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Original Article

# Coadministration of glycogen-synthase kinase 3 inhibitor with morphine attenuates chronic morphine-induced analgesic tolerance and withdrawal syndrome

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## Abstract

*Background*: Glycogen-synthase kinase 3 (GSK3) is involved in many signaling pathways and is associated with a host of high-profile pathophysiological states. However, its role in morphine tolerance, especially naloxone-precipitated withdrawal syndrome, has not been well investigated. The present study was undertaken to study the role of GSK3 in chronic morphine exposure.
*Methods*: Adult male Sprague–Dawley rats were subjected to intraperitoneal (i.p.) injections of morphine (10 mg/kg) twice daily for 6 consecutive days, and tail-flick tests were conducted to evaluate changes of morphine-induced antinociception. GSK3 inhibitor, SB216763 or SB415286, was i.p. injected prior to morphine to investigate the influences on morphine tolerance. There were four groups receiving morphine plus vehicle (2% dimethyl sulfoxide), morphine plus SB216763 (0.6 mg/kg) or SB415286 (1.0 mg/kg), GSK3 inhibitor alone, or dimethyl sulfoxide: as the control group. On Day 7, naloxone (i.p., 1 mg/kg) was administered and naloxone-precipitated withdrawal behaviors were individually compared between groups.
*Results*: Repeated morphine exposure in this study led to progressive shortening of tail-flick latencies and produced six of nine observed naloxone-precipitated withdrawal behaviors. Coadministration with SB216763 or SB415286 significantly prevented antinociceptive tolerance and alleviated parts of withdrawal syndrome. Both inhibitors could similarly reverse withdrawal behaviors including grooming, chewing, and ptosis, but did not affect withdrawal behaviors of penis licking and defecation.
*Conclusion*: The results demonstrate the importance of GSK3 in reducing chronic morphine-induced tolerance and withdrawal syndrome. Although GSK3 is involved in diverse physiological functions, aiming at GSK3-related pathway could still be a potential tool to improve therapeutic quality in clinical morphine treatment.
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*Keywords:* glycogen synthase kinase; morphine tolerance; naloxone; withdrawal

## 1. Introduction

Morphine is widely used in relieving pain in medical care such as cancer pain, chronic pancreatitis, neuropathic pain, and somatic pain in aged patients who are contraindicated to

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invasive treatments. However, chronic morphine exposure is often accompanied with the development of analgesic tolerance and risk of withdrawal symptoms, which force patients to escalate the doses to achieve an adequate analgesic effect and be very cautious of abrupt cessation of morphine use. Also, chronic morphine users easily become dependent on drugs and are susceptible to addiction. All the above conditions ultimately diminish the clinical usefulness of morphine and lead to socioeconomical problems.[1−3]

A growing list of molecules, such as excitatory amino acid receptors,[4−7] adenyl cyclase/cAMP/PKA pathway,[8,9] MAPK/ERK,[10] protein kinase C translocation and activation, and nitric oxide release,[11,12] have been recognized as the targets altered by repeated opiate administrations, and are advocated to be involved in morphine tolerance. Meanwhile, new evidence has revealed that phosphatidylinositol 3-kinase/Akt cascade may also participate in regulating opiate-induced responses via phosphorylating the downstream effector, glycogen synthase kinase-3 β (GSK3β), particularly after chronic administration of morphine. Supporting data indicate that acute application of opioid agonists stimulated μ-opioid receptor and subsequently enhanced Akt activity *in vitro*[13,14] and *in vivo*[15]; however, repeated morphine treatments significantly depressed the Akt phosphorylation level.[15] In addition, coinjections of GSK3 inhibitors, such as lithium salt,[16,17] BIO, or SB216763,[18] with morphine were found to attenuate the chronic morphine-induced tail-flick tolerance in rodents in responses to thermal stimulation. Parkitna et al[18] further claimed that reversal efficacy was always associated with an increase in abundance of GSK3β phosphorylation.

