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Research report

Nicotine increases eclampsia-like seizure threshold and attenuates microglial activity in rat hippocampus through the α7 nicotinic acetylcholine receptor

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ABSTRACT

Objective: A considerable number of studies have demonstrated that nicotine, a α7-nicotinic acetylcholine receptor (α7-nAChR) agonist, can dampen immune response through the cholinergic anti-inflammatory pathway. Evidence suggests that inflammation plays a critical role in eclampsia, which contributes to maternal and fetal morbidity and mortality. In the present study, possible anti-inflammation and neuro-protective effects of nicotine *via* α7-nAChRs have been investigated after inducing eclampsia-like seizures in rats.

Methods: Rat eclampsia-like models were established by administering lipopolysaccharide (LPS) plus pentylenetetrazol (PTZ) in pregnant rats. Rats were given nicotine from gestation day (GD) 14–19. Then, clinical symptoms were detected. Seizure severity was recorded by behavioral tests, serum levels of inflammatory cytokines were measured by Luminex assays, microglia and astrocyte expressions were detected by immunofluorescence, and changes in neuronal number in the hippocampal CA1 region among different groups were detected by Nissl staining.

Results: Our results revealed that nicotine effectively improved fetal outcomes. Furthermore, it significantly decreased systolic blood pressure, and maternal serum levels of Th1 cytokines (TNF-α, IL-1β, IL-6 and IL-12P_{70}) and an IL-17 cytokine (IL-17A), and dramatically increased eclampsia-like seizure threshold. Moreover, this attenuated neuronal loss and decreased the expression of microglial activation markers of the hippocampal CA1 region in the eclampsia-like group. Additionally, pretreatment with α-bungarotoxin, a selective α7-nAChR antagonist could prevent the protective effects of nicotine in eclampsia-like model rats.

Conclusion: Our findings indicate that the administration of nicotine may attenuate microglial activity and increase eclampsia-like seizure threshold in rat hippocampus through the α7 nicotinic receptor.

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1. Introduction

Eclampsia is characterized by mal seizures that cannot be attributed to other causes in women with preeclampsia, and complicate 1.4% of all deliveries worldwide (Abalos et al., 2013). It has been reported that eclampsia has caused nearly 13% of all maternal deaths worldwide, and is one of the top five causes of maternal and fetal mortality and morbidity (Nour, 2008). The precise mechanism leading to the development of eclamptic seizures has not unveiled. Evidence suggests that inflammatory mediators decreased the seizure threshold and implied that inflammation may play an important role in the pathogenesis of eclampsia (Huang et al., 2014). Furthermore, experimental evidence has shown that inflammation, especially neuroinflammation, is a common substrate in eclampsia of different etiologies (Johnson et al., 2014). Therefore, the use of anti-inflammatory drugs in eclampsia might be a promising therapeutic strategy. Numerous reports have introduced the concept of the "cholinergic anti-inflammatory pathway" , which modulates systemic inflammatory responses by regulating α7-nicotinic acetylcholine receptors (α7-nAchRs) in macrophages (Wang et al., 2003).

Nicotine, an α7-nAChR agonist, has been proven to be an anti-inflammatory in the animal model of colitis (Eliakim et al., 1998),

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peritonitis (van Westerloo et al., 2005), arthritis (van Maanen et al., 2009), and central nervous system (CNS) inflammation (Shi et al., 2009). Recently, our laboratory demonstrated that a similar cholinergic pathway may regulate macrophage activation in the cervix during pregnancy (Yang et al., 2014b). In the CNS, nicotine can readily pass into the brain parenchyma and cross the blood–brain barrier, owing to its lipid solubility. This explains its direct effect on specific neuron receptors, and nicotine has been shown to play a forceful anti-inflammatory role through α7-nAChR in glial cells (Liu et al., 2012). Furthermore, epidemiological studies have consistently reported that incidences of neurodegenerative diseases such as Alzheimer's and Parkinson diseases often appear on the higher side in non-smokers than smokers (Allam et al., 2007; Mihailescu and Drucker-Colin, 2000). Nicotine might have brain protective potential through its anti-inflammatory property. However, to date, this hypothesis has not been tested in an eclampsia-like rat model.

We have previously studied the LPS plus PTZ induced eclampsia-like rats model, which adequately mimics eclampsia in humans and serves as a good tool for researching potential the mechanism underling eclampsia-like seizures induced by inflammation (Huang et al., 2014). In this study, we investigated whether nicotine has a protective effect on maternal patients, especially on the CNS, through an anti-inflammatory mechanism.

2. Results

2.1. Systolic blood pressure

Systolic blood pressure (SBP) results in the experimental groups are shown in Table 1. On GD 17, SPB levels increased in LPS-treated rats compared with non-pregnant and normal pregnant rats ($P<0.01$). After PTZ administration, SPB slightly increased in non-pregnant and normal pregnant rats. Furthermore, PTZ administration elicited SPB levels to further increase in LPS-treated rats ($P<0.01$). However, the pretreatment of nicotine dramatically attenuated the increase in SBP levels, compared with the pre-eclampsia (PE)+PTZ group ($P<0.01$); while α-bungarotoxin (α-BGT) significantly reversed the protective effect of nicotine, as evidenced by elevated SPB levels compared with the PE+Nic+PTZ group ($P<0.01$).

