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Suvorexant Attenuates Morphine Tolerance in Mice Through Modulation of DRD2 Gene Expression in The Brain

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ABSTRACT

Background & Objective: The emergence of tolerance to morphine presents an obstacle to its therapeutic use. Suvorexant (SUV) has demonstrated efficacy in mitigating the addictive properties of drugs. Nevertheless, the exact pathways through which SUV exerts its influence remain poorly elucidated. This study investigated whether SUV influences the development of morphine tolerance and examined its impact on DRD2 and NR1 gene expression in the mouse brain.

Materials & Methods: The study involved 28 male mice, which were randomly allocated into four groups. Morphine tolerance was induced through repeated morphine injections. Clonidine (0.1 mg/kg), SUV (90 mg/kg), and normal saline were administered (*ip*) 30 minutes before morphine injection. Tail-flick and open field tests were performed on day 4. Quantitative assessment of DRD2 and NR1 gene expression was performed using RT-PCR.

Results: Repeated morphine injections led to a notable decrease ($P < 0.001$) in reaction time. Both SUV ($P<0.05$) and clonidine ($P<0.001$) indicated a significant reduction in the progression of morphine tolerance. SUV significantly reduced the elevated relative expression of the DRD2 gene (fold change = 1.628 ± 0.8659, $P < 0.05$) but did not alter the expression of the NR1 gene ($P > 0.05$).

Conclusion: This finding indicated that SUV reduced tolerance to morphine. SUV administration decreased the relative expression of the DRD2 gene but did not affect NR1 gene expression. To our knowledge, these findings provide the first evidence that SUV attenuates morphine tolerance predominantly by modulating the dopaminergic system.

Keywords: Orexin, Suvorexant, Morphine, Drug Tolerance, Dopamine Receptor D2

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1. Introduction

Opioid addiction is recognized as a chronic yet treatable condition, marked by the emergence of tolerance, dependence, and withdrawal symptoms upon cessation of use (1). Globally, it is estimated that over 16 million individuals are affected by opioid use disorder (OUD), contributing to more than 120,000 deaths annually (2). Among opioids, morphine stands out as one of the most potent analgesics for therapeutic purposes (3). Despite their potent analgesic efficacy, the therapeutic use of opioid medications is markedly restricted by the inevitable onset of tolerance and physical dependence (4).

The pathogenesis of opioid use disorder is a multifaceted process, stemming from a complex interplay of molecular adaptations, cellular modifications, and behavioral shifts that manifest across both acute and chronic timelines (5). The reinforcing properties of opioids are predominantly mediated by the stimulation of key mesolimbic pathway structures, notably the NAc (nucleus accumbens) and the VTA (ventral tegmental area). This pharmacological stimulation facilitates a surge in dopaminergic neurotransmission within the NAc, which is intrinsically linked to the generation of euphoric states (6). However, excessive and prolonged opioid use disrupts the regulation of dopamine reward pathways in the brain (7-9). Accumulating evidence suggest that dopamine–glutamate receptor cross-talk in striatal medium spiny neurons is mediated by receptor heteromers, notably D1 receptor –GluN1 and D2 receptor –GluN2B complexes. In vivo, elevations in dopamine (e.g., after psychostimulant exposure) enhance D2R–GluN2B coupling within the postsynaptic density microdomain, which displaces CaMKII from GluN2B, lowers CaMKII-sensitive Ser1303 phosphorylation, and suppresses NMDAR currents (10). These receptor heteromers contribute to drug-induced adaptations in a temporally distinct manner: D1–NMDAR complexes regulate ERK-dependent synaptic and transcriptional plasticity during the induction phase, whereas D2–NMDAR complexes are primarily engaged in sustaining sensitization and mediating rewarding effects following abstinence and subsequent drug re-exposure (11, 12).

Besides dopamine, various other neurotransmitter systems contribute to morphine addiction by modulating or interacting with the dopaminergic circuitry (13). For instance, orexin can regulate the activity of dopamine neurons within the VTA, thereby influencing dopamine release in associated downstream pathways. Orexin acts as an excitatory regulator of dopamine-producing neurons and contributes to the development of behaviors related to addiction (4). Collectively, evidence suggests that the orexin system positively influences brain reward pathways (14). Consequently, extensive research has investigated the therapeutic potential of orexin receptor (OXR) antagonists in the treatment of drug addiction (4). Accumulating evidence from preclinical studies suggests that orexin receptor (OXR) antagonists are effective in suppressing morphine-seeking behavior, inhibiting the development of conditioned place preference (CPP), and mitigating the progression of both tolerance and physical dependence (15-19). However, the mechanisms through which OXRs can counteract the development of morphine tolerance are less studied.

