuronal cell death in the hippocampus after cerebral ischemia [11].

In the female, E_2-mediated CREB phosphorylation in hippocampus occurs via ligand-activated estrogen receptors (ERs); viz. alpha (ER-α) and beta (ER-β). Recently, we demonstrated that nicotine directly hinders E_2-mediated intracellular signaling, in an *ex vivo* model of hippocampal slice cultures which are devoid of blood flow [29]. Importantly, chronic nicotine exposure decreased ER-β but not ER-α protein levels in the hippocampus of female rats [27–29]. Our studies also showed that nicotine exposure reduced protein levels of phosphorylated CREB (pCREB) in hippocampus of female rats which suggested possible defects in hippocampal plasticity that could be responsible for exacerbated previously reported ischemic damage due to nicotine [28,29]. Furthermore, we demonstrated that 17β-estradiol-mediated CREB phosphorylation in the hippocampus occurs via ER-β activation [28] and a study supports a key role for ER-β in hippocampus-dependent memory and cognition [5]. Estradiol-17β-mediated phosphorylation of CREB also involves activation of calcium–calmodulin kinase II (CaMKII) [17,30]. Calcium–calmodulin kinase II activation is also known to phosphorylate NMDA receptor subunit NR2B [9,21]. Phosphorylation of NR2B and CREB contributes to synaptic response in the hippocampus [1,33]. Based on these findings, we hypothesize that chronic nicotine exposure in female rats: (1) alters hippocampal neuronal survival, (2) alters hippocampal synaptic plasticity and (3) inhibits E_2-mediated phosphorylation of NR2B and CREB in the hippocampus.

2. Materials and methods

All animal procedures were carried out in accordance with the Guide for the Care and Use of Laboratory Animals published by the U.S. Public Health and procedures involving animal subjects were approved by the Animal Care and Use Committee of the University of Miami. Female Sprague-Dawley rats weighing 290 ± 20 g were used for this study. To monitor stages of the estrous cycle, we collected vaginal smears from rats daily between 9:00 and 10:00 am and identified cell types microscopically as described previously [30]. Only rats showing at least three consecutive normal (4 days) estrous cycles were used for experiments. Osmotic pumps containing nicotine hydrogen tartrate dissolved in normal saline or saline were implanted in rats for 16 days. To implant the osmotic pump, an area on the back between the shoulders (3 cm × 6 cm) was shaved and an incision was made to permit subcutaneous implantation of osmotic minipump (type 2ML2, Alzet Corp., Palo Alto, CA). The pumps delivered a dose of 4.5 mg/kg/day of nicotine hydrogen tartrate (equivalent to 1.5 mg/kg/day of nicotine free base). In adult female rats, the cyclic variations of 17β-estradiol reflect on ischemic outcome and that a higher endogenous estrogen level at proestrus stage protects CA1 neurons against cerebral ischemia. Thus, to maintain consistency in experimental outcome, rats were sacrifice on proestrus stage (plasma estradiol levels 38.7 ± 4.4 pg/ml [30]) of estrous cycle in the following experiments. In those instances where rats were not in the proestrus stage on the last scheduled day of treatment, we extended the treatment by 1 day.

Twelve rats were randomly assigned to either nicotine ($n = 6$) or saline ($n = 6$) treatment. At the end of nicotine/saline treatment rats were anesthetized with isoflurane and perfused with formalin, acetic acid and methanol (FAM) as described [30]. The head was removed and immersed in FAM at 4 °C for 1 day. The brains were then removed from the skull, and coronal brain blocks were embedded in paraffin; 10-μm coronal sections were stained with hematoxylin and eosin. Hematoxylin and eosin stained sections were visualized at 40× magnification under a Nikon microscope equipped with a Sony CCD camera coupled to an MCID image analyzer (Imaging Research, St. Catherines, Ontario, Canada). For each animal, normal neurons were counted in the CA1 region of each hippocampus by an investigator blinded to the experimental conditions. Coronal brain sections were made at the level of 3.8 mm from bregma. For each section, 18 fields per sections were obtained, three slides per rat were counted and mean count from three slides was obtained [29,30]. The data are presented as number of live neurons (mean ± S.E.M.) in saline vs. nicotine exposed female rats.

