(120) Physiological relevance of a rodent model of degenerative disc disease

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The American Pain Society estimates that 45% of the U.S. population seeks medical help for chronic pain at some point in their lives. Those affected include the 15% of Americans with persistent back pain. There are many potential sources including degenerative disc disease (DDD), which is one of the primary causes of chronic low back pain (LBP). Natural age related degeneration of lumbar intervertebral discs (IVDs) is common, but abnormal degeneration can occur, often resulting in pain, instability, and biomechanical movement disadvantages. IVDs are articular joints between vertebra and they act to distribute loads placed on the spine through hydrostatic pressures. The disc is composed of the exterior annulus fibrosus surrounded by ligaments and the central nucleus pulposus. The presence of nerve fibres and nerve endings in the lumbar IVDs and in the adjacent longitudinal ligaments has been demonstrated by many authors. In healthy discs, innervation is mostly limited to the posterior and anterior longitudinal ligaments and the superficial layers of the annulus fibrosus. Human IVDs are supplied by a variety of nerve fiber types including C- and A-delta fibers (substance P and CGRP), A-beta fibers (myelin basic protein) and sympathetic fibers entering from the sympathetic nerve truck. Specialized sensory nerve endings have also been described (i.e. pacinian corpuscles and golgi tendon organs). The goal of this study is to assess if the rat is of potential use to develop a relevant, rodent model of DDD-related LBP. Lumbar IVD innervation will be assessed in rats by immunohistochemistry to examine total innervation and fiber type(s). Preliminary results suggest that IVD innervation in rat and human are similar. Supported by grants from the Canadian Institute for Health Research (LSS) and the American Pain Society (MM).

(121) CG100649, a novel dual-acting COX-2 and carbonic anhydrase inhibitor: Preclinical safety evaluations

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CG100649 is a novel dual-acting cyclooxygenase-2 (COX-2) and carbonic anhydrase (CA) inhibitor which is currently in phase II clinical trials in Europe. CG100649 was negative in the bacterial Ames assay and in the in vivo mouse micronucleus assay at oral doses up to 1250 mg/kg). The mutagenic potential of CG100649 was further investigated in the unscheduled DNA synthesis assay in rat liver. CG100649 administered to rats at oral doses of 62.5 and 125 mg/kg (male) and 7.5 and 15 mg/kg (female) failed to induce repairable DNA lesions in liver. Male rats tolerated target doses up to 5.0 mg/kg/day for 28 days, however females showed treatment-related histopathological findings in the intestines at target doses of 1.0 mg/kg/day and higher. The systemic exposure was greater in females rats which is commonly observed in rats due to a lower metabolizing capacity in females. The general activity and behavior in rats was not altered by the oral administration of CG100649 at single dose levels of up to 30 mg/kg. Similarly, oral treatment of CG100649 did not significantly affect the respiration rate or end tidal volume in conscious rats. Administration of oral doses up to 30 mg/kg CG100649 to awake cynomolgus monkeys had no marked effect on arterial blood pressure, heart rate or lead II ECG parameters (RR, PR, QT, QTcF and QTcQ intervals or QRS duration), waveform or rhythm in the 8 hours following dosing. Treatment with 2 ìg/ml CG100649 in HEK293 cells stably transfected with hERG cDNA produced no inhibition of hERG tail current. In whole body radiography (QWBPI) studies in rats, the highest radioactivity was associated with whole blood and tissues with high blood perfusion such as liver, lung, kidney, and bone marrow which also have the highest CA activity. These data project a favorable safety profile for CG100649 in humans.

Animal Pain Models–Other

(122) An engineered zinc finger protein repressor of TrkA reduces nociception in a mouse model of bone cancer pain

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Society for Neuroscience abstract

(123) Vibration exposure induces mechanical hyperalgesia in lean but not fatty Zucker rats

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Repeated use of powered hand-tools can result in the development of vibration-induced neuropathy in the hands of workers. It has been hypothesized that workers with metabolic syndrome or diabetes may be at greater risk of developing a vibration-induced neuropathy. However, these workers are usually excluded from epidemiological studies, so their risk of developing a vibration-induced neuropathy is unknown. The goal of this study was to use a rat-tail model of hand-arm vibration syndrome to characterize changes in sensory nerve function that occur in response to vibration exposure in fatty Zucker rats, an animal model of metabolic syndrome. Rats were exposed to tail vibration or restraint-control conditions 4 h/day for 10 days. Aβ, Aδ, and C-fiber function was assessed using transcutaneous electrical stimulation at 3 different frequencies. Average thresholds at each frequency were analyzed using mixed-model ANOVAs. Thresholds were measured before and after vibration exposure on days 1, 5 and 10. Previous data from our lab demonstrated that repeated exposure to vibration results in a reduction in Aβ and Aδ fiber thresholds and demyelination of tail nerves in Sprague Dawley rats. In this study vibration also resulted in a reduction in Aβ-fiber thresholds in lean (control) but not in fatty Zucker rats, suggesting vibration may have increased sensitivity to mechanical stimuli in lean rats. The increase in Aβ-fiber sensitivity was associated with an increase in circulating calcitonin-gene related peptide (CGRP) concentrations in lean rats. In contrast, circulating CGRP concentrations were reduced by vibration in fatty rats. Vibration did not affect Aδ- or C-fiber thresholds in either group of rats. These findings suggest that metabolic disorder or diabetes may not increase the risk of developing a vibration-induced neuropathy. They also suggest that changes in circulating CGRP levels may serve as an early biomarker for detecting vibration-induced nerve injuries in workers.