Suvorexant (SUV), a dual orexin receptor antagonist (DORA), is a clinically approved hypnotic agent with a favorable tolerability profile, and is indicated for the management of insomnia (20). Given that orexin signaling contributes to the regulation of reward and addiction pathways through both OXR1 and OXR2 receptors (21), SUV offers supporting evidence that the orexin system is implicated in the development of opioid tolerance. This study, therefore aimed to explore the capacity of suvorexant to mitigate morphine-induced antinociceptive tolerance in mice. Mechanistic exploration focused on quantifying gene expression changes in two critical mediators of neuroadaptation: the NMDA receptor subunit NR1 and the dopamine D2 receptor (DRD2). The integration of behavioral and molecular datasets was intended to provide a mechanistic framework for understanding how orexin receptor inhibition modulates opioid tolerance.

2. Materials and Methods

2.1 Compounds and reagents

The compounds in this study included naloxone hydrochloride (Caspian Tamin, Iran), clonidine (Vazonidin) tablets (Tolid Daru, Tehran, Iran), morphine (morphine sulphate, Daru Pakhsh, Iran), and suvorexant (Trademax, China).

2.2 Animals

Twenty-eight adult male outbred mice (*Mus musculus*, 25–30 g) were obtained from the central animal facility (Kashan University of Medical Sciences). They were randomly divided into four experimental groups (n = 7). The mice were housed under controlled environmental conditions (12/12 h cycle, 23 ± 2 °C, 50 ± 10% relative humidity). Throughout the study, animals had free access to food and water. All procedures adhered to ethical guidelines (Ethics Approval No.: IR.KAUMS.AEC.1402.010).

2.3 Study design

To induce tolerance to morphine's analgesic properties, mice received subcutaneous (*sc*) injections of morphine at escalating doses [50 (8 AM), 50 (12 PM), and 75 (4 PM) mg/kg, over three days] (19). To examine the influence of the tested agents, mice were given intraperitoneal (*ip*) injections of either normal saline, clonidine (CLO, 0.1 mg/kg), or SUV (90 mg/kg) 30 min before each morphine injection. A 90 mg/kg dose of SUV was selected based on earlier preclinical evidence indicating its effectiveness in reducing morphine tolerance in mice (19, 22). (Table 1)

2.4. Assessment of tolerance

On the first and fourth days of the study, mice were given a single dose (10 mg/kg, *sc*) of morphine. Thirty minutes after administration, the analgesic efficacy of morphine was evaluated using a tail-flick (Ugo Basile, Italy) apparatus. The response latency for each animal was recorded (maximum cut-off time =10 sec) (19).

2.5 Open-field Test (Locomotor Activity)

Locomotor activity was evaluated on day 4 using the open-field test (100 × 100 cm, surrounded by 50 cm walls). Each mouse was placed in the center of the open-field apparatus, and its locomotor activity (measured by the number of squares traversed) was recorded by a camera during a 10-minute session.

2.6. Real-Time PCR

After behavioral testing was completed, the animals were euthanized, and whole-brain tissues were immediately collected, snap-frozen in liquid nitrogen, and stored at −80 °C to preserve RNA integrity. Total RNA (1 µg) was extracted using a commercial RNA extraction kit (Parstous, Mashhad, Iran), and reverse transcription was performed with the RevertAid First-Strand cDNA Synthesis Kit (Parstous, Mashhad, Iran). Quantitative gene expression analysis was performed by real-time PCR (RT-qPCR) on an ABI 7500 system (Applied Biosystems, USA) using SYBR Green master mix (Ampliqon, Denmark). The primers in this experiment were as follows: *DRD2*, forward: ATCTCTTGCCCACTGCTCTTTGGA, reverse: ATAGACCAGCAGGGTGACGATGAA; *NR1*, forward: CGGCTCTTGGAAGATACAG, reverse: GAGTGAAGTGGTCGTTGG; and *GAPDH*, forward: AACTTTGGCATTGTGGAAGG, reverse: ACACATTGGGGGTAGGAACA. Relative gene expression was normalized to GAPDH as the reference gene and quantified using the $2^{-\Delta\Delta Ct}$ (Livak) method. All experiments were repeated in triplicate.

2.7 Data analysis

Data are summarized as mean ± SD. Statistical analyses were performed using Prism software (version 8, USA). Comparisons among groups were performed through one-way ANOVA, followed by Tukey's multiple-comparison procedure, with statistical significance defined at $P < 0.05$. For behavioral experiments, effect size indices (Cohen's d and Hedges' g, the latter with small-sample adjustment) were also computed to evaluate the magnitude of group differences. Gene expression data obtained from qPCR are reported as relative fold changes together with the respective P values.

