This research investigated age-related changes in visceral pain and referred muscle hyperalgesia in an animal model of artificial ureteral calculosis.
Methods: Ninety Sprague-Dawley male (M) and female (F) rats were subdivided in groups depending on sex and age: 6-months (15M, 15F), 12-months (15M, 15F) and 24-months (15M, 15F). All underwent artificial stone implantation in the left ureter. Spontaneous visceral pain behaviour [number/duration of "ureteral crises" (UC)] was video-recorded for 4 days post-operatively, electrical vocalization thresholds of the left oblique muscle were measured daily for 2 days pre- and 4 days post-operatively.
Results: UC parameters were significantly higher in F than M at 6 months ($p < 0.05$); they decreased progressively with age in all rats with a significant trend in females ($p < 0.02$). UC were still higher in F than M at 12 and 24 months, but the difference was no longer significant. Muscle hyperalgesia (maximal threshold decrease in the post vs pre-operative period) was significantly and directly correlated to visceral pain behaviour in both sexes at 6 months ($p < 0.001$). Hyperalgesia increased with age in both M and F and its correlation with pain behaviour disappeared.
Conclusions: Visceral pain expression is higher in females than males in young age. Visceral pain decreases while referred muscle hyperalgesia increases with age in both sexes, though more in females. The results show a different impact of aging on direct and referred visceral pain phenomena in the two sexes.

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A CHRONIC ANIMAL MODEL FOR THE STUDY OF MIGRAINE

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Migraine is a neurovascular disease which is characterized by recurrent unilateral headache which lasts 4 to 72 hours. It can produce photo and phono fobia, and in most of the cases, also incapacity. The main theories about its pathophysiology include central and peripheral sensitization and cortical spreading depression. So far, the experimental approach for the study of migraine has been developed in acute animal models. Considering the fact that this pathology is of chronic nature and that the phenomena described for acute events differs from that of chronic ones, this study aims to propose a chronic model of migraine. All procedures were approved by our institutions' project commission and the IASP's ethics committee. After 7 days of habituation to the observation conditions and laboratory personnel, under general anaesthesia (pentobarbital 40 mg/kg) a guide cannula was positioned and fixed over the meninge. On day two postsurgery, the rat was placed in an observation box, after 15 minutes of observation we delivered 2 μl of inflammatory soup (histamine, bradykinin, serotonin 1 mM and PGE2 0.1 mM) and observed for another 45 minutes. The rat was video recorded for 7 days and the following behaviours were analysed: facial grooming, body grooming, freezing, exploration and rest. Our results show that the meningeal infusion of inflammatory soup increases nociceptive behaviours related to headache: rest, facial grooming and freezing. These changes gradually increased over the 7 day period of analysis. This model can contribute to further understand the pathophysiology and the study of novel therapeutic approaches.

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ABNORMAL ENCODING OF CHOICES AND REWARDS IN ORBITOFRONTAL CORTEX IN MONOARTHRITIC RATS

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The orbitofrontal cortex (OFC) is fundamental for the update of reward value in decision making tasks in humans and animals. Previous works in rats have shown that lesions of the OFC, as well as chronic pain lead to impairment in the Rodent Gambling Task akin to the Iowa Gambling Task (Bechara et al., 1994). Here we used multielectrode recordings to study orbitofrontal cortex activity in rats performing this task during control and chronic pain conditions. As previously reported, control animals developed preference for low risk choices while monoarthritic rats developed preference for high risk choices. Neuronal activity showed that control animals present a higher proportion of cells that differentially fire for high and low risk choices during the whole task, while monoarthritic animals only presented this differential activity in the second half of the task. Comparison of neuronal responses to rewards showed that control animals presented a higher proportion of cells with differential firing rates for high and low risk rewards, but that the pain group presented an increased number of cells that differentially fired for rewarded and non rewarded trials in the low risk lever. These results show for the first time altered orbitofrontal cortex processing during decision-making deficits in chronic pain conditions and support the notion that chronic pain alters the reward/aversion system.
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DEXKETOPROFEN AND TRAMADOL INTERACTION IN A MODEL OF MONOARTICULAR CHRONIC INFLAMMATORY PAIN IN MICE

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Chronic musculoskeletal pain is one of the main causes of pain and disability in adults. Monotherapy is seldom adequate, and analgesic-drug combinations are being introduced to improve outcomes. In control mice, we have reported synergy between dexketoprofen (DEX), a mixed cyclo-oxygenase inhibitor, and tramadol (TRM) a weak opioid with monoaminergic activity. In the present investigation, we assessed the effects of the combination in a model of chronic inflammatory pain in mice. Animals received an intraplantar injection (30 μl) of Complete Freund's Adjuvant. Thermal hyperalgesia (Hot Plate test) and plasma extravasation (Evan's blue) were evaluated 7 days afterwards. We obtained dose-response relationships for each drug individually and combined in a 1:1 proportion. Isobolograms and interaction indexes (II) were used to establish interactions. In control animals (no-inflammation), ED50's in the Hot Plate test were 120.6±9 and 25.25±1 mg/kg for DEX and TRM, respectively, while the ED50 of the combination was 59.6±1 (II = 0.8). During inflammation, ED50 of the combination significantly ($p < 0.01$) decreased 10.57±0.2 mg/kg (II = 0.14). The anti-exudative effects of DEX and TRM individually, produced ED50's of 16±0.3 and 7±0.7 mg/kg, respectively, while that of the combination was 1.34±0.2 mg/kg (II = 0.10). The results show that antinociceptive synergy exists between the two drugs in control conditions, and that synergy is enhanced in the presence of chronic inflammatory pain. Moreover, intense synergy exists on plasma

extravasation suggesting that the combination could be particularly useful in patients with chronic musculoskeletal pains.
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Reference(s)

