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Research report

The cerebral protective effect and mechanism of action of vitamin B6 adjuvant ceftriaxone in experimental pneumococcal meningitis

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ABSTRACT

Background: Pneumococcal meningitis is one of the most common infectious diseases with a high-mortality rate and long-term neurological sequelae, affecting up to 50% of survivors. Pneumococcal compounds are pro-inflammatory mediators that induce an innate immune response and tryptophan degradation through the kynurenine pathway. Vitamin B6 (vitB6) is an important vitamin which acts as a cofactor at the active sites of enzymes that catalyze a great number of reactions involved in the metabolism of tryptophan through the kynurenine pathway and may thus limit the accumulation of neurotoxic metabolites and preserve the cellular energy status. The aim of this study was to investigate the neuroprotective effect of adjuvant treatment with vitB6 in pneumococcal meningitis.

Methods: The effects of vitB6 on the clinical symptoms, the expression of kynureninase (KYN), Kynurenic acid (KYNA), nicotinamide adenine dinucleotide (NAD) and cytokines in brain tissue and memory of infant Wistar rats subjected to pneumococcal meningitis were researched. At the same time, Kynurenine 3-monooxygenase (KMO) inhibitor Ro 61-8048 was applied in order to further investigate the brain protective effect of vitB6 in bacterial meningitis.

Results: Adjuvant therapy of bacterial meningitis with vitB6 could improve the clinical symptoms, learning performance, lead to the maintenance of cellular NAD+ and ATP homeostasis and significantly down-regulate the levels of cytokines in the brain tissue by affecting the KYN pathway.

Conclusions: Adjuvant treatment with vitB6 in pneumococcal meningitis could exert neuroprotective effect via increasing the preservation of cellular energy through affecting the KYN pathway and reducing of the inflammatory response.

1. Introduction

Pneumococcal meningitis is a life-threatening disease associated with high mortality and morbidity rates. With the advent of antibiotics and pneumococcal vaccination, the morbidity and mortality of the disease decline significantly, but still about 50% of survivors suffer from long-term neurological sequelae (Schmidt et al., 2006), such as hearing loss, seizure, motor abnormalities, learning and memory impairment and mental retardation which are correlated with cellular damage, mainly in the cerebral cortex, hippocampus and inner ear (Bedford, 2001; Lepage and Dan, 2013; Neal and Gasque, 2013). In the study, in order to reduce animal mortality and morbidity, we used ceftriaxone early.

Inflammatory response can be induced which leads to the activation of several metabolic pathways in pneumococcal meningitis. The kynurenine (KYN) pathway (KP) has been shown to be activated which leads to the accumulation of KYN metabolites in the hippocampus in experimental pneumococcal meningitis (Bellac et al., 2006; Bellac et al., 2010). The KYN pathway have also been documented to be involved in several inflammatory brain diseases and neurodegenerative diseases, including multiple sclerosis, cerebral malaria, cancer and etc (Bellac et al., 2010; Guillemin et al., 2007; Fatokun et al., 2013; Mándi and Vécsei, 2012; Campbell et al., 2014; Reyes Ocampo et al., 2014). The pathogenesis of pneumococcal meningitis is initiated by activation of the immune system of the host through activating the nuclear factor kappa B and subsequently triggering the production of pro-inflammatory cytokines and chemokines, and the expression of co-stimulatory molecules (Hirst et al., 2004; Barichello et al., 1999). This pro-inflammatory environment induces tryptophan degradation

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through the kynurenine pathway which induces the accumulation of KYN metabolites such as 3-hydroxykynurenine (3-HKYN),3-hydroxyanthranilic acid (3-HAA), or quinolinic acid (QUINA) (Stone, 2001; Stone et al., 2003; Schwarcz, 2004). Kynurenine 3-hydroxylase and kynurenine 3-monooxygenase (KMO) are the key enzymes of the KYN pathway (Fig. 1). To clarify the role of vitB6 in brain protection through the KYN pathway in pneumococcal meningitis, we specifically inhibited KMO. The neurotoxic mechanism of 3-hydroxykynurenine and 3-hydroxyanthanilic acid involves the generation of reactive oxygen intermediates, depletion of endogenous antioxidants and lipid peroxidation (Vecsei et al., 2013). Quinolinic acid acts as a neurotoxin, gliotoxin, pro-inflammatory mediator and pro-oxidant molecule (Guillemin, 2012) and shows a cytotoxic effect. While KYNA; another metabolite through the kynurenine pathway, is an antagonist of the excitotoxic N-methyl-D-aspartate (NMDA) receptor and can protect from excitotoxic brain damage in experimental pneumococcal meningitis (Bellac et al., 2006). Although KYNA has neuroprotective effect, if the accumulation of KYNA is beyond the normal physiological level in the CNS, it can cause glutamatergic hypofunctioning and then lead to cognitive dysfunction (Olney et al., 1991). Furthermore, the catabolism of TRP through the KYN pathway is the exclusive de novo synthesis pathway for NAD+ (Bellac et al., 2006). The NAD+ is an essential cofactor in various cellular reactions, including adenosine triphosphate synthesis and DNA repair. Therefore, the KYN pathway induced in pneumococcal meningitis may influence the degree of neuronal tissue damage by affecting the KYNA production and NAD+ supply (Bellac et al., 2006; Ha and Snyder, 2000).

