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The mineralocorticoid receptor antagonist spironolactone enhances morphine antinociception

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Aims: Spironolactone, an antimineralocorticoid, has been reported to potentiate the cataleptic effect of morphine in the rat. Since no previous research exists on the matter and the interaction might be clinically significant, the effects of spironolactone on morphine antinociception and pharmacokinetics in the rat were investigated.

Methods: Male SD rats were used to assess the effects of spironolactone on acute morphine-induced antinociception, development of morphine tolerance, and established morphine tolerance in the tail-flick and hot plate tests. Spironolactone was also administered with loperamide to assess whether spironolactone enhances the brain distribution of the acknowledged P-glycoprotein substrate across the blood–brain barrier.

Results: Spironolactone had no antinociceptive effects of its own but when co-administrated with morphine the antinociceptive effect of morphine was greatly enhanced. Morphine concentrations in the brain were increased fourfold in the spironolactone co-administrated group. Spironolactone did not inhibit the formation of pro-nociceptive morphine-3-glucuronide, nor did inhibit the development of tolerance. The peripherally restricted opioid, loperamide, had no antinociceptive effects by itself, but co-administration with spironolactone produced a clear change in the hot plate test.

Conclusions: Although mineralocorticoids have been proposed to take part in pain signaling, in our setting spironolactone did not have antinociceptive properties of its own. The increased antinociceptive effect of morphine is apparently caused by the increased morphine brain concentrations. We suggest this to be due to P-glycoprotein inhibition, as indicated by the loperamide assay. The clinical relevance of P-glycoprotein inhibition by spironolactone should be studied.

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Expression of calcium/calmodulin-dependent protein kinase II in dorsal root ganglia in diabetic rats 6 months and 1 year after diabetes induction

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Aim: The aim of this study was to compare expression of total calcium/calmodulin-dependent protein kinase II (tCaMKII) and its α, β, γ and δ isoforms in dorsal root ganglion (DRG) in rat models of diabetes mellitus type I (DM1), 6 months and 1 year after diabetes induction.

Methods: A total of 45 male Sprague-Dawley rats weighing 160–200 g were assigned into four experimental groups: 6-months DM1 and its control group, 1-year and its control group. For the induction of DM1, after overnight fasting animals were injected intraperitonealy with 55 mg/kg of the streptozotocine (STZ). Rats were sacrificed 6 months and 1 year after the diabetes induction. The L4 and L5 ganglions were removed, fixed, embedded in freezing medium and sectioned on a cryostat. Immunofluorescence analysis was performed for detection of tCaMKII and its α, β, γ and δ isoforms. Image J software was used for analysis of immunofluorescence.

Results: The diabetes was successfully induced as confirmed by measurement of glucose levels and weight increase. Analysis of tCaMKII expression in DRGs revealed no differences between DM1 and control animals after 6 and 12 months. In diabetic animals, the expression of α and β isoforms decreased significantly after 6 months, compared to the controls, while decrease of γ and δ was observed after one year of diabetes in diabetic animals.

Conclusions: The observed changes in the expression of CaMKII isoforms reveal plastic changes of this enzyme during the chronic diabetic state and may be involved in the chronic neuropathic pain development.

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Histamine in the locus coeruleus attenuates neuropathic hypersensitivity

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Aims: Among brain structures receiving efferent projections from the histaminergic tuberomammillary nucleus is the pontine locus coeruleus (LC), a structure involved in descending noradrenergic control of pain. Here we studied whether histamine in the LC is involved in descending regulation of neuropathic hypersensitivity.

Methods: Peripheral neuropathy was induced by unilateral spinal nerve ligation (SNL) in the rat with a chronic intracerebral and intrathecal catheter for drug administrations. Mechanical hypersensitivity in the injured limb was assessed by monofilaments. Heat nociception was assessed by determining radiant heat-induced paw flick.

Results: Histamine in the LC (ipsilateral to nerve injury) produced a dose-related (1–10 μg) mechanical antihypersensitivity effect (maximum effect at 15 min and duration of effect 30 min), without influence on heat nociception. Pretreatment of LC with