The 3rd Chiba University-Mahidol University Joint Symposium on Pharmaceutical Sciences

Program and Abstract Book

hosted by Faculty of Pharmacy, Mahidol University
Thursday August 2, 2018

Venue: Room 606, Rajaratana Building, Faculty of Pharmacy, Mahidol University
Bangkok, Thailand
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Abstract

Differential modulation of spinal nociceptive processing by aspirin-triggered resolvin D1 in rat pain model

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Resolvins are families of specialised proresolving mediators (SPMs) that have been recently identified. Harnessing the actions of the resolvin pathways has the potential for the treatment of a wide range of conditions associated with overt inflammatory signalling. Aspirin-triggered resolvin D1 (AT-RvD1 also known as 17R-RvD1) is a docosahexaenoic acid (DHA)-derived resolvin generated by the acetylation of cyclooxygenase-2 (COX-2) by aspirin. AT-RvD1 has previously shown a robust analgesic effect in behavioural models of pain e.g. neuropathic pain form mechanical nerve injury and inflammatory arthritis. We have investigated acute effects of spinally applied AT-RvD1 on evoked responses of spinal neurones in vivo in rat pain models from different causes, including, carrageenan (CAR)-induced acute inflammatory pain, monosodium iodoacetate (MIA)-induced chronic osteoarthritic (OA) pain and paclitaxel (PCX)-induced chronic peripheral neuropathic pain. Arrays of relevant spinal gene expressions following the pain model induction were also examined. AT-RvD1 demonstrates the differential inhibition of spinal nociceptive processing in different models of pain. The inhibitory effects of AT-RvD1 was evident in CAR and PCX models. Spinal administration of AT-RvD1 (15 ng/50ul) produced rapid and robust inhibition of electrical stimulus-evoked responses of spinal neurons (30-50% inhibition on nociceptive fibre responses and central excitability) selectively in CAR-treated but not in control rats. AT-RvD1 (15 and 150 ng/50ul) inhibited low intensity mechanical stimulus-evoked responses only in PCX-treated rats in a dose-dependent manner (35-70% inhibition). AT-RvD1 produced a dose dependent inhibition of cold (acetone)-evoked responses in PCX rats (70-80% inhibition), however the spinal neurones in the control rats were also inhibited to a similar degree. The robust AT-RvD1-mediated inhibition of the spinal neurones seen in these two models suggests that spinal cord is the major site of action of AT-RvD1 in acute inflammatory pain and PCX-induced neuropathic pain. On the contrary, the AT-RvD1-mediated inhibition of evoked neuronal responses in the MIA model was very limited (10-15% inhibition on Aδ-fibre responses). The inhibition of AT-RvD1 in pain models may be underpinned by unique spinal changes of resolvin system, especially an increase in the mRNA expression of 5-lipoxygenase activating protein (FLAP), encoding a protein determining endogenous resolvin synthesis, in the carrageenan and PCX models which was not seen in the MIA model. Our data provide for the first time the evidence of heterogeneous spinal plasticity of the resolvin system in different types of pain and support further investigation of AT-RvD1 as a novel analgesic.

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