Resiniferatoxin induced alteration of neurotrophic factors in the dorsal root ganglia of allodynic rats
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BACKGROUND CONTEXT: Vanilloid receptor 1 (VR1) is expressed only on C-fiber and A-delta-fiber neurons, mediates various noxious stimuli (capsaicin, heat, protons), and acts as a molecular integrator for nociception. Resiniferatoxin (RTX) is a potent and specific VR1 agonist that selectively eliminates VR1-positive neurons. Our previous study suggested that RTX injection into the dorsal root ganglia (DRG) improves tactile allodynia and suppresses thermal hyperalgesia. Immunohistochemistry examination showed that suppression of tactile allodynia and thermal hyperalgesia was associated with the extent of elimination of VR1 positive neurons. Our current study aims to define the neurotrophic factor changes after VR1-positive neuronal elimination.

PURPOSE: Define the alteration of neurotrophic factors and their possible function following RTX injection into the DRGs in neuropathic rats.

STUDY DESIGN/SETTING: NA

PATIENT SAMPLE: NA

OUTCOME MEASURES: NA

METHODS: Twenty-four rats were subjected to a photochemically induced sciatic nerve injury. The rats that developed tactile allodynia and hyperalgesia were treated by RTX injection in the ipsilateral L3-L6 DRGs. Mechanical allodynia was tested by measuring the paw-withdrawal response to mechanical stimuli (von Frey filaments ranging from 1 to 26 g). If a filament induces 3 paw withdrawals out of 5 stimuli, the value of the filament in grams was considered the withdrawal threshold of the paw. If the withdrawal value was under 8 grams, the rat was classified as allodynic. Thermal hyperalgesia was tested by measuring the paw-withdrawal response to noxious heat stimuli (light beam on the hot plate). If the paw withdrawal latency on the injured side was 30% shorter than intact side, the rat was considered to experience thermal hyperalgesia. These rats were tested for 3 days after RTX injection, after which they were euthanized, and the DRGs were harvested for immunohistochemical analysis for P75, NT3, NGF, and trkA.

RESULTS: Tactile allodynia was totally suppressed by RTX in most rats (n=14) and improved in the rest (n=4). DRG immunohistochemical analysis showed the expected selective ablation of the VR1-positive neurons. The DRGs from allodynic rats showed a decreased expression of P75, while the ones from non-allodynic as well as RTX-treated rats exhibited persistence of P75 expression, mostly in the large cells. Neurotrophin 3 (NT3) expression was paradoxically decreased in the DRGs of non-allodynic and allodynic rats, but completely eliminated in the DRGs of RTX-treated rats. NGF and TrkA showed mixed changes.
CONCLUSIONS: This study demonstrates that VR1-positive neurons mediate both thermal hyperalgesia and tactile allodynia in neuropathic rats. The underlying mechanisms for RTX-induced pain mediation may involve neurotrophic factors, in that P75 appears to have a protective role, while NT3 may have dual effects. These data provide new insights into the potential treatment of neuropathic pain.