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Track A: Drug design, fundamental & translational sciences

PSWC-ABS-1408

The β-lactam Clavulanic Acid without Antibacterial Activity mediates Glutamate Transport-sensitive Pain-relief in the Chronic Constriction Injury Rat Model of Neuropathic Pain

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Backgrounds: Following nerve injury, down-regulation of astroglial glutamate transporters (GluTs) and subsequently extracellular glutamate accumulation is one of the factors contributing to nociceptive signaling. Some β-lactam antibiotics e.g. ceftriaxone can upregulate GluTs and display analgesic effect in chronic pain models. Following nerve injury, down-regulation of astroglial glutamate transporters (GluTs) and subsequently extracellular glutamate accumulation is one of the factors contributing to nociceptive signaling.

Aims: The effect of another β-lactam, clavulanic acid (CA), with negligible antibiotic activity, is tested along with ceftriaxone on neuropathic pain behavior and the expression of GLT1, its splice variant GLT1b, and glutamate-aspartate transporter (GLAST) in spinal cord.

Methods: Sprague-Dawley rats. Chronic constriction injury (CCI). Western blotting. Cultured astrocytes from rodents and humans.

Results: Repeated injection of CA alleviated CCI-induced mechanical and thermal hypersensitivity. In parallel CA restored the down-regulation of GLT1b, in spinal cord of CCI rats, whereas ceftriaxone failed to affect any GluT here. However, both CA and ceftriaxone up-regulated the GLT1 expression in rat and human spinal astrocyte cultures. Furthermore, CA increased expression of GLT1b and GLAST in rat astrocytes in a dose-dependent manner.

Summary/Conclusion: For the first time it is demonstrated that CA in chronic dosing, could mitigate neuropathic pain and up-regulate GluTs both *in vivo* and *in vitro*, also in human cells. The study sets the perspectives for developing new β-lactam-based analgesics, devoid of antibacterial activity, for treatment of chronic pain

Disclosure of Interest: None Declared

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In: Poster Presentation on Tuesday, 23 May 2017, 12:30-14:00
Type: Poster
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Abstract:
BackgroundsFollowing nerve injury, down-regulation of astroglial glutamate transporters (GluTs) and subsequently extracellular glutamate accumulation is one of the factors contributing to nociceptive signaling. Some β-lactam antibiotics e.g. ceftriaxone can upregulate GluTs and display analgesic effect in chronic pain models. Following nerve injury, down-regulation of astroglial glutamate transporters (GluTs) and subsequently extracellular glutamate accumulation is one of the factors contributing to nociceptive signaling.AimsThe effect of another β-lactam, clavulanic acid (CA), with negligible antibiotic activity, is tested along with ceftriaxone on neuropathic pain behavior and the expression of GLT1, its splice variant GLT1b, and glutamate-aspartate transporter (GLAST) in spinal cord.MethodsSprague-Dawley rats. Chronic constriction injury (CCI). Western blotting. Cultured astrocytes from rodents and humans.ResultsRepeated injection of CA alleviated CCI-induced mechanical and thermal hypersensitivity. In parallel CA restored the down-regulation of GLT1b, in spinal cord of CCI rats, whereas ceftriaxone failed to affect any GluT here. However, both CA and ceftriaxone up-regulated the GLT1 expression in rat and human spinal astrocyte cultures. Furthermore, CA increased expression of GLT1b and GLAST in rat astrocytes in a dose-dependent manner.Summary/ConclusionFor the first time it is demonstrated that CA in chronic dosing, could mitigate neuropathic pain and up-regulate GluTs both in vivo and in vitro, also in human cells. The study sets the perspectives for developing new β-lactam-based analgesics, devoid of antibacterial activity, for treatment of chronic pain