Ten rats were randomly assigned to either nicotine ($n = 5$) or saline ($n = 5$) treatment. At the end of nicotine/saline treatment rats were sacrificed (only if in proestrous stage of estrous cycle) to perform electrophysiology. On the day of experiment, one rat each from the nicotine and saline groups were anesthetized with isoflurane, decapitated, the brain removed and the right hippocampus dissected free and placed in chilled high sucrose sectioning medium containing the following (in mM): 100 sucrose, 60 NaCl, 3 KCl, 1.25 NaH_2PO_4, 28 $NaHCO_3$, 0.5 $CaCl_2$, 7 $MgCl_2$, 0.6 ascorbic acid, and 5 glucose. The hippocampus was mounted on a block of agarose and 350 μm slices were cut with a Leica VT1000 vibratome maintained at 6 °C. Slices were then placed for a minimum of 1 h in a holding chamber containing artificial cerebrospinal fluid (CSF) containing the following (in mM): 125 NaCl, 2.5 KCl, 1.25 NaH_2PO_4, 25 $NaHCO_3$, 2 $CaCl_2$, 1 $MgCl_2$, and 25 glucose. Two slices one each from saline and nicotine treated rats were transferred to an interface-type recording chamber maintained at 35 °C. We performed electrophysiology recording in parallel on two slices (one each of saline and nicotine) in the same recording chamber in order to minimize any differences in time between sacrifice of animals from which we are recording. Bipolar stimulation electrodes were placed in the Schaffer collaterals and a glass recording micropipette was placed nearby in the stratum radiatum of subfield CA1. Electrical monopolar pulses were delivered from a Grass S48 stimulator at an intensity sufficient to elicit field EPSPs at half-maximum amplitude. Field potentials were recorded using an Axopatch 2B amplifier, Digidata analog-to-digital converter, and Clampex 8.0 software. A strict software-controlled protocol was used which recorded 30 min of baseline data at a stimulation rate of 1/min, a paired-pulse facilitation sequence in which stimulation pulse pairs were delivered at intervals of 20, 40, 80, 160, 320 and 480 ms, tetanic stimulation consisting of 2 consecutive 100 Hz, 20 pulse trains delivered at an interval of 20 s, and a 1 h post-tetanus recording period. EPSP amplitude was measured off-line. EPSP amplitudes were normalized to the mean of the 30 min pre-tetanus values. These experiments were performed by an investigator blinded to experimental conditions. Mixed model was used to compare the mean differences among groups and the interaction between time and group by accommodating the within-subject correlation.

To investigate the effects of E_2, rats ovariectomized ($n = 4$) seven days prior were treated with E_2 (5 μg/kg; i.p.) or vehicle (oil) and 48 h later rats were sacrificed [30]. The remaining left hippocampi from the second set of nicotine/saline-exposed rats or from E_2-treated ovariectomized rats were homogenized, fractionated, and Western blotting as well as quantification of blots was performed as described previously [30]. The antibodies used were: rabbit polyclonal anti-ER-β, anti-CaMKII (1:5000; Promega), anti-phospho-CREB (pSer133; 1:1000; Cell Signaling Tech.), anti-NR2B (at Ser 1303; 1:1000; Abcam, MA, USA); anti-NR2B (1:1000; Cell Signaling Technology Inc., MA, USA) and monoclonal anti-lamin (1:10,000; Sigma). The data is presented as mean value ± S.E.M. and results from the densitometric analysis were analyzed by a two-tailed Student's t test and a $p < 0.05$ was considered statistically significant.

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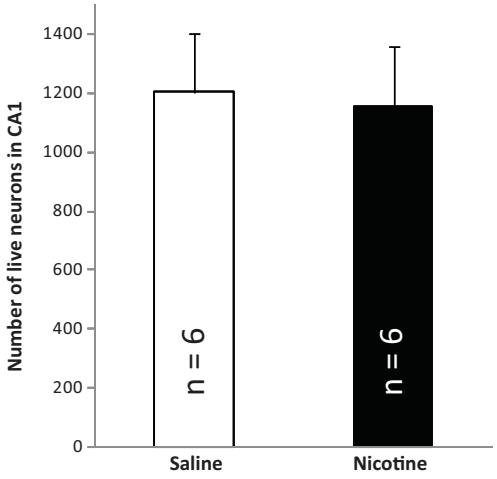

Fig. 1. Histological assessment in hippocampus CA1 region of female rats exposed to saline or nicotine. No significant difference was observed between the two groups.

3. Results

First we investigated the effects of nicotine on hippocampal CA1 neuronal survival. The number of live neurons in the CA1 region of saline-exposed rats was 1204 ± 105 ($n = 6$). The neuronal counts are expressed as number of live neurons per CA1 region of hippocampus. Chronic nicotine exposure did not significantly alter the number of live neurons (1136 ± 56; $n = 6$) in CA1 region of hippocampus in female rats (Fig. 1A).