GSK3 is a cellular Ser/Thr kinase originally found to be involved in glucose synthesis, and was soon recognized as an important intracellular signaling involved in regulating cell cycle, development, oncogenesis, and neuroprotection.[19] Lithium, a nonselective GSK3 inhibitor has long been used in bipolar disease, and recently, diverse types of GSK3 inhibitors have been proposed as potential therapeutic agents for diseases such as diabetes, Alzheimer's disease, and colon cancer[20] in preclinical studies. Although the significance of GSK3 in modulating morphine function has been stated,[17,18,21,22] the only tested effect on tolerance was given via intrathecal route, but no data regarding withdrawal syndrome are available. We designed this study using systemic administration of morphine with different GSK3 inhibitors to investigate the effects on nociceptive thresholds and naloxone-precipitated withdrawal behaviors following chronic morphine exposure. The study's purposes were to explore the role of GSK3 signaling pathway in ameliorating chronic morphine-induced complications and serve as a preclinical study for potential clinical application.

## 2. Methods

### *2.1. Animal preparations*

The study was performed on male Sprague−Dawley rats (weighing 200−250 g). Rats were housed in groups of three in an environment of 23 ± 0.5°C with a 12-hour dark/light cycle. Food and water were available *ad libitum*. All experimental procedures were conducted in accordance with guidelines approved by the Guidelines for the Care and Use of Experimental Animals of Shin-Kong Memorial Hospital (Taipei, Taiwan), which was based on the Codes for Experimental Use of Animals from the Council of Agriculture, Taiwan.

### *2.2. Drug injections*

There were two types of GSK3 inhibitors, SB216763 and SB415286 (Tocris Cookson Ltd., Bristol, Avon, UK), used in this study. They were initially dissolved in dimethyl sulfoxide (DMSO) and were then diluted to adequate concentrations for injection with a final DMSO concentration of 2%. Therefore, 2% DMSO solution was used as a vehicle in the control group. The selected doses of SB216763 and SB415286 had been reported in previous heart reperfusion studies for providing a cardioprotective effect.[22−25] Animals were randomly divided into four groups (at least 7 rats in each group) as follows: (1) morphine plus vehicle group (Mor-Veh): morphine was intraperitoneally (i.p.) injected at a dose of 10 mg/kg 30 minutes after vehicle administrations (2% DMSO at a volume of 1 mL/kg, i.p.) twice/day (at 09:00 and 17:00) for 6 successive days; (2) morphine plus GSK3 inhibitor (Mor-S2 or Mor-S4) group: SB216763 (i.p., 0.6 mg/kg) or SB415286 (i.p., 1 mg/kg) prior to morphine injections at the same time course in the Mor-Veh group; (3) DMSO (Veh) group: animals were subjected to i.p. DMSO as the naïve control; and (4) SB (S2 or S4) group: rats received SB216763 or SB415286 alone as the sham control. Drugs in Veh and SB control groups were given according to the abovementioned protocol for 6 days. All four groups received an injection of morphine (i.p., 10 mg/kg) on the morning of Day 7. To investigate morphine abstention-induced withdrawal syndrome, subcutaneous naloxone (1 mg/kg) was injected in the Mor-Veh, Mor-S2, and Mor-S4 groups 2 hours after the last morphine injections on the Day 7 of the experiment.

### *2.3. Nociceptive threshold tests*

Tail-flick response to an external heat nociception was used to evaluate the analgesic effect of morphine. The test latency was defined as the duration of a withdrawal reaction to a radiant heat projection from an algesic machine (Tail Flick Analgesia Meter MK-303B, Muromachi Kikai, Tokyo, Japan). The heat intensity of the light bulb was set to result in basal latencies within 6−8 seconds, and the cutoff time was set at 15 seconds. The tail flick responses to different treatments were examined 30 minutes after drug injections on Day 1, Day 2, Day 3, Day 5, and Day 7. Baseline withdrawal threshold, i.e., "basal latency", was determined 2 days prior to the experiment. At each time-point, three tail flick tests separated by at least 2-minute intervals were measured and averaged as the "test latency". The percentage of maximal possible antinociceptive effect (MPE) representing the analgesic result is defined by the equation: $\text{MPE\%} = [(\text{test latency} - \text{basal latency})/(\text{cutoff time} - \text{basal latency})] \times 100$.

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