

Targeting ion channel trafficking mechanisms for novel analgesics



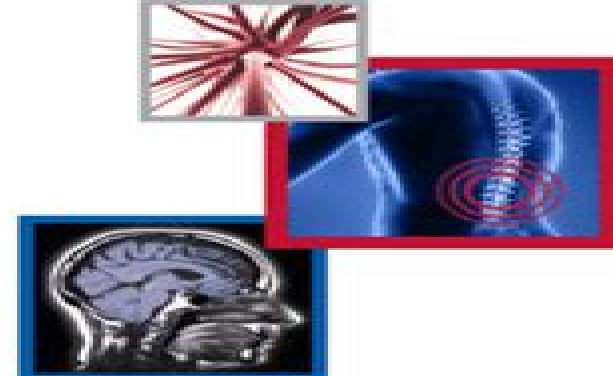
Arin Bhattacharjee*

In February of this year, the *New York Times* reported on the increasing number of brazen robberies occurring at pharmacies throughout the USA. One thief in Rockland (ME, USA) brandished a machete and leapt over the pharmacy counter to grab oxycodone. He gulped down some of it even before he fled. In Florida, thousands of doses of oxycodone pills are dispensed in pain clinics, resulting in some calling the highway that leads into Florida, I-75, the 'Oxy Express'. In 2008, Ohio pharmacists dispensed 4.8 million prescriptions for hydrocodone medications, one for every 2.5 people in the state [10]. Although we have been treating pain effectively for millennia, the need for efficacious, safe but especially nonaddictive analgesics remains strong. We require analgesics that can specifically act on peripheral pain-sensing neurons and not centrally to avert addiction. In this article, I argue that the future of pain research must include the development of compounds that directly target the ion channel trafficking machinery of nociceptors.

Analgesics act by reducing the firing properties of neurons within the pain pathway. For treatment of mild pain, non-steroidal anti-inflammatory drugs (NSAIDs)

"Perhaps the Drug Enforcement Agency, with its billion-dollar budget, could devote a portion of its resources to fund research whose sole purpose is to develop nonaddictive analgesics. It may be as cost effective as trying to protect pharmacies from bandits gallivanting down the Oxy Express."

are recommended. These agents reduce algogenic substances, such as prostaglandins, which directly affect the firing properties of nociceptive neurons. NSAID use is widespread; however, gastrointestinal and renal toxicities associated with these agents are prevalent, with an estimated 10–20% of NSAID patients experiencing dyspepsia [11]. The development of cyclooxygenase-2 selective inhibitors, which minimize gastrointestinal effects, seemed promising, but their severe cardiovascular toxicities have dramatically restricted their use. Vioxx®, the most famous of the cyclooxygenase-2 inhibitor drug class, had to be removed from the market owing to its toxic effects. For moderate-to-severe pain, moderate opioid agonists, such as hydrocodone, strong opioid agonists, such as oxycodone, or even morphine are used. These agents act on opioid receptors in the CNS, especially on descending pathways originating from the periaqueductal gray matter, to block pain transmission in the dorsal horn of the spinal cord. They can also act presynaptically by inhibiting neurotransmitter release from the central terminations of nociceptors in the spinal cord. Opioids do so via μ -receptors, ultimately affecting potassium and calcium conductances. As



"If we can elucidate the molecular underpinnings of nociceptor hyperexcitability, it will lead to better and safer analgesics. Unfortunately, within the USA, the NIH devotes only a fraction of a percentage of its total budget to pain research and ... it is unclear where the impetus will come for the development of novel channel targeted drugs."

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