Secondly, we tested the hypothesis that nicotine hinders hippocampal synaptic plasticity. To investigate defects in synaptic function we monitored post-tetanic potentiation (both short and long term) and paired-pulse facilitation. Field EPSPs were recorded in stratum radiatum of hippocampal slices from saline- or nicotine-exposed rats. Pre-tetanus, 30 min and 90 min post-tetanus fEPSPs amplitude and initial slop were measured offline. Mixed model analysis revealed significant interaction between time and group ($p = 0.0002$) and showed no difference in means at times of −30 min ($p = 0.45$), −15 min ($p = 0.84$) and −10 min ($p = 0.45$) before tetanus injection, but lower means for the nicotine group at the post-tetanus recording time of 2 min ($p = 0.01$) was observed (Fig. 2B). Another marker of synaptic dysfunction following nicotine exposure was demonstrated when we measured paired-pulse modulation (Fig. 3). The results showed significant depression at 40 ms ($p = 0.01$), and 80 ms ($p = 0.05$) of paired-pulse stimulations in nicotine-exposed rats as compared to the saline group (Fig. 3).

Thirdly, we tested the hypothesis that nicotine inhibits E_2-mediated phosphorylation of NR2B and CREB in hippocampus. The results demonstrated that nicotine reduced protein levels of ER-β, pCREB, CaMKII, NR2B and pNR2B in the hippocampus of nicotine-exposed female rats (Fig. 4A). We also confirmed that E_2 regulates phosphorylation of NR2B and CREB in hippocampus. The results of Western blot analysis presented in Fig. 4B showed that E_2-treatment significantly increased protein levels of ER-β, pCREB, CaMKII, NR2B and pNR2B.

4. Discussion

Chronic nicotine exposure attenuates hippocampal synaptic function without obvious neuronal loss in female rats. The results also suggest that observed synaptic dysfunction might be a consequence of the loss of E_2-signaling. Estrogen influences N-methyl-D-aspartate receptors (NMDARs)-mediated synaptic transmission by two mechanisms: (1) by increasing the number of NMDARs at synapse assemblies preferentially containing NR2B subunits and, (2) by inducing a functional modification (e.g., phosphorylation of NR2B) which increases the probability of the channels opening [33]. Confirmation of the first mechanism is demonstrated by inhibition of NR2B, which prevented the E_2-induced increase in LTP magnitude [33]. In support of the second mechanism, functional modification of NR2B includes phosphorylation sites at serine 1303 (S1303) and serine 1480 (S1480) [10,26]. Phosphorylation of NR2B at serine 1303 (S1303) in hippocampal neurons is mediated via CaMKII [26]. The present results confirm that E_2 increased protein levels of CaMKII, pNR2B and pCREB in the hippocampus of ovariectomized rats. Furthermore, in a recent study we demonstrated that the silencing of ER-β in hippocampus of female rats reduced pCREB following E_2 treatment, suggesting that E_2-mediated CREB phosphorylation occured via ER-β [28]. Nicotine reduced ER-β as well as pCREB and pNR2B protein levels, suggesting that nicotine could inhibit ER-β-mediated E_2-signaling leading to phosphorylation of NR2B and CREB, which might be responsible for the observed loss of synaptic function in the hippocampus of female rats. Additionally, a study showed that hippocampal slices prepared from wild-type female mice incubated with a selective ER-β agonist (WAY-200070) showed significantly enhanced theta burst stimulation-induced potentiation compared to vehicle-treated slices from the same animals [22], thus supporting a key role for ER-β in hippocampus-dependent synaptic plasticity. In contrast to the above findings suggesting role for ER-β in maintaining hippocampal synaptic functions, ER-α has also been implicated in regulation of hippocampus-dependent memory function in female mice [13]. This contradiction suggests that both

