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Development of Opioid Tolerance and Endoplasmic Reticulum Stress

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Abstract

Opioids are potent analgesics, widely used to control acute and chronic pain. While repeated administration of opioids, particularly morphine, induces tolerance that reduces the effectiveness of the analgesic, the precise molecular mechanism for the development of tolerance remains uncertain. Opioids bind to the μ opioid receptor (MOR) to activate various signaling molecules, leading to a decrease in neuronal excitability. Chronic morphine tolerance may be derived from adaptations in the intracellular signal transduction of post-MOR activation.

Many physiological and pathological conditions, such as secretory demands, ischemia, hypoxia, and genetic mutations, can cause aberrant protein folding and the accumulation of misfolded proteins in the endoplasmic reticulum (ER). These insults lead to ER stress and initiate the unfolded protein response (UPR). Recent studies have suggested that chronic ER stress might modulate intracellular signaling pathways, resulting in several chronic disorders, such as type II diabetes. Binding immunoglobulin protein (BiP) is an ER chaperone that is central to ER functioning. Recently, our studies in mice suggest that BiP may play an important role in the development of morphine tolerance. We also found that a chemical chaperone, which improves ER protein folding capacity, attenuated the development of morphine tolerance. Thus, the modulation of ER functions by chemical chaperones and other drugs may lead to a new direction for the prevention of morphine tolerance.

Keywords: Analgesics; Endoplasmic reticulum (ER); Immunoglobulin; Voltage; Phosphorylation

Introduction

Opioids like morphine have been widely used clinicaly as effective analgesics for acute and chronic pain. When opioids are used, the importance of care for side effects such as nausea, drowsiness and constipation is emphasized. In addition, continuous use of opioids developes tolerance in which the analgesic effect becomes attenuated. In this paper, we mainly discuss endoplasmic reticulum (ER) stress as one of the molecular mechanisms for the development of opioid tolerance.

ER stress response

The ER provides a folding environment for newly synthesized secretory and membrane proteins [1]. Secretory proteins are synthesized by ribosomes and translocated cotranslationally or posttranslationally to the ER. These newly synthesized proteins interact with ER molecular chaperones, such as immunoglobulin heavy chain-binding protein (BiP), calnexin, calreticulin and protein disulfide isomerase, to become properly folded and assembled into a mature protein complex for transport along the secretory pathway. Aberrant protein folding, due to extracellular stimuli such as ischemia and oxidative stress, or genetic mutations leads to the accumulation of misfolded proteins in the ER, which in turn evokes the unfolded protein response (UPR) [2]. The UPR reduces the amount of misfolded proteins [3] by inducing the production of ER chaperones that promote protein folding, reducing general protein synthesis, and enhancing the degradation of misfolded proteins via a ubiquitin-proteasome system, termed ER-associated degradation (ERAD) [4].

A further overload of misfolded proteins initiates apoptosis, leading to diverse human disorders [5,6]. such as neurodegenerative diseases [7-9] and cardiomyopathies [10]. Another distinct mechanism for human disorders caused by ER stress is the alteration of signal transduction pathways during the UPR. Obesity causes ER stress that induces UPR, which may disturb insulin receptor signaling through hyperactivation of c-Jun N-terminal kinase (JNK) and subsequent serine phosphorylation of insulin receptor substrate-1 (IRS-1), resulting in type II diabetes (Figure 1).

Recent studies suggest that ER stress is involved in pain disorders such as diabetic peripheral neuropathy [11] and orofacial inflammatory pain [12]. Our previous studies in mice suggest that an ER chaperone, BiP, may play an important role in the development of morphine tolerance. We also found that a chemical chaperone, which improves ER protein folding capacity, attenuated the development of morphine tolerance [13].

Analgesic mechanism and tolerance formation of opioid

Morphine is the main component of opium alkaloids from opium poppy. While morphine had been thought to exert an analgesic effect by acting on nerve system, it became clear that there are opioid receptors in the brain [14-16]. Subsequently, δ-opioid receptor gene was first identified [17,18], followed by μ, κ and ORL1 (opioid receptor-like 1) opioid receptor genes. Since analgesic effects of morphine were lost in mice deleted with μ opioid receptor (MOR) gene, MOR was confirmed to be responsible for morphine analgesic signaling [19].