Table 1. Study design.

Groups	Treatment Regimen	Morphine (mg/kg, s.c.)	Administration Route	Exposure Duration (days)
1	Normal saline	-	ip	3
2	Normal saline	+	ip	3
3	Clonidine (0.1 mg/kg)	+	ip	3
4	Suvorexant (90 mg/kg)	+	ip	3

3. Result

3.1 Effects of suvorexant (SUV)

Effects of suvorexant (SUV) on morphine-induced antinociceptive tolerance. On day 1, no significant variations in pain tolerance were observed across the experimental groups (Figure 1A) ($P > 0.05$). However, by day 4 (Figure 1B), morphine administration markedly reduced ($P < 0.001$, Cohen's $d = –2.75$, 6.903±1.024) the reaction time compared to control (9.253±0.6439). Conversely, CLO (0.1 mg/kg) significantly ($P<0.001$, $d=3.56$, 9.615±0.3333) extended the reaction time to painful stimuli compared to the morphine group. Furthermore, co-administration of SUV (90 mg/kg) led to a notable increase ($P<0.05$, $d =1.58$, 8.266±0.6695) in reaction time relative to the morphine group. To elucidate the pharmacological impact of the treatments on morphine-induced tolerance, we expressed the behavioral data as the percentage of maximum possible effect (%MPE), as illustrated in Figure 2.

3.2 Effects of SUV and Morphine on locomotor activity

Repeated morphine administration significantly decreased ($P < 0.001$, $d = –2.29$, 98.00±85.30) locomotor activity compared to the control (345.0±126.6). Similarly, CLO (0.1 mg/kg) treatment also caused a notable decline ($P < 0.01$, $d = –3.75$, 29.33±41.31) in locomotor activity compared to the control. However, co-treatment with SUV (90 mg/kg) did not significantly enhance ($P > 0.05$, $d = 0.68$, 157.8±90.91) locomotor activity levels compared to either the CLO or morphine groups (Figure 3).

3.3 Effects of SUV on DRD2 and NR1 mRNA levels

The expression levels of the DRD2 and NR1 genes were quantified using quantitative PCR (qPCR). The findings demonstrated a notable increase in the relative expression of both DRD2 (fold change = 3.523±0.9097) and NR1 (fold change = 3.080±1.201) in the morphine group compared with the control ($P < 0.05$). However, treatment with SUV significantly downregulated DRD2 gene expression (fold change = 1.628±0.8659, $P < 0.05$) compared to morphine, whereas it had no significant effect ($P > 0.05$) on NR1 expression compared to morphine (fold change = 1.883±0.3062) (Figure 4).