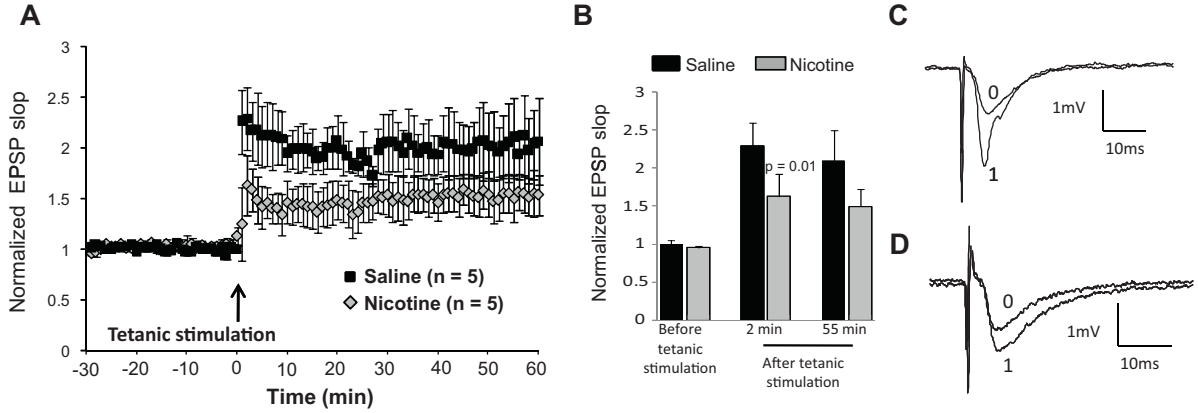

Fig. 2. (A and B) Normalized EPSP slops of 2× 100 Hz tetanic stimulation trains separated by 20 s in hippocampal slices harvested from rats pretreated chronically with either nicotine or saline. (C and D) represents example recordings from saline and nicotine exposed rat hippocampal slices.

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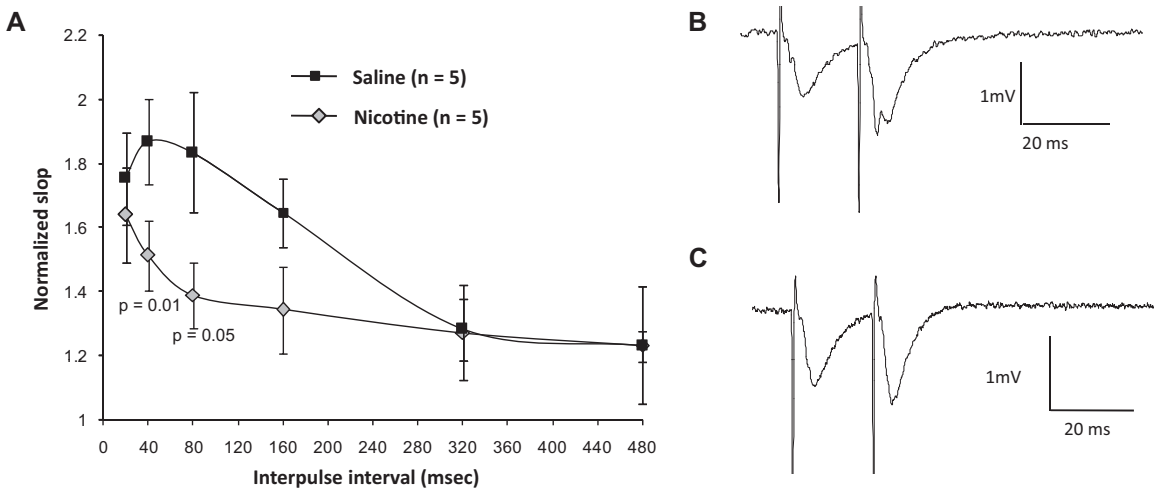

Fig. 3. (A) Relative slop of paired-pulse stimulation given at intervals of 20, 80, 160, 320 and 480 ms. (B and C) represents example recordings from saline and nicotine exposed rat hippocampal slices.

estrogen receptors are crucial for neuronal synaptic function, survival and work via different mechanisms and require investigation in depth.

Our functional analysis of synaptic plasticity at the Schaffer collateral–CA1 synapse of rats chronically exposed to nicotine indicated impairment of paired-pulse facilitation and early post-tetanic potentiation. A simple explanation is that chronic nicotine in some manner affects pre-synaptic calcium regulation, since residual pre-synaptic calcium plays a role in both synaptic facilitation and post-tetanic potentiation (see [8] for a review). However, it remains possible that chronic nicotine exposure may affect other downstream plasticity effectors such as protein kinase C, which has been shown to be involved in post-tetanic potentiation presynaptically [6] and in early potentiation post-synaptically [34].

