European Journal of Pharmacology 783 (2016) 85–91

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Neuropharmacology and analgesia

Effects of alpha-7 nicotinic acetylcholine receptor positive allosteric modulator on lipopolysaccharide-induced neuroinflammatory pain in mice

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ARTICLE INFO

Article history:
Received 21 December 2015
Received in revised form
29 April 2016
Accepted 2 May 2016
Available online 3 May 2016

Keywords:
Nicotinic receptor
Alpha- 7 positive allosteric modulator
Neuroinflammatory pain
Microglia
Hippocampus
Mice

ABSTRACT

Evidence indicates that microglial activation contributes to the pathophysiology and maintenance of neuroinflammatory pain involving central nervous system alpha-7 nicotinic acetylcholine receptors. The objective of the present study was to determine the effects of 3a,4,5,9b-Tetrahydro-4-(1-naphthalenyl)-3*H*-cyclopentan[*c*]quinoline-8-sulfonamide (TQS), an alpha-7 nicotinic acetylcholine receptor positive allosteric modulator (PAM), on tactile allodynia and thermal hyperalgesia following lipopolysaccharide (LPS)-induced microglial activation in hippocampus, a neuroinflammatory pain model in mice. In addition, we examined the effects of TQS on microglial activation marker, an ionized calcium-binding adapter molecule 1 (Iba-1), in the hippocampus may be associated with neuroinflammatory pain. Pretreatment of TQS (4 mg/kg) significantly reduced LPS (1 mg/kg)-induced tactile allodynia and thermal hyperalgesia. Moreover, pretreatment of methyllycaconitine (3 mg/kg) significantly reversed TQS-induced antiallodynic and antihyperalgesic responses indicating the involvement of alpha-7 nicotinic acetylcholine receptor. Pretreatment of TQS significantly decreased LPS-induced increased in hippocampal Iba-1 expression. Overall, these results suggest that TQS reduces LPS-induced neuroinflammatory pain like symptoms via modulating microglial activation likely in the hippocampus and/or other brain region by targeting alpha-7 nicotinic acetylcholine receptor. Therefore, alpha-7 nicotinic acetylcholine receptor PAM such as TQS could be a potential drug candidate for the treatment of neuroinflammatory pain.

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1. Introduction

Neuroinflammatory pain characterized by hyperalgesia and allodynia (Ren and Dubner, 1999), is a major public health concern around the world and is difficult to ameliorate by currently available therapeutic strategies (Dworkin et al., 2007). For example, a number of pharmacological agents are used in the management of neuroinflammatory pain including sodium channel blockers (Finnerup et al., 2005), anticonvulsants (Finnerup et al., 2002), antidepressants (Cardenas et al., 2002), opioids (Attal et al., 2002; Siddall et al., 2000), and cannabinoids (Lynch and Campbell, 2011). However, majority of these therapeutic agents have limited efficacy or produce undesirable adverse effects. Thus, there is a need to develop effective therapeutics for neuroinflammatory pain management involving novel brain targets and mechanisms.

Neuronal nicotinic acetylcholine receptors are ligand-gated ion channels composed of α and β subunits that assemble to form hetero- or homo-pentomers (Gotti et al., 2007; Taly et al., 2009). Emerging evidence indicates that nicotinic acetylcholine receptors have been implicated in mediating pain in animal models that are widely distributed and expressed on neuronal cells and on non-neuronal cells such as microglia in the central nervous system (CNS) including hippocampus (Dineley et al., 2015; Gaimarri et al., 2007; Vincler, 2005). Previous evidence indicates that hippocampus is involved in pain production and maintenance (Covey et al., 2000; Khanna and Sinclair, 1989; Martuscello et al., 2012; McEwen, 2001; Spengler et al., 2007). Given this, the research focus has shifted to develop new drug candidates that would selectively target specific nicotinic acetylcholine receptor subtypes with the purpose of maintaining the antinociceptive effects while reducing the adverse effects that are seen with non-selective agonists (Umana et al., 2013) in the CNS. In this regard, nicotinic agonists particularly alpha-7 nicotinic acetylcholine receptor agonists have received significant attention for neuroinflammatory pain by targeting microglial alpha-7 nicotinic acetylcholine receptor (Medhurst et al., 2008). It is widely recognized that

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http://dx.doi.org/10.1016/j.ejphar.2016.05.003
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microglial cells activation in the CNS plays a critical role in the onset and maintenance of neuroinflammatory pain (Austin and Moalem-Taylor, 2010). Lipopolysaccharide (LPS), an exogenous ligand, is widely used for microglial activation in the CNS (Silverman et al., 2014). Recent reports indicate that LPS enhances nociceptive sensitivity to pain stimuli resulting in allodynia and thermal hyperalgesia likely due to increased microglial activation in the CNS (Yoon et al., 2012). Moreover, alpha-7 nicotinic acetylcholine receptor agonists have been found to reduce neuroinflammatory pain in preclinical studies due to their ability to decrease CNS microglial activation (Loram et al., 2010; Pocock and Kettenmann, 2007). However, distinctive properties of alpha-7 nicotinic acetylcholine receptors including low likelihood of channel opening and rapid desensitization, may limit the therapeutic usefulness of ligands binding solely to conventional agonist binding sites (Papke et al., 2009; Uteshev et al., 2002). Thus, new enthusiasm for therapeutics targeting alpha-7 has come from the discovery of alpha-7 nicotinic acetylcholine receptor positive allosteric modulators (PAMs) that work effectively on the intrinsic factors which reduce alpha-7 ion channel activation (Williams et al., 2011).

