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Increased Expression of HCN2 Channel Protein in L4 Dorsal Root Ganglion Neurons Following Axotomy of L5 Spinal Nerve Injury: Possible Role in Peripheral Neuropthic Pain

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Peripheral neuropathic pain (PNP) is characterized by chronic spontaneous pain and/or hypersensitivity to normally painful or nonpainful stimuli. This pain results partly from abnormal hyper excitability of dorsal root ganglion (DRG) neurons that convey sensory information from the periphery to the central nervous system. Previous studies have shown, using a modified version of the lumbar 5 (L5)-spinal nerve ligation model of PNP (model is termed mSNA and involves L5-spinal nerve taxonomy plus loose ligation of the lumbar 4 (L4)-spinal nerve with neuro inflammation-inducing chromic-gut), that L4 DRG neurons exhibit increased spontaneous activity, the key characteristic of aberrant neuronal hyper excitability. However, the underlying ionic and molecular mechanisms of the hyper excitability of L4 DRG neurons are incompletely understood resulting in difficulty treating this condition in patients. This hyper excitability could result from changes in expression and/or function of ion channels including the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (composed of HCN1-HCN4 subunits), which are active near the neuron's resting membrane potential and produce an excitatory inward current that depolarizes the membrane potential making the generation of an individual action potential more likely. In this presentation, data will be discussed suggesting a role for HCN channels in hypersensitivity associated PNP. The data were obtained from studies performed in a rat model of PNP, and aimed at examining whether: (a) expression of HCN1–HCN3 channels is altered in L4 DRG neurons which are essential for transmission of evoked pain in the mSNA model and which contribute to chronic spontaneous pain, and (b) local (intraplantar) blockade of these HCN channels, with a specific blocker, ZD7288, attenuates chronic spontaneous pain and/or evoked pain. The findings of these studies revealed: (1) a significant increase in HCN2-immunoreactivity in small (<30 μm) DRG neurons (predominantly IB4-negative neurons), and in the proportion of small neurons expressing HCN2 (putative nociceptors); (2) no significant change in HCN1- or HCN3-immunoreactivity in all cell types; and (3) attenuation, with ZD7288 (100 μM intraplantar), of chronic spontaneous pain behavior (spontaneous foot lifting) and mechanical, but not, heat hypersensitivity. The results suggest that peripheral HCN channels are involved in the mechanisms of spinal nerve injury-induced PNP, and that HCN channels, possibly HCN2, represent a novel target for PNP treatment. The findings are consistent with those of previous studies suggesting a pivotal role for HCN channels, specifically HCN2, in chronic inflammatory and neuropathic pain that afflicts a vast number of patients across the globe.

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Effect of Resveratrol Treatment on the Pharmacokinetics of Diclofenac in Healthy Human Volunteers

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The purpose of the present study was to assess the effect of resveratrol (RSV) treatment on the pharmacokinetics of diclofenac (DIC) in healthy human volunteers. The open-label, two period, sequential study was conducted in 12 healthy human volunteers. A single dose of RSV 500 mg was administered daily for 10 days during treatment phase. A single dose of DIC 100 mg was administered during control and after treatment phases under fasting conditions. The blood samples were collected after DIC dosing and analyzed by HPLC. Treatment with RSV significantly enhanced maximum plasma concentration (Cmax) (1.73 to 2.91 μg/mL), area under the curve (AUC) (5.05 to 9.95 μg h/mL), half life (T1/2) (1.12 to 1.76 h) and significantly decreased elimination rate constant (Kel) (0.71 to 0.41 h(-1)), apparent oral clearance (CL/F) (14.58 to 6.48 L/h) of DIC as compared to control. The geometric mean ratios for Cmax , AUC, T1/2 , Kel and CL/F of DIC were 1.75, 2.12, 1.65, 0.61 and 0.47, respectively were outside the limits of 0.8-1.25, which indicates clinically significant interaction between DIC and RSV. The results suggest that the altered pharmacokinetics of DIC might be attributed to RSV mediated inhibition of CYP2C9 enzyme. Therefore, combination therapy of DIC along with RSV may represent a novel approach to reduce dosage and results in reduced gastrointestinal side effects of DIC.

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