VitB6 optimizes the kynurenine pathway by acting as a cofactor in the metabolism of tryptophan through two enzymes, kynurenine aminotransferase and kynurenine 3-hydroxylase (van de Kamp and Smolen, 1995). Ro-61-8048 is a potent and selective inhibitor of kynurenine 3-hydroxylase and KMO. By studying the effects of Ro-61-8048, the protective effect of vitB6 on brain injury through KYN pathway in pneumococcal meningitis can be further confirmed. In addition, vitB6 has been shown to reduce hippocampal apoptosis by increasing the expression of brain derived neurotrophic factor (BDNF) in experimental pneumococcal meningitis (Zysset-Burri et al., 2013). Furthermore, vitB6 can prevent cognitive impairment in experimental pneumococcal meningitis through the up-regulation of BDNF (Barichello et al., 2014). However, little research has been done on the changes of KYN, KYNA, NAD+ and ATP in experimental pneumococcal meningitis treated by vitB6.Administration of vitB6 may attenuate neural cell apoptosis in bacterial meningitis (BM) by preventing both the accumulation of neurotoxic intermediates through the KYN pathway and the depletion of cellular energy by enhancing the de novo synthesis of NAD+.

In the present study, we evaluated the effects of vitB6 on the clinical symptoms, KYN, KYNA, NAD+ and ATP expression and memory in infant Wistar rat model of pneumococcal meningitis. To further explore the mechanism, we not only observed the changes of inflammatory factors but also observed the expression of kynurenine 3-monooxygenase (KMO) in brain tissue of experimental pneumococcal meningitis through pharmacological inhibition of the pathway at the level of kynurenine 3-hydroxylase by Ro-61-8048.

2. Methods

2.1. Ethics statement

This study was performed in strict accordance with the guidelines of the NIH's Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80–23, revised 1996).

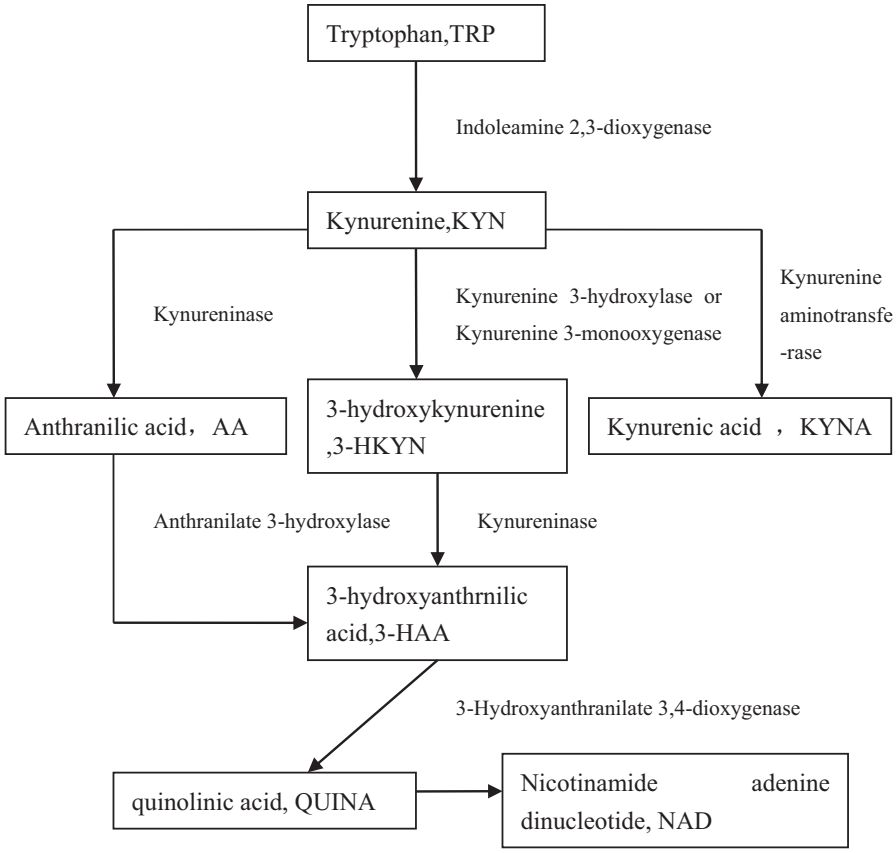

Fig. 1. Schematic of the kynurenine pathway in the rat brain.