Given this, the evidence supports the involvement of microglia in neuroinflammatory pain involving alpha-7 nicotinic acetylcholine receptor in the CNS; it is likely that TQS might exert similar effects on hippocampal microglia. Therefore, we have hypothesized that TQS might reduce microglial dependent pain by decreasing LPS-induced microglial activation in the hippocampus. In the present study, we have determined the antihyperalgesic and antiallodynic effects of TQS following systemic administration of LPS. Additionally, we have examined the effects of TQS on microglial Iba-1 expression in the hippocampus.

2. Materials and methods

2.1. Animals

All experiments were carried out on naïve male C57BL/6J mice purchased from Jackson Laboratory (Bar Harbor, ME, USA). Animals were housed in groups of four in standard shoebox cages ($29 \times 18 \times 12$ cm), under standard laboratory conditions (22 ± 2 °C, relative humidity 50–60%) and maintained on a 12-h light/dark cycle (lights on at 0600 h) with free access to food and water. Mice were 10–12 weeks of age at the start of the experiment. The behavioral experiments were conducted between 0900 and 1600 h in a blind fashion with respect to treatment. All procedures were in compliance with the National Institutes of Health guidelines for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee at South Dakota State University. Good Laboratory Practice and ARRIVE guidelines were obeyed. All efforts were made to ensure minimal animal suffering.

2.2. Drugs and chemicals

Lyophilized LPS (*Escherichia coli,* serotype 055:B5) and methyllycaconitine (MLA) were purchased from Sigma-Aldrich (St. Louis, MO, USA) and were dissolved in normal saline (0.9% NaCl). TQS was purchased from Tocris Bioscience (Ellisville, MO, USA) and was reconstituted in normal saline having 1% dimethyl sulphoxide and 0.5% tween 80. All chemicals were administered intraperitoneally in a volume of 10 ml/kg of body weight.

2.3. Induction of tactile allodynia and thermal hyperalgesia

Tactile allodynia and thermal hyperalgesia were induced by LPS (1 mg/kg) administered intraperitoneally six h prior to pain tests as described previously with some modification (Yoon et al., 2012; Fig. 1). Control animals received an equal volume of vehicle.

2.4. Tactile allodynia

A standardized testing method was used to measure tactile allodynia as described previously (Chaplan et al., 1994), six h after LPS administration. Briefly, mice were acclimatized to the wire mesh boxes (Stoelting, Inc., Wood Dale, IL, USA) for 4 consecutive days before testing for tactile allodynia. On the day of testing, mice were allowed to habituate for 30 ± 5 min. A logarithmic series of calibrated von Frey filaments (Stoelting, Inc., Wood Dale, IL, USA) were to measure 50% paw withdrawal threshold using up-down method of Dixon with some modification (Dixon, 1980). A series of filaments starting with one that had 0.16 g buckling weight were applied perpendicularly to right/left hind paw at its plantar surface. Lifting of the right hind paw was recorded as positive score and the next light force filament was then applied for next measurement. If paw withdrawal did not occur within 5 s, the next larger filament was applied. This procedure was continued until four measurements were taken after initial positive response or until five consecutive negative scores (0.6, 1, 1.4, 2; 2.0 g was given the score) or four consecutive positive scores (0.16, 0.07, 0.04, 0.02, 0.008; 0.008 g score was given). Von Frey filaments were applied at several s of intervals thus leading to resolution of any behavioral response to previous stimuli. Ambulation was recorded as ambiguous response, and if it was resulted, stimulus was repeated. The resulting sequence of positive and negative score was used to calculate 50% paw withdrawal threshold. 50% g paw withdrawal threshold$=(10^{(Xf+K\delta)})/10000$, where δ=Log value of mean difference between stimuli, Xf=Log value of final von Frey filament force used and K=tubular value for pattern of positive and negative responses.

2.5. Thermal hyperalgesia

Thermal hyperalgesia was measured six h after LPS administration by determining changes in hind paw withdrawal latency using a plantar analgesia apparatus (IITC Life Science Inc., Woodland Hills, CA) as described previously (Yoon et al., 2012). Briefly, paw withdrawal (latency) was measured using an intense heat source to stimulate thermal receptors in the sole of the foot. Each mouse was subjected to latency time on hot plate maintained at 54.0 ± 0.1 °C in Plexiglas chamber. Animals licking, flicking or jumping was recorded as positive response. Latency for each mouse was calculated as a mean of three measurements. Thirty s was selected as a cut-off time to prevent tissue damage.

2.6. Western blot analysis

Mice were killed six h after LPS administration; their hippocampi were dissected out, frozen in dry ice, and stored at -80 °C until analysis. Western blot analysis was performed as described previously with some modifications (Yoon et al., 2012). Briefly, brain tissue samples were homogenized in modified RIPA buffer containing Dulbecco's Phosphate-buffered saline (Atlanta Biologicals, Lawrenceville, GA, USA), 0.1% sodium dodecyl sulfate (Fisher Scientific, Fair Lawn, New Jersey, USA), 1% Igepal CA-630 (Sigma-Aldrich, St. Louis, MO, USA), and protease inhibitor mix (complete, Mini, Roche, Indianapolis, IN, USA). Each sample was centrifuged ($17{,}000 \times g$, 20 min at 4 °C) and supernatant was collected. Total protein concentration in the hippocampal samples was determined by bicinchoninic acid assay (Pierce, Rockford, IL, USA). Equal amounts of protein (50 μg) were loaded onto 12% gels for sodium dodecyl sulfate polyacrylamide gel electrophoresis using

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