

Plenary lecture:

“Painful peripheral neuropathies due to chemotherapy”

Garry Bennett

Improvements in chemotherapy have increased the cancer patient’s life span, but these drugs produce severe side-effects, including a sensory neuropathy that is often accompanied by a chronic neuropathic pain syndrome. There are no proven treatments to prevent the neuropathy per se or the pain syndrome, and the pain is resistant to standard analgesics. Chemotherapy-evoked painful peripheral neuropathy affects tens of thousands of patients. For some, it compromises or prevents aggressive use of therapy with life-saving anti-tumor activity; for others it contributes to a serious decrease in the quality of life. Chemotherapeutics in the taxane and vinca alkaloid classes are among the most effective drugs for the treatment of solid tumors, but they are also most often associated with a painful peripheral neuropathy. The cause of the pain is not known.

It is now possible to reproduce this painful peripheral neuropathy in rats receiving the taxane drug, paclitaxel (Taxol®), or the vica alkaloid, vincristine. The animals have long-lasting mechano-hyperalgesia, mechano-allodynia, and cold-allodynia, but little or no heat-hyperalgesia. The hyperalgesia and allodynia are relatively resistant to opioids, and NMDA receptor blockers are without effect (in contrast to their invariable efficacy in models of post-traumatic painful peripheral neuropathy). Ethosuximide and gabapentin, drugs that bind to calcium channels, are effective.

Quantitative time-course electron-microscopy shows that there is no degeneration of A- or C-fibers in the sural nerve; thus arguing against the generally accepted hypothesis that this is a dying-back neuropathy like that seen in diabetics. Moreover, examination of axonal microtubules reveals no more than trivial abnormality, suggesting that there is no disruption of axoplasmic transport. However, sensory afferent axons are found to contain a significant number of mitochondria that are swollen, vacuolated, and have disrupted cristae. Studies using anti-oxidant therapies and intrathecally administered calcium chelators confirm their analgesic efficacy, and this is consistent with the presence of increased free radicals and dysregulation of calcium homeostasis due to mitochondrial dysfunction. Electrophysiological studies show an abnormal spontaneous discharge in primary afferent A-delta and C-fibers, but not in A-beta fibers.

We propose the hypothesis that chemotherapy-evoked painful peripheral neuropathy is secondary to a drug-evoked effect on axonal mitochondria.

Symposium: Lessons from the laboratory:

“Complex Regional Pain Syndrome Type I (RSD): Pain due to trauma-evoked microvascular disease?”

Garry Bennett

We have developed an animal model (chronic post-ischemia pain; CPIP) that creates a CRPS-I –like syndrome by occluding the blood flow to one hind paw for 3 hr under general anesthesia. Following reperfusion, the treated hind paw exhibits an initial phase of hyperemia and edema, followed by mechano-hyperalgesia, mechano-allodynia, and cold-allodynia that last for at least one month; heat-hyperalgesia appears to be absent. Light-microscopic analysis of the tibial nerve from beneath the tourniquet shows that nearly all of these animals have no sign of a direct nerve injury. We have electron microscopic data that shows that the ischemia-reperfusion (I-R) injury produces a microvascular pathology, the slow flow/no-reflow phenomenon, in the distal digital muscles and digital nerves. Slow flow/no-reflow, an extensively studied sequela of cardiac infarction, is an I-R injury to the microvascular epithelia. The result is impaired nutritive blood flow and ischemia that produces a subacute inflammatory process that includes the generation of free radicals and pro-inflammatory cytokines. We hypothesize that in at least a subset of CRPS-I patients the condition is initiated similarly by an I-R injury and inflammatory response to deep tissue trauma. Subsequently, the slow flow/no-reflow phenomenon aggravates and maintains deep tissue ischemia and inflammation, leading to the activation and sensitization of muscle nociceptors, and the ectopic activation of afferent axons due to endoneurial ischemia and inflammation.