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Background and aims. Modulation of pain signaling at many levels in the nervous system involves adrenergic pathways. Despite the signaling role of alpha2 receptors in these pathways, alpha2 KO mice have normal baseline sensitivity to thermal stimuli. We hypothesized that a pain phenotype would become apparent in the presence of stress and that alpha2A KO mice would be useful for investigating the effect of stress on pain sensation.

Methods. Wild-type (WT) and alpha2A KO mice were exposed to 10 min ultrasonic sound stress (24–75 kHz, 100 dB) and tested for paw withdrawal latency (PWL) on a 50 °C hotplate. The effects of adrenalectomy, guanethidine sympathectomy and pretreatment with the alpha1 antagonist prazosin or the alpha2 antagonists rauwolscine and idazoxan were assessed.

Results. Exposure to ultrasonic (versus sham) stress resulted in 3-fold elevation in plasma corticosterone levels and significantly prolonged PWL in WT mice. In alpha2A KO mice the corticosterone elevation was blunted and PWL significantly shortened following ultrasonic stress. Alpha2A KO mice subjected to adrenalectomy still exhibited stress-induced thermal hyperalgesia. Guanethidine sympathectomy or prazosin did not affect baseline thermal sensitivity, but blocked stress-induced thermal hyperalgesia in alpha2A KO mice. WT mice and rats pretreated with rauwolscine and idazoxan also exhibited stress-induced hyperalgesia.

Conclusions. Alpha2A KO mice, and WT mice and rats pretreated with alpha2 antagonists, exhibited stress-induced hyperalgesia, rather than stress-induced analgesia. This finding reflects a balance in the effects of stress on pain, probably via spinal inhibitory pathways and sympathetic nerves, that is shifted towards analgesia by alpha2A receptors.

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379

DYSFUNCTION OF MENINGEAL CAPSAICIN-SENSITIVE AFFERENT NERVES IN A RAT MODEL OF DIABETIC NEUROPATHIC PAIN

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Neuropathic alterations associated with diabetes affect cephalic pain mechanisms and vascular responses mediated by sensory nerves. Capsaicin-sensitive nociceptive afferents innervate the rat dura mater and may elicit vasodilatation through the release of calcitonin gene-related peptide (CGRP). Therefore, this study was initiated to reveal diabetes-induced alterations in the function of nociceptors of the dura mater by studying capsaicin-induced vasodilatation in vivo and CGRP release in vitro using laser Doppler flowmetry and measurement of peptide levels, respectively. Diabetes was induced with streptozotocin in adult male Wistar rats. In a cranial window preparation, epidural application of capsaicin (10^{-7} to 10^{-6} M) produced distinct vasodilatory responses in control animals. In diabetic rats, capsaicin-induced vasodilatation was significantly reduced or even abolished 6 but not 2 or 4 weeks after the induction of diabetes. However, vasoconstriction, a non-neurogenic response to capsaicin at higher concentrations (10^{-5} M) was not altered in diabetic rats. The vasodilatory effects of histamine (10^{-5} M), acetylcholine (10^{-4} M) and CGRP (10^{-5} M) were similar in control and diabetic animals. In diabetic rats, in vitro experiments revealed a significant decrease in capsaicin-induced release of CGRP. In conclusion, the present study revealed a marked reduction in sensory neurogenic vasodilatation in streptozotocin-treated rats indicating an impairment of meningeal nociceptor function. The findings suggest that diabetes-induced alterations in neurogenic inflammatory reactions resulting in a limited removal of inflammatory mediators and/or tissue metabolites from meningeal tissue may contribute to the enhanced incidence of headaches in diabetics.

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380

LACOSAMIDE: OVERVIEW OF THE ANALGESIC EFFICACY IN ANIMAL MODELS OF PAIN

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Lacosamide is a novel investigational analgesic which is currently being evaluated in phase III clinical trials in patients suffering from painful diabetic neuropathy. It has a novel dual mode of action: it enhances the slow inactivation of voltage-gated sodium channels and modulates collapsin response mediator protein 2. The aim of the current experiments was to profile lacosamide in various animal models for chronic pain.

