Opioid Tolerance

Subjects: Others

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Opioids are potent analgesics widely used to control acute and chronic pain, but long-term use induces tolerance that reduces their effectiveness. The US Food and Drug Administration (FDA) define opioid tolerance as follows (https://www.fda.gov);
Patients are considered opioid tolerant if they are taking, for 1 week or longer, at least:
- Oral morphine–60 mg daily
- Transdermal fentanyl–25 mcg/h
- Oral oxycodone–30 mg daily
- Oral hydromorphone–8mgdaily
- Oral oxymorphone–25mgdaily
- Equianalgesic daily dose of another opioid

: opioid misuse | opioid tolerance | opioid-induced hyperalgesia | mu opioid receptor | ER stress | unfolded protein response (UPR) | pharmacological chaperone

1. Introduction

Opioids such as fentanyl and morphine are widely used as excellent analgesics for both acute pain (e.g., during surgery) and chronic pain (e.g., in cancer patients) [1][2]. However, the increases in addiction and overdose death due to opioid misuse arising from prescriptions made by medical institutions, especially in the United States where opioid analgesics have been heavily used in recent years, have become serious social problems. US government agencies have declared the Opioid Crisis as a national emergency [3][4]. Chronic use of opioids induces tolerance that reduces analgesic effects, and opioid-induced hyperalgesia increases painful sensation throughout the entire body [5], resulting in increased opioid doses, more addiction, and even shorter life span [6][7]. About 16,000 deaths, or 36% of the 44,000 drug overdose deaths in the United States in 2013, were associated with prescribed opioids (2013 National Survey on Drug Use and Health). Approximately 9.9 million people aged 12 or older in 2018 misused prescription pain relievers, corresponding to 3.6% of the US population (2018 National Survey on Drug Use and Health).

Opioid tolerance develops due to multifaceted mechanisms such as altered intracellular signal transductions in sensory neurons, inflammation of neurons and glial cells, and reconstitution of neural circuits [8]. Opioids act via mu opioid receptors (MORs) expressed on the plasma membrane of primary sensory neurons, as well as various neurons in the cerebrum, brainstem, and dorsal horn of the spinal cord; opioid binding to MORs suppresses

ascending nociceptive transmission and enhances descending pain inhibitory pathways, resulting in analgesia. MORs activate various signaling molecules through heterotrimeric guanine nucleotide-binding proteins (G proteins) [9], leading to an analgesic effect. MOR activation also induces G-protein-coupled receptor kinases to phosphorylate MORs [10][11], which can then be recognized by β-arrestins and internalized by clathrin-coated vesicles [12]. Transient uncoupling of MORs from signaling pathways due to their phosphorylation and subsequent intracellular trafficking causes opioid desensitization. β-arrestin-2 deletion enhances morphine analgesia and prevents the development of tolerance, but not dependence [12][13]. Most internalized MORs eventually return to the cell surface, resulting in re-sensitization [14][15][16]. Chronic morphine tolerance may accompany adaptations of the intracellular signal transduction of post-MOR activation, including increased activity of protein kinase A [17] and protein kinase C [18], and up-regulation of N-methyl-D-aspartate receptor signaling [19][20][21][22]. Chronic morphine treatment also activates the glycogen synthase kinase 3β (GSK3β) and Src kinase pathways, while inhibition of these kinases has been shown to diminish morphine tolerance and restore analgesia [23][24][25].

2. Data, Model, Applications and Influences

Dobashi et al. previously reported that signaling from the endoplasmic reticulum (ER) contributed to the development of morphine tolerance [24]. Accumulation of misfolded proteins in the ER induced the unfolded protein response (UPR) that causes diverse pathological conditions. Persistent overload of misfolded proteins causes a diverse array of disorders due to impaired functional protein synthesis and cell death [26][27], including neurodegenerative disease [28], dilated cardiomyopathy [29], and renal disease [30]. Another distinct mechanism by which ER stress causes human disease is that the UPR alters signaling pathways required for important cellular functions [31]. Obesity causes ER stress that induces the UPR, which may attenuate insulin receptor signaling through hyperactivation of c-Jun N-terminal kinase and serine phosphorylation of insulin receptor substrate-1. Crosstalk between the UPR and insulin receptor signaling has been shown to cause insulin resistance in type II diabetes [32]. Chronic morphine administration may alter signal transduction due to persistent MOR activation [33]. In addition, MOR signaling may induce the UPR via calcium (Ca^{2+}) kinetics, and the ER is the main store of Ca^{2+}. MOR activation induces the ER to release Ca^{2+} into the cytoplasm [34]. ER chaperones including BiP are Ca^{2+}-binding proteins, and the release of Ca^{2+} may disturb protein folding and induce the UPR. It has been shown that ER stress activates Src kinase [35] and GSK3β [36][37]. MOR-signaling also induces the activation of these kinases, which has been associated with tolerance formation [23][24][25]. GSK3β plays important roles in a variety of human disorders, including inflammation, Alzheimer's disease, mood disorders, diabetes, and cancer [38]. Thus, a mechanism similar to that occurring in type II diabetes might underlie the crosstalk between the UPR and analgesic signal transduction through MORs.

Okuyama et al. examined the effects of pharmacological chaperones on opioid tolerance development by assessing thermal nociception in mice [39]. The pharmacological chaperones, such as 4-phenyl butyric acid (PBA) and tauroursodeoxycholic acid (TUDCA) facilitate protein folding in the ER, and function as proteostasis regulators [40]. Pharmacological chaperones suppressed the development of morphine tolerance and restored analgesia. Chaperones alone did not cause analgesia. Those results suggest that ER stress may facilitate morphine tolerance

due to intracellular crosstalk between the UPR and MOR signaling. Pharmacological chaperones may be useful in the management of opioid misuse.

Opioids such as oxycodone and fentanyl have been prescribed for chronic pain, but the efficacy of long-term therapy has not been demonstrated [41][42][43]. High doses of opioid preparations for chronic pain can cause unfavorable side effects such as tolerance, hyperalgesia, addiction, and even death [44][45][46]. Buprenorphine, methadone, and naltrexone are currently used to reduce opioid use [46][47]. Buprenorphine and methadone are less preferred options because they themselves are opioids. Pharmacological chaperones such as PBA and TUDCA ameliorate opioid tolerance and maintain morphine's analgesia. Moreover, the analgesic effect of opioids could be recovered by pharmacological ER chaperone administration even after tolerance had been induced [39]. Both PBA and TUDCA have few clinical side effects and may be effective treatments for opioid misuse through the reduction of opioid usage. Pharmacological chaperones may represent a promising therapeutic option for maintaining opioid analgesia without increasing prescriptions.

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