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ACUTE AND CHRONIC EFFECTS OF NIMESULIDE IN A MODEL OF OSTEOARTHRITIC PAIN

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The aim of the present study was to investigate the acute and chronic effects of nimesulide, a selective inhibitor of cyclooxygenase isoform 2 (COX-2) in a rat model of osteoarthritic pain.
Male Sprague Dawley rats (160–190 g) received an intra-articular injection of monosodium iododacetate (MIA; 1 mg/50 μl) or saline into the left knee joint. Behavioural testing (weight-bearing and hindpaw mechanical withdrawal thresholds (PWT) of the ipsilateral and contralateral limbs) was carried out for 14 days post-injection when rats received a single oral dose of nimesulide (10 $mgKg^{-1}$) or vehicle (2% methylcellulose). Pain behaviour was assessed before and at 40 min intervals post-drug administration for 2 h. The same group of rats subsequently received a single daily oral dose of nimesulide for 6 days (days 15–20), with pain behaviour assessed 1 h following drug administration. Behavioural testing was carried out until day 28.
Intra-articular injection of MIA produced a pronounced decrease in weight-bearing and PWT on the ipsilateral paw compared to saline-treated rats, suggesting the appearance of referred pain. Acute administration of vehicle did not reverse MIA-induced changes in weight-bearing or PWT and had no effect in saline-treated rats. Acute oral administration of nimesulide significantly reversed MIA-evoked changes in PWT and weight bearing compared to vehicle-treated rats. These changes were maintained for the duration of drug treatment and, in the case of PWT, did not return back to control levels following cessation of drug treatment. These data demonstrate persistent anti-nociceptive effects of chronic nimesulide and its potential to modulate the referred pain associated with joint injury.

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INFLUENCE OF AMYGDALOID GLUTAMATERGIC RECEPTORS ON SENSORY AND AFFECTIVE PAIN-RELATED RESPONSES IN THE NEUROPATHIC RAT

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Introduction: The central amygdala (CeA) mediates emotional behaviours and contains neurons that respond to painful stimuli. Our recent results suggest that group I metabotropic glutamate receptors –mGluR1R and mGluR5R- may influence pain-related responses in nerve-injured animals but the precise roles played by various subtypes of amygdaloid glutamate receptors have not yet been fully elucidated. In this study, we attempt to characterize further the pain-regulatory roles of amygdaloid glutamate receptors in nerve-injured rats.
Materials and Methods: Neuropathy was induced by unilateral ligation of the tibial and common peroneal nerves. Various glutamate receptor antagonists were microinjected into the CeA ipsi- or contralateral to nerve injury, or bilaterally. Limb withdrawal response induced by monofilament stimulation of the hind paw was used as an index of the sensory-discriminative aspect of pain, and an aversive place-conditioning test as an index of the affective-emotional component of pain.
Results: Amygdaloid administration of an antagonist of the mGluR1R, mGluR1/5R or NMDA-R attenuated in a dose-related fashion affective pain-related behavior. The strongest attenuation of affective pain-related behavior was induced by an antagonist of the mGluR1, particularly following administration to the CeA contralateral to nerve injury. Attenuations of affective pain-related behaviors by amygdaloid administrations of glutamate receptor antagonists were associated with decreased limb withdrawal responses, and this suppression in the index of sensory pain component was also strongest following administration of the mGluR1 antagonist.
Conclusions: The mGluR1 in the CeA, particularly contralateral to peripheral nerve injury, plays an important role in both sensory and affective pain-related responses following nerve injury.

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MEASURING PAIN PERCEPTION IN PLACE-ESCAPE-AVOIDANCE PARADIGM AFTER EXPERIMENTAL SPINAL CORD INJURY

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Background and Aim: Neuropathic pain following spinal cord injury (SCI) in humans can be severe, disabling and difficult to treat. With a prevalence of 50% in SCI, chronic neuropathic pain presents a significant health care issue.
Pain sensation comprises both a sensory-discriminative and an affective-motivational component. Unfortunately the latter can be extremely difficult to measure. Ideally, the experimental setting enables the animal to express the experiences and level of pain through voluntary behaviour, though at present neither good nor validated models for measuring central pain exists. The place-escape avoidance model (black/ white box) is a potential solution aiming to determine perceived pain intensity by measuring the repression of natural place preference to escape a painful stimulation.
Method: Rats with either one of 4 different types of SCI or from a control group were tested in a biased box with one black side (natural preference) and one white side (natural avoidance). Mechanical stimulation was repeatedly applied either at-level or below-level in the black side. Time spent in black versus white side subsequently served as primary outcome.
Results and Conclusion: Our results indicate at-level hyperalgesia following contusion injury (compared to sham), but no below-level hyperalgesia was observed after contusion, compression or excitotoxic injury (compared to naive). The below-level findings are in concordance with results obtained by measurements of supra-spinal responses and in contrast to measurements of brisk paw-withdrawal following mechanical stimulation.

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PREGABALIN'S EFFICACY IS IPSILATERALLY RESTRICTED IN AN ANIMAL MODEL OF NEUROPATHIC PAIN

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Nervous system symmetry may allow unilateral injuries to precipitate bilateral consequences through peripheral, spinal and/or supraspinal circuits. Importantly, there are bilateral non-segmental projections of rostral ventromedial medulla (RVM) facilitatory output neurones, some of which release 5HT in the spinal cord. Following nerve injury, this output is enhanced and creates a state permissive for the inhibitory actions of pregabalin (PGB), a situation that is mimicked in naive animals by the pharmacological activation of facilitatory spinal 5HT3 receptors. We unilaterally nerve-ligated rats to investigate whether systemic doses of PGB that inhibit ipsilateral dorsal horn neurones could inhibit the contralateral