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EFFICACY OF TAPENTADOL, A NOVEL CENTRALLY ACTING ANALGESIC WITH DUAL MODE OF ACTION, IN ANIMAL MODELS OF CHRONIC NEUROPATHIC PAIN

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Background. Tapentadol [(−)-(1*R*,2*R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol] is a novel analgesic with a dual mode of action: μ-opioid receptor (MOR) agonism ($K_i = 0.1$ μM for rat MOR binding), and noradrenaline (NA) reuptake inhibition ($K_i = 0.5$ μM for rat synaptosomal NA reuptake inhibition). Due to its dual mode of action tapentadol is an interesting candidate for the treatment of neuropathic pain conditions.

Methods. The effects of tapentadol and gabapentin, the current standard in neuropathic pain treatment, were investigated in four rat models of neuropathic pain: vincristine-induced polyneuropathy (VPN), diabetic polyneuropathy (DPN), spinal nerve ligation (SNL), and chronic constriction injury (CCI).

Results. Tapentadol was much more potent than gabapentin, and resulted in numerically higher maximum effect values in each model. The ED50 values of tapantadol/gabapentin, respectively, were 5.1 mg/kg ip/372 mg/kg po (VPN), 8.9 mg/kg ip/225 mg/kg ip (DPN), 8.2 mg/kg ip/92.6 mg/kg ip (SNL), and ~13.0 mg/kg ip/214 mg/kg po (CCI). The maximum effects (expressed as %MPE) of tapentadol/gabapentin, respectively, were 74%/69% (VPN), 100%/80% (DPN), 108%/91% (SNL), and 89%/65% (CCI).

The noradrenergic contribution to the analgesic efficacy was demonstrated in SNL rats, where the analgesic effect of tapentadol (10 mg/kg iv) was antagonized by the α2-adrenoceptor antagonist yohimbine (2.15 mg/kg ip) as well as by the MOR antagonist naloxone (0.3 mg/kg ip).

Daily administration of equianalgesic doses of tapentadol (6.81 mg/kg ip) and gabapentin (215 mg/kg ip) for two weeks did not reveal development of tolerance to the analgesic effect for either compound.

Conclusions. Tapentadol is a novel centrally acting analgesic with both mechanisms of action contributing to its broad efficacy profile in several animal models of neuropathic pain.

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BOTULINUM NEUROTOXINS: NEW FRONTIERS IN NEUROPATHIC PAIN THERAPY?

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Background and aims. A number of studies have underlined a significant use of Botulinum neurotoxins (BoNTs) in the human therapy of several movement and autonomic disorders. Recently, a potential role of BoNTs as new therapeutic agent in pain relief has also been suggested. In particular, it has been demonstrated that serotype-A (BoNT/A) is able to induce analgesia in inflammatory pain conditions. The goal of the present research was to assess if BoNT/A was able to relieve also neuropathic pain symptoms.

Methods. The chronic constrition injury of sciatic nerve (CCI) was used as model of neuropathic pain in CD1 male mice. The onset of neuropathy was assessed by measuring, at different time intervals from postoperative day 3 to day 81, the sensitivity of both hindpaws to non-noxious punctuate mechanical stimuli.

Results. Peripheral administration of BoNT/A strongly reduced the mechanical allodynia associated with the neuropathy and significantly speed up the functional recovery of the injuried paw. Remarkably, a single non-toxic dose of BoNT/A was sufficient to induce anti-allodynic effects, which lasted for at least three weeks. For comparison, we tested also the effect of BoNT/B, and we found that, contrary to BoNT/A, it was unable to counteract the neuropathic pain.

Conclusions. This result is particularly relevant since neuropathic pain is poorly treated by current drug therapies. This communication enlarges our knowledge on potentially new medical uses of BoNT/A in efforts to improve the health human conditions, with very important implications in the development of new pharmacotherapeutic approaches against the neuropathic pain.

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CHRONIC POST-ISCHEMIA PAIN: A NOVEL ANIMAL MODEL SUGGESTS THAT ISCHEMIA–REPERFUSION (I–R) INJURY, NO-REFLOW AND CHRONIC TISSUE ISCHEMIA CONTRIBUTE TO CRPS-I

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Chronic post-ischemia pain (CPIP) is an animal model of CRPS-I produced by prolonged (3 h) I–R