Opposite interactions between endothelin-1 sensitization and post-incisional pain in the rat hindpaw

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Both injection of the peptide endothelin-1 (ET-1) and incision in the rat paw lead to ETA-R-dependent cutaneous mechanical sensitization. Repeated injections of ET-1 show a long-lasting desensitization (20% of control response occurs to a second injection given 24h after the first injection). In the present experiments we sought to determine if desensitization of the response to ET-1 would also appear as a reduction in the post-incisional hyperalgesia.

This was done by comparing the effect of a preceding injection of ET-1 (400 µM, 4 nmoles) on the pain response to a subsequent incision. Post-incisional sensitivity was determined by the number of times a paw was withdrawn during each episode of 10 punctate mechanical stimuli by a stiff nylon monofilament: (von Frey filaments :VFHs; 15 gm – for testing hyperalgesia).

After control incisions, at the lateral edge of the hindpaw, under sevoflurane anesthesia, the VFH response rose from a pre-operative baseline value of 2.5/10 to 9/10 (on post-operative days 1 -3; POD1-3), then returned to the pre-operative level by POD5. Incisions in paws that had been injected with ET-1 24h previously showed the same peak VFH response, 9/10, but occurring much earlier, at 2h post-operative, yet this heightened response decayed exponentially and much more rapidly, with half decay occurring at POD2, full recovery at POD4. Area-under-the curve for responses measured over the full period of post-operative hyperalgesia (POD 0-7) was reduced by 48% by the pre-operative ET-1 injection.

The reciprocal interaction was examined by assessing responses to ET-1 (100µM, 1 nmole) in naïve and post-incisional (7d) paws. Control responses to ET-1 showed Total hindpaw Flinches during the first 75 min (TF) = 97±12 (n=7) and relatively low Maximum Flinch Frequencies at the highest time of activity (MFF=23±4/5 min). Responses of these naïve paws to stimulation by a 15 g VFH, measured immediately after the spontaneous flinching test period, were minimally elevated, rising from 2.5/10 to 4.3/10, and returning to baseline 1 day later. One week after an incision, however, when post-incisional hyperalgesia had totally recovered, the number of spontaneous flinches after ET-1 rose to 162±37 (n=8), and the maximum flinch frequency rose to 39±10. Responses to VFH after ET-1's injection into incised paws were elevated to 8.5/10 in the first 1-2 h, and recovered to half this level one day later, returning to baseline values in 3 days.

These results show that post-incisional hyperalgesia in the paw is suppressed by a pre-injection of ET-1, but the response to ET-1 is enhanced by a preceding incision. We interpret this difference to reflect the local desensitization of ET-A receptors in the paw after ET-1's pre-incisional injection, versus the central sensitization, in spinal cord and, perhaps, brain that follows incision.