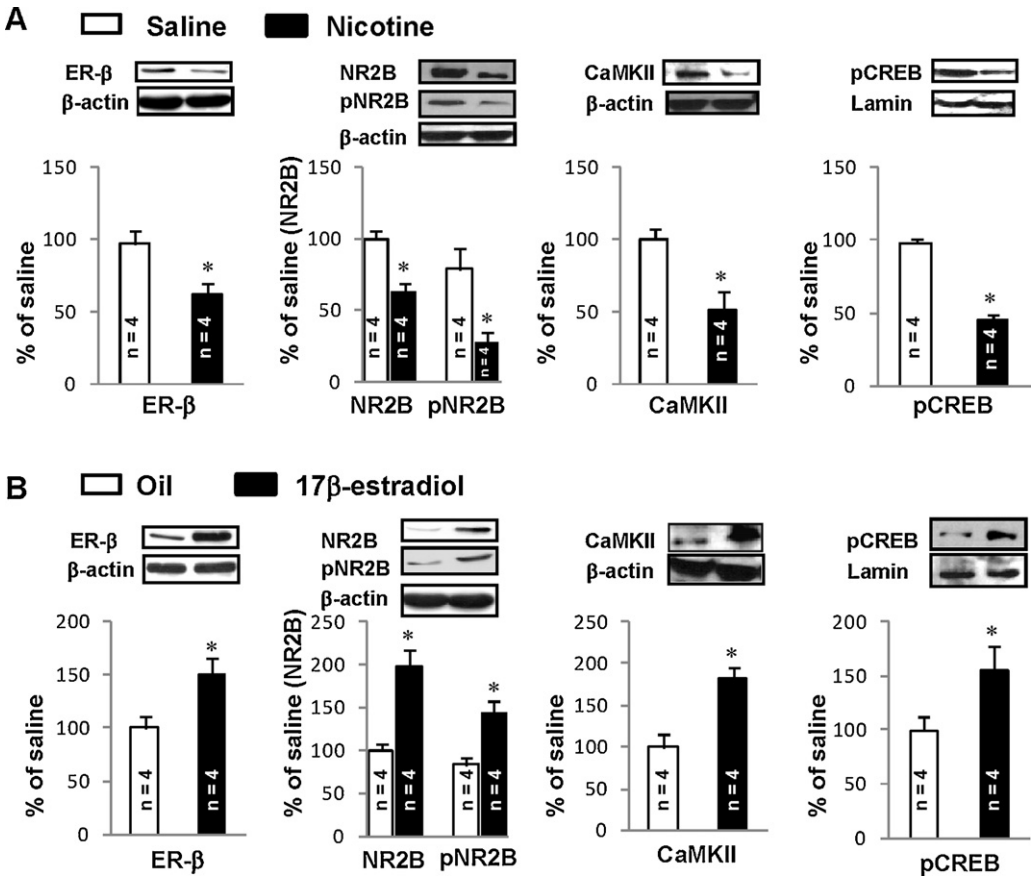

Fig. 4. (A and B) Top panel of each figure shows representative immunoblots and the bottom panel depicts densitometric analysis of immunoblots; viz. ER-β, NR2B, pNR2B, CaMKII and pCREB from nicotine- and E_2-exposed naive or ovariectomized rats, respectively. Statistical significance $^*p < 0.05$ vs. saline/oil.

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Determining the exact sites of action and molecular mechanisms of chronic nicotine exposure on synaptic plasticity in the female brain will require future investigation.

In contrast to our current results, prior studies demonstrated LTP enhancement following nicotine application; however, those studies mainly investigated the acute effects of nicotine on LTP or were conducted on male experimental animals [14,31]. Biological responses to nicotine are gender-specific [12]. Therefore, discrepancies observed between the present results and prior literature might owe to differences in the duration of nicotine exposure or sex. Furthermore, nicotinic acetylcholine receptor-mediated increased Ca^{2+} influx after nicotine is implicated to be responsible for CA1 neuronal damage in the hippocampi of adolescent mice [25]. Here we failed to observe hippocampal neuronal death after nicotine, which could owe to differences in age of the experimental animals between the two studies, because developing cells are less capable of buffering calcium than mature cells [20].

5. Conclusion

Chronic nicotine attenuates short-term synaptic plasticity and the observed synaptic defects might be a consequence of loss of estradiol-17β-signaling in hippocampus. Future studies directed to investigate the interaction between nicotinic and estrogen receptors and their impact on synaptic plasticity might help understand the unique effects of nicotine on the female brain.

Conflict of interest

The authors declare that there are no conflicts of interest.

Funding

This study was supported by AHA grants [# 0730089N; 11GRNT7370069, APR], the James and Esther King Biomedical Research Program, Florida Department of Health [# 07KN-10, APR], Sex and Gender Influences on Addiction and Health: A Developmental Perspective [5 P50 DA024584-05], Stanley J. Glaser Foundation Research Grant and the Drs. Chantal and Peritz Scheinberg Research Fund [APR].

Acknowledgments

We thank to Dr. Miguel A. Perez-Pinzon for scientific discussion of this study and Dr. Brant Watson for critical reading of this manuscript.

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Please cite this article in press as: A.P. Raval, et al., Chronic nicotine exposure inhibits estrogen-mediated synaptic functions in hippocampus of female rats, Neurosci. Lett. (2012), http://dx.doi.org/10.1016/j.neulet.2012.04.015