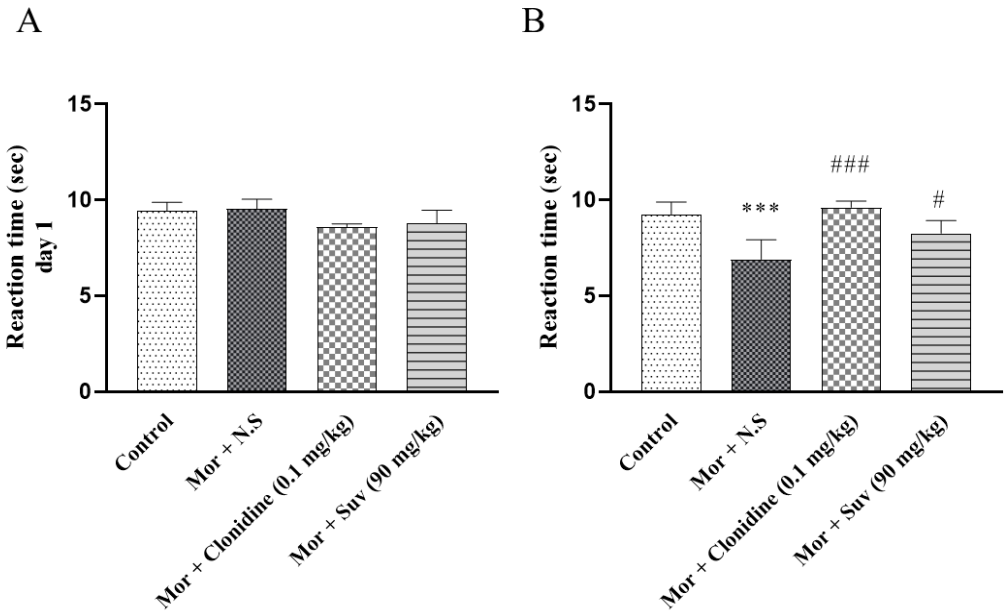


Figure 1. The effect of suvorexant (SUV) on the development of tolerance to the analgesic effects of morphine. A: Tail-flick test on day 1. B: Tail-flick test on day 4. Animals received repeated morphine injections for three consecutive days (50, 50, and 75 mg/kg, s.c.). Suvorexant (90 mg/kg), clonidine (0.1 mg/kg), or normal saline was administered intraperitoneally 30 minutes before each morphine dose. The control group received only normal saline. Data are presented as mean ± SD (n = 7 per group). Statistical comparisons were conducted using one-way ANOVA followed by Tukey's post hoc test. *** $P < 0.001$ compared with the control group. ### $P < 0.001$ and # $P < 0.05$ compared with the morphine group. Mor: Morphine, N.S: Normal saline, Suv: Suvorexant (**Prepared by Authors, 2025**).

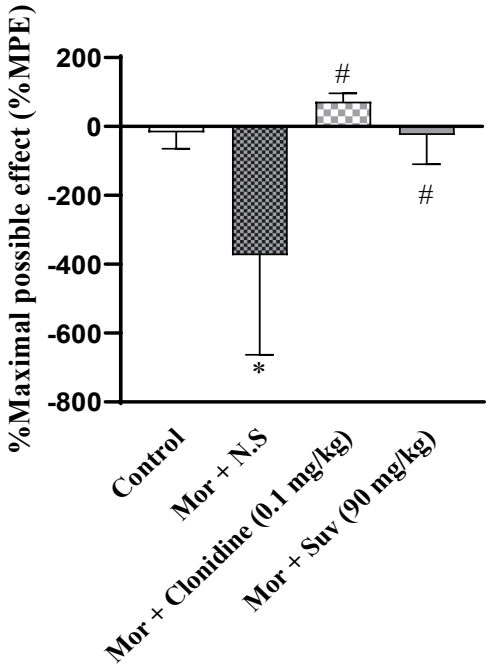


Figure 2. Data are expressed as the percentage of the maximal possible effect (%MPE), calculated as %MPE = [(drug latency − basal latency) / (cut-off latency − basal latency)] × 100. The cut-off time was set at 10 seconds. All values are presented as mean ± SD. * $P < 0.05$ compared with the control group. # $P < 0.05$ compared with the morphine group. Mor: Morphine, N.S: Normal saline, Suv: Suvorexant (**Prepared by Authors, 2025**).

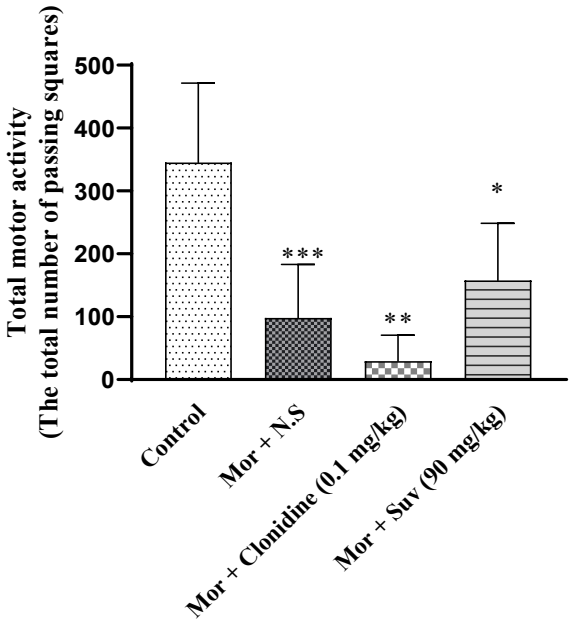


Figure 3. Comparison of locomotor activity among the experimental groups on day 4. Mice received repeated morphine injections for three consecutive days (50, 50, and 75 mg/kg, s.c.). Suvorexant (90 mg/kg), clonidine (0.1 mg/kg), or normal saline was administered intraperitoneally 30 minutes before each morphine dose, while the control group was treated with normal saline alone. On day 4, locomotor activity was assessed for 10 minutes. Data are presented as mean ± SD (n = 7 per group). Statistical comparisons were performed using one-way ANOVA followed by Tukey's post hoc test. * P < 0.05, ** P < 0.01 and *** P < 0.001 compared with the control group. Mor: Morphine, N.S: Normal saline, Suv: Suvorexant (**Prepared by Authors, 2025**).

