Opiate hyperalgesia: peripheral neurons are all excited to see glutamate

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Introduction

Repeated administration of opiates leads to a state of paradoxical pain named opiate hyperalgesia (OHI), which is unrelated to opiate tolerance or withdrawal. OHI exacerbates preexisting pain and makes post-operative pain difficult to treat. In the CNS, the activity of nociceptive neurons is enhanced and glutamate transporters are down-regulated. Little is known regarding the contribution of the peripheral nervous system to OHI.

Methods

Rats received 7 days of morphine (10 to 40 mg/kg BID). On day 8th, the dorsal root ganglia (DRG) were removed and bathed in artificial CSF (aCSF). Small DRG neurons were visualized with a microscope equipped with infrared DIC. Whole cell patch clamp recording was obtained. Verification was made that opiate withdrawal was not involved by adding morphine (5 uM) in the perfused aCSF.

Results

In morphine treated rats, the small DRG neurons demonstrated significant increase in excitability, shown by a dramatic decreased in rheobase (203.7 ± 13.6 pA vs. 267.7± 29.8pA in controls, $p < 0.05$, $n = 30$) and membrane threshold (-20.3 ± 1.1 mV vs. -13.3 ± 1.7 mV in controls, $p < 0.001$, $n = 25$).

Increased response to glutamate was also found in small neurons, which displayed an inward current of 781.0 ± 197.0 pA, compared to controls (229.1±49.2 pA, $p<0.001$. Agonists for each receptor subtype were examined. No difference was discerned for AMPA, or DHPG (group I mGluR agonist) induced currents between morphine treated and controls. Interestingly, NMDA decreased inward currents in the morphine group (33.4±7.9 pA vs. 554.0±174.1 pA in controls, $n=12$, $p<0.01$).

Conclusions

OHI involves glutamatergic transmission in both the peripheral and central nervous system. This forces us to re-evaluate the role opiate therapy in chronic pain.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the importance of opiate hyperalgesia, 2) Discuss the molecular mechanisms involved in the generation of opiate hyperalgesia.

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References

Tompkins DA and CM Campbell. Curr Pain Headaches Rep, 15:129-136 (2011).