Opioid receptors are cell surface receptors with seven transmembrane, belonging to the heterotrimeric guanine nucleotide-binding protein (G protein)-coupled receptor superfamily. The homology of amino acid sequences of transmembrane region among μ, δ, and κ receptors has been maintained, whereas the carboxyl terminal of intracellular domain and the amino terminal of extracellular domain are very different. The main endogenous ligand for MOR is β-endorphin that binds to MOR to activate various signaling molecules through Gα subunit of inhibitory Gi proteins, leading to a decrease in neuronal excitability by the inhibition of voltage-dependent calcium

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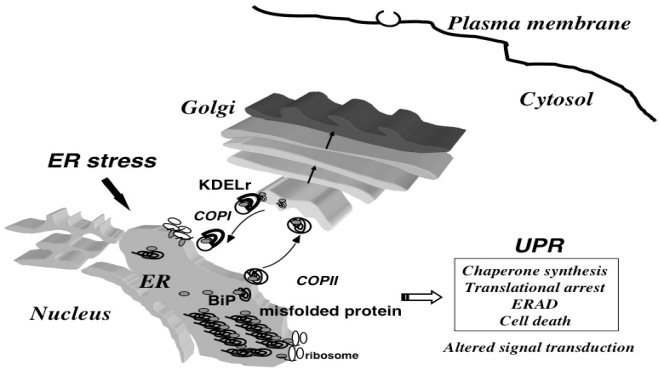

Figure 1: Many physiological and pathological conditions can cause aberrant protein folding and the accumulation of misfolded proteins in the ER. These insults lead to ER stress and initiate the UPR.

channels and the activation of inwardly rectifying potassium channels [20]. Activation of MOR also induces the phosphorylation of MOR by G-protein-coupled receptor kinases [21,22]. Phosphorylated MOR is recognized by arrestins [23], and internalized by clathrin-coated vesicles. The transient uncoupling of MOR from signaling pathways due to the phosphorylation and intracellular trafficking of MOR causes opioid desensitization. Most of the internalized MORs return to the cell surface, resulting in resensitization [24-26] (Figure 2).

Signal transduction upon MOR activation

Chronic morphine tolerance may be derived from adaptations in the intracellular signal transduction of post-MOR activation, as morphine does not induce effective MOR phosphorylation and internalization [27]. Persistent MOR activation on the cell surface may alter signal transduction, including changes in MOR-coupled G proteins from Giα to Gsα [28], increased activity of protein kinase C [29], and the upregulation of N-methyl-D-aspartate receptor signaling [30]. These changes may contribute to the development of morphine tolerance. Chronic morphine treatment also activates the cyclin-dependent kinase 5 and glycogen synthase kinase 3β (GSK3β) signaling pathway, while the inhibition of them diminishes morphine tolerance and restores analgesia in rats [31] (Figure 2b).

GSK3β is expressed ubiquitously and is one of the central molecules in intracellular signal transduction [32]. It may play an important role in diverse physiological and pathological states [33]. We focused on GSK3β as a key signaling molecule in the MOR signaling pathway. GSK3β is a serine/threonine kinase. The kinase activity is inactivated by the phosphorylation of Ser9 and enhanced by the dephosphorylation of Ser9 and the phosphorylation of Tyr216. The p90 ribosomal S6 kinase [34], Akt [35], protein kinase C [36] and protein kinase A [37] have been demonstrated to phosphorylate GSK3β at Ser9. MOR activation also phosphorylates GSK3β at Ser9 through the PI3K/Akt pathway [32]. On the other hand, the regulatory mechanism for the activation of GSK3β remains uncertain in comparison to that for its inactivation. ZAK1 [38], Fyn tyrosine kinases [39] and transient increases in intracellular Ca^{2+} [40] have been reported to phosphorylate GSK3β at Tyr216 to activate the kinase. In addition, ER stress has been also reported to induce the activation of GSK3β [41,42].

Possible crosstalk between mor analgesic signal transduction and the UPR

Chronic morphine administration may cause altered signal transduction through persistent MOR activation on the cell surface. A mechanism similar to that occurring in type II diabetes would be possible in the crosstalk between MOR analgesic signal transduction and the UPR. We speculate that the UPR signaling might attenuate the MOR signaling, thus causing the development of morphine tolerance.

BiP, (or GRP78) is an ER chaperone that is central to ER functioning. Our studies in mice suggest that BiP may play an important role in the development of morphine tolerance, possibly through the modulation of GSK3β signaling. We have previously produced knock-in mice expressing a mutant BiP in order to elucidate the physiological processes that are sensitive to BiP function in adulthood [43]. The mutant BiP protein lacks the retrieval carboxyl-terminal KDEL sequence [44,45] that normally functions to return BiP to the ER from the secretory pathway by the KDEL receptor in the Golgi complex. This mutant allows us to examine the effects of a defect in ER function without completely eliminating BiP function.

The kinase activity of GSK3β is regulated by its phosphorylation status. Phosphorylation of residue Ser9 inactivates the activity, whereas dephosphorylation of Ser9 and phosphorylation of Tyr216 enhance the activity [32]. We evaluated the phosphorylation status of GSK3β in the brain stems of wild-type and heterozygous mutant BiP mice using specific antibodies against phosphorylated Tyr216 GSK3β and phosphorylated Ser9 GSK3β [13]. After chronic morphine injection intraperitoneally for 5 days, the wild-type mice developed morphine tolerance, whereas the mutant BiP mice remained less tolerant to morphine. Because we injected morphine intraperitoneally, both spinal and supraspinal neurons were supposed to be affected. Neurons with MOR expression in the periaqueductal gray (PAG) matter contribute to morphine tolerance [46-48]. With repeated morphine treatment, the mutant BiP brain stems showed low levels of phosphorylation of Tyr216 in GSK3β, in contrast to the prominent phosphorylation in wild-type mice by western blotting. These brains were also sectioned and double-immunostained with antibodies raised against MOR and tyrosine-phosphorylated GSK3β. MOR-immunopositive neurons in the PAG region of wild-type brains showed more enhanced expression of tyrosine-phosphorylated GSK3β significantly than those in the mutant BiP brains.

