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EC PHARMACOLOGY AND TOXICOLOGY
Editorial

Psalmotoxin (PcTx1) Blocks Acid-Sensing Ion Channel 1a (ASIC1a) in Animal Models: Implications for Neurological and Autoimmune Disease Therapy

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Received: January 18, 2017; **Published:** March 09, 2017

Neurological diseases represent approximately seven percent of the global burden of disease [1]. In the United States alone, stroke ranks third and Alzheimer's disease ranks sixth in leading causes of death [2]. Epilepsy and seizure disorders affect over 2 million people in the United States [3] with 450,000 epilepsy patients that are considered to be "pharmacoresistant," where no viable treatment has been identified [4]. Another disease that is of interest is rheumatoid arthritis, which can affect up to 1% of adults [5]. In each of these neurological disorders, a significant amount of tissue damage is produced as the result of acidic changes that occur during the acute disease process. Acid-sensing ion channels (ASICs), a family of voltage-insensitive, proton-gated channels, that are present in the central and peripheral nervous systems have been found to play a critical role in pH changes related to tissue acidosis. All ASIC subunits exhibit different pH sensitivities that detect a vast range of physiological pH. The acid-sensitivity of ASICs and the role acidity plays in the nervous system invokes interest in these receptors as pharmacological targets.

ASIC1 is the predominant ASIC expressed in the CNS [6]. These receptors are found in the spinal cord and in various brain regions such as the cortex, hippocampus, periaqueductal gray (PAG), striatum, and amygdala. ASIC1 in the CNS is believed to contribute to apoptosis after ischemia due to the high permeability to calcium (Ca^{2+}) and pH levels that fall below 6.5 in the cerebral tissues. ASIC1a is coupled by the activation of Ca^{2+}/calmodulin-dependent protein kinase II cascade and the N-methyl-D-aspartate glutamate receptor. Regulation of acidity that leads to tissue destruction and disease sequelae would prove beneficial to mitigate or perhaps even halt the disease process.

ASIC channels interact with a variety of natural venom toxins, such a sea anemone or cone snail toxins. Psalmotoxin-1 (PcTx1) is a venom toxin found in nature and isolated from the venom of *Psalmopeous cambridgei*, the Trinidad Chevron tarantula [7]. PcTx1 toxin antagonizes the ASIC1a subtype with nanomolar affinity (~3nM) and increases the channel's sensitivity to protons. Recently, acid-sensing ion channels containing ASIC1a and ASIC2a have been shown to be sensitive to PcTx1, with the more robust inhibition observed when two ASIC1a subunits are present [8]. ASIC antagonism, specifically focused on the ASIC1a containing receptors, has the potential to lead to specific therapeutic targeting in neurological and autoimmune/inflammatory disorders.

Stroke

The deprivation of oxygen due to decreased blood flow during an ischemic stroke leads to a decrease in extracellular pH (6) and subsequent accumulation of lactic acid in surrounding brain tissues. Though the mechanism is under investigation, this acidic environment leads to neuronal injury. In a study by McCarthy and colleagues, it was demonstrated that isolated PcTx1 was neuroprotective two hours after induction of stroke in a conscious spontaneously hypertensive rat model [9]. Additionally, there were reduced cortical and striatal infarct volumes (72-hrs post stroke) which were positively correlated with improved neurological scores, motor function, and neuronal tissue protection. Although PcTx1 exhibited efficacy in a rodent model of stroke, more work is needed to assess the efficacy of PcTx1 in clinical examples of stroke.

Epilepsy

In a study by Yang., *et al*. increased ASIC1a expression was found on reactive hippocampal astrocytes of temporal lobe epilepsy (TLE) patients and epileptic mice. ASIC1a activation resulted in intracellular increases of Ca^{2+} levels of reactive astrocytes. It is believed that activation of Ca^{2+} signaling leads to a release of gliotransmitters, which are factors that are released from glia that alter neuron and other glia activity. Examples of gliotransmitters are glutamate, D-serine, and ATP, and could increase the likelihood of epileptic seizures [10]. PcTx1 demonstrated controversial effects in a kainate-induced model of epilepsy by showing a reduction in seizures [11] yet appear to affect seizure severity [12].

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease that involves progressive inflammatory conditions of the joints and surrounding soft tissues, ultimately leading to joint destruction. Acid hydrarthrosis is an important factor in RA, inducing acidosis-related articular chondrocyte apoptosis. ASIC1a receptors respond to the decrease in pH by increasing levels of Ca^{2+}, leading to articular chondrocyte injury [13]. Zhou., *et al*. showed that blockade of ASIC1a with PcTX1 dramatically reduced the expression of pro-apoptotic proteins, thus potentially slowing progressive tissue destruction [14].

Other Neurological Diseases

While it has been demonstrated that PcTx1 has a beneficial effect in blocking ASIC1a channels in ischemic stroke, epilepsy and RA in animal models, other neurological diseases that have ASIC1a involvement in the disease pathway should be evaluated. Additionally, acidosis appears to trigger the release and aggregation of beta-amyloid and could factor into Alzheimer's disease. Moreover, ASIC1a channels inhibited by nM concentrations of beta-amyloid seem to be associated with learning and memory deficits. In multiple sclerosis, ASIC1a channels have been associated with axonal degeneration due to spinal cord acidosis in a murine model [15]. This observation is supported by evidence of overexpression of ASIC1a in axons from chronic brain lesions of patients with progressive MS [16]. This overexpression of ASIC1a was also found to be present in dopaminergic neurons of Parkinson's patients and in rodent models [17].

In summary, preliminary animal models using PcTx1 to effectively block ASIC1a channels in stroke, epilepsy, and rheumatoid arthritis show promising results for the use of the toxin as an adjunct therapy for reducing tissue damage with traditional therapies. Several other neurological disorders that involve ASIC1a in the disease pathway are also potential targets for PcTx1, such as Parkinson's disease and multiple sclerosis. There is potential for using this ASIC1a toxin antagonist and drug candidates that mimic the PcTx1 mechanism of action for treating these disorders.

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Volume 3 Issue 4 March 2017