Lacosamide in the dose range 3–30 mg/kg given i.p. was evaluated in the streptozotocin (STZ) model for diabetic neuropathic pain, the vincristine model for chemotherapy-induced neuropathic pain, a bone cancer model, the monosodium iodo acetate (MIA) model for osteoarthritic pain and the tumour necrosis factor alpha (TNFa) model for chronic muscle pain. In each model various endpoints were assessed including thermal and tactile allodynia and thermal and tactile hyperalgesia.

In the STZ model lacosamide was active on all pain parameters. Moreover, when compared to clinically used analgesics such as amitryptiline, pregabalin, gabapentin, levetiracetam, lamotrigine or venlafaxine lacosamide was the compound with the broadest efficacy. Lacosamide was also active in models for cancer pain, as evidenced by potent effects against vincristine-induced hyperalgesia and bone cancer pain. Furthermore, muscle hyperalgesia induced by TNFa was more potently reduced by lacosamide as compared to pregabalin. Finally, lacosamide attenuated arthritic pain induced by MIA in rats.

These results suggest that lacosamide may specifically have antihyperalgesic activity under conditions of chronic neuropathic, cancer, inflammatory and musculoskeletal pain.

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381

DIFFERENTIAL PHARMACOLOGY OF TRPV1 ANTAGONISTS DETERMINES THE MAGNITUDE OF BODY TEMPERATURE CHANGES IN RATS

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The vanilloid receptor TRPV1 is a cation channel that serves as a polymodal detector of pain-producing stimuli such as capsaicin, protons and heat. TRPV1 antagonists that block capsaicin, proton and heat activation act as anti-hyperalgesics in animal models of pain, suggesting their utility as analgesics. Recently, we showed that TRPV1 antagonists representing various chemotypes cause an increase in body temperature (hyperthermia) in multiple species suggesting that TRPV1 is tonicly activated in vivo and regulates body temperature.

In an effort to eliminate hyperthermia associated with TRPV1 antagonism, we have characterized several molecules exhibiting differential pharmacology in vitro using agonist-induced $45Ca^{2+}$ uptake assays and in vivo by radiotelemetry.

Some TRPV1 antagonists blocked capsaicin but modulated proton and heat activation differentially. For example, some capsaicin antagonists blocked heat activation but potentiated proton activation, whereas others potentiated both proton and heat activation. Radiotelemetry experiments showed that antagonists of capsaicin that potentiate both proton and heat activation cause a marked drop in body temperature (hypothermia). However, compounds like JYL1421, which block capsaicin and potentiate pH 5 activation, did not cause significant changes in body temperature. A variety of other combinations of antagonism or potentiation of these different modes of TRPV1 activation resulted in mild to marked hyperthermia or hypothermia in rats.

Results of these studies indicate that body temperature regulation are a predominant function of TRPV1. Interestingly, it appears that the ability of capsaicin antagonists to potentiate proton activation results in lack effects on body temperature.

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382

ASSESSMENT OF NEUROPATHIC PAIN AND LOCOMOTOR DEFICITS USING THE CATWALK GAIT ANALYSIS

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A large number of neurological disorders, including spinal cord injury, are associated with neuropathic pain and deficits in a wide range of locomotor functions. Although there is a range of test specifically designed to assess neuropathic pain or locomotion, a test which can measure both phenomena is lacking. Obviously, neuropathic pain and locomotor deficits may both affect the gait of the animal. Therefore, the recently developed CatWalk gait analysis could be a test that appreciates both pain behavior and locomotor deficits. In the present study, we tested whether a range of gait parameters, which can be linked with pain behavior, are also altered after spinal cord injury in the adult rat. The pain-related gait parameters were selected from an additional study