2.2. Pregnancy outcome

The entire set of data is summarized in Table 2. Nicotine and α-BGT had no effect on fetal weight, placenta weight and fetal crown-rump. Furthermore, live fetal number was significantly lower in the P+PTZ group compared with the P group ($P<0.05$). In addition, live fetal number, fetal weight and crown-rump length were significantly lower following maternal LPS exposure in the PE group, compared with the P group ($P<0.05$). Furthermore, the percentage of fetal resorption increased compared with the P group ($P<0.05$), but the decrease in placental weight did not reach a significant level. After PTZ administration, live fetal number, fetal weight, crown-rump length and placental weight significantly decreased in the PE+PTZ group, compared with the P group ($P<0.05$); while the percentage of fetal resorption was significantly higher than in the P group ($P<0.05$), which was expected. Nicotine administration significantly alleviated the eclampsia-induced decrease in live fetal number, fetal weight, crown-rump length and placental weight, and the increase in the percentage of fetal resorption and malformation in the PE+Nic+PTZ group. In the PE+α-BGT+Nic+PTZ group, α-BGT dramatically blocked the protective effects of nicotine on pregnancy outcome in eclampsia-like rats.

Table 1
Systolic blood pressure values of rats before and after PTZ administration.

Group (*n*)	Systolic blood pressure (mmHg)		
	Baseline	LPS	PTZ
NP (8)	108 ± 2.4	–	–
P (8)	112 ± 3.4	–	–
NP+PTZ (8)	–	–	125 ± 0.6*
P+PTZ (8)	–	–	126 ± 3.4*
PE (8)	–	131 ± 3.9*	–
PE+PTZ (8)	–	128 ± 1.4*	154 ± 1.7**
PE+Nic+PTZ (8)	–	126 ± 1.4*	140 ± 1.7** #
PE+α-BGT+Nic+PTZ (8)	–	129 ± 1.1*	152 ± 2.9**

LPS, lipopolysaccharide; PTZ, pentylenetetrazol; NP, non-pregnancy; P, pregnancy; PE, preeclampsia; Nic, nicotine; α-BGT, α-bungarotoxin.
Data are presented as mean ± S. E. Metopomuscopteryx in the NP+PTZ, P+PTZ, PE+PTZ, PE+Nic+PTZ and PE+α-BGT+Nic+PTZ groups, SBP values were measured before and after PTZ injection in all rats.

* $P<0.01$, compared with baseline values.
** $P<0.01$, compared with baseline and LPS values.
\# $P<0.01$, compared with the PE+PTZ and PE+α-BGT+Nic+PTZ groups.

2.3. Nicotine increase eclampsia-like seizure threshold

Animals had higher behavioral seizure scores in the P+PTZ group compared to the NP+PTZ group ($P<0.01$, Fig. 1); but latency to seizure, duration of seizures, latency to stage-5 seizures, duration of stage-5 seizures and incidence rate of stage-5 seizures were similar (Table 3). In the E group, latency to onset seizure was significantly less than in the P+PTZ and NP+PTZ groups ($P<0.01$), respectively; but the incidence rate of stage-5 seizures was higher compared to the NP+PTZ group ($P<0.01$, Table 3). Furthermore, behavioral seizure scores were higher compared to the NP+PTZ and P+PTZ groups ($P<0.01$, Fig. 1); but the duration of seizure, latency to stage-5 seizures and the duration of stage-5 seizures were similar (Table 3). In addition, compared with the PE+PTZ group, nicotine induced a significantly prolonged latency to onset seizure, and decreased the incidence rate of stage-5 seizures and behavioral seizure scores; but the duration of seizures and latency to stage-5 seizures were similar in the PE+Nic+PTZ group (Table 3). In the PE+α-BGT+Nic+PTZ group, α-BGT considerably blocked the protective effects of nicotine on eclampsia-like seizure behaviors (Fig. 1).

2.4. Effects of nicotine on eclampsia-like model serum Th1/Th2/IL-17 cytokine synthesis

PTZ also had no effect on inflammatory cytokine synthesis in the NP+PTZ and P+PTZ groups. This array identified seven Th1 cytokines (TNF-α, IFN-γ, IL-2, IL-1β, IL-6, IL-12p_{70}, and GM-CSF) and an IL-17 cytokine (IL-17A), in which mean concentrations were significantly higher in the PE or PE+PTZ group, compared with the NP and P groups. Serum Th2 cytokine (IL-4 and IL-10) levels were statistically less in the PE or PE+PTZ group, compared with the NP and P groups, respectively. The elevated levels of Th1 and Th17 cytokines were partly attenuated by nicotine administration (TNF-α, IL-1β, IL-6, IL-12p_{70} and IL-17A), and the decreasing level of Th2 cytokine was also partly elevated (IL-4, Fig. 2). In the PE+α-BGT+Nic+PTZ group, the effects of α-BGT were evident through blocking the nicotine mediated inhibition of Th1 and IL-17 cytokine synthesis, as well as the nicotine regulated promotion of Th2 cytokine synthesis in maternal peripheral system. However, no significant changes in serum concentrations of IL-2, IFN-γ, GM-CSF and IL-10 were found in the PE+Nic+PTZ group, compared with the PE and PE+PTZ groups, respectively. Surprisingly, other cytokines, namely IL-1α, G-CSF, IL-5 and IL-13, between groups did not show any statistically significant difference.

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