These observations suggest that chronic MOR stimulation by repetitive morphine injection may activate GSK3β and that the

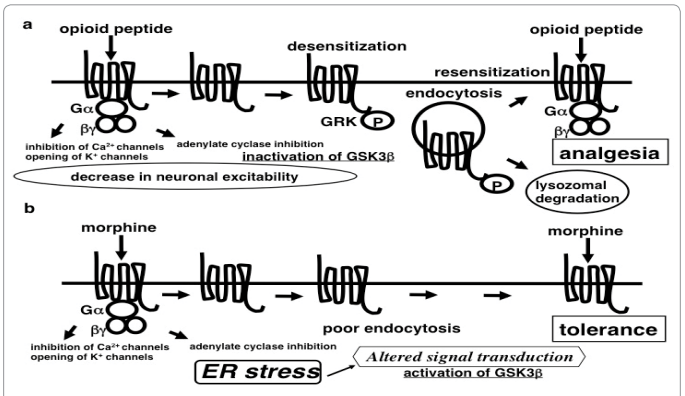

Figure 2: a. Opioids bind to the μ opioid receptor (MOR) to activate various signaling moleculedecrease in neuronal excitability. Activation of MOR also induces the phosphorylation and internalization of MOR. The transient uncoupling of MOR from signaling pathways causes opioid desensitization. Most of the internalized MORs return to the cell surface, resulting in resensitization. b. Chronic morphine tolerance may be derived from adaptations in the intracellular signal transduction of post-MOR activation, as morphine does not induce effective MOR phosphorylation and internalization. Persistent MOR activation on the cell surface may cause ER stress and alter signal transduction.

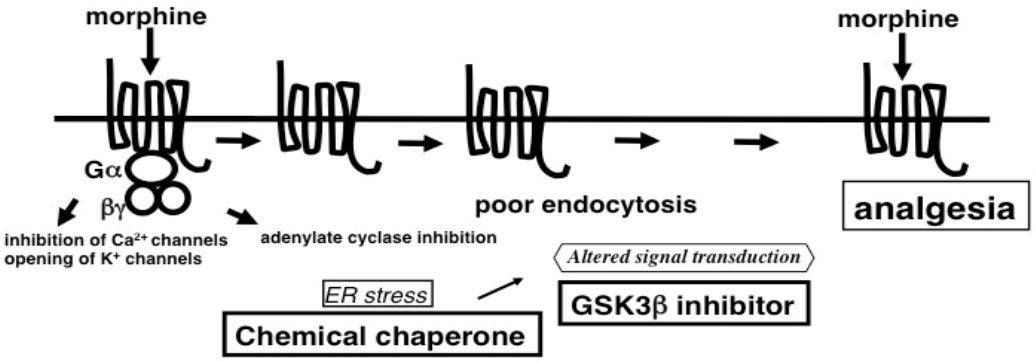

Figure 3: Chronic MOR stimulation by repetitive morphine injection may activate GSK3β. The regulatory mechanism between BiP and GSK3β may possibly contribute to the development of morphine tolerance. Chemical chaperones that support ER functions may reduce the development of tolerance.

activation of GSK3β may be related to the development of morphine tolerance. Mice with the mutant BiP may be defective in the activation of GSK3β and show less less tolerant to morphine. In fact, we showed that co-administration of morphine and a GSK3β inhibitor in wild type mice did not develope the tolerance [13] (Figure 3).

Chemical chaperone attenuates the development of Morphine tolerance

In order to confirm that an ER chaperone like BiP may mediate the development of morphine tolerance, we examined the effect of a chemical chaperone on morphine tolerance [13]. Tauroursodeoxycholic acid (TUDCA) is a derivative of endogenous bile acids that is thought to increase ER folding capacity and suppresses the expression of BiP [49,50]. We administered TUDCA together with morphine twice a day for 5 days in wild-type mice, and hot plate tests were performed at the first and the tenth treatments. The response latencies of the mice receiving both TUDCA and morphine were significantly longer than those of control mice with morphine alone after the tenth treatment. Thus, TUDCA prevented the development of morphine tolerance, suggesting a mechanistic relationship between an ER chaperone and morphine tolerance. The modulation of morphine analgesia by TUDCA reveals a potential clinical application of chemical chaperones that can modulate ER functions for the prevention of morphine tolerance.

Conclusion

Studies above suggest that morphine tolerance may be related to ER stress. Thus, the modulation of ER functions by chemical chaperones and other drugs may lead to a new direction for the prevention of morphine tolerance.

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