

# ***MOLECULAR PHARMACOLOGY OF VANILLOID RECEPTOR-1 IN ANIMAL MODELS IN VIVO AND IN CELLULAR SYSTEMS IN VITRO***

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1. In *in vivo* experiments, we investigated the effect of epidurally administered resiniferatoxin (RTX). Epidural RTX induced dose-dependent, prolonged and regional anesthesia with minimal systemic effects. The analgesic efficacy of epidural RTX exceeded that of the systemic administration. Furthermore, depletion of vanilloid receptor-1 (VR1) sites were detected in the spinal cord. Elimination of VR1 binding corresponded with the regional effect of epidural RTX treatment.
2. *In vitro* experiments were designed to test recombinant VR1-expressing cell systems, and to compare their pharmacological and functional properties with those of the nociceptive sensory neurons. Heterolog VR1-expressing cells showed appropriate similarity to „native” neurons for modelling vanilloid-evoked electrophysiological and morphological changes.
3. VR1 localization was found in the internal membranes in both native neurons and in recombinant VR1-transfected cells.
4. VR1-dependent elevation of intracellular calcium occurred even in the absence of external calcium, indicating the existence of functionally active VR1-pool in the endoplasmic reticulum (ER).
5. VR1-specific neuron depletion can be achieved by the administration of RTX, an ultrapotent agonists of VR1. Selective ablation of VR1-expressing nociceptive neurons may be responsible for the analgesic effect of vanilloid agonists.
6. High-affinity, saturable, specific [<sup>3</sup>H]RTX binding can be detected in various regions of the monkey brain. Pharmacological properties of the centrally located VR displayed appropriate pharmacological similarity to the peripheral VR1 receptor. Tissue distribution of VR located in the brain was found to be similar to that of other species (rat, human).
7. RTX showed 7-fold weaker affinity to VR1 detected in monkey than to the rat VR1. Similar difference was only 3-fold for the favour of human.
8. Species related differences should be concerned to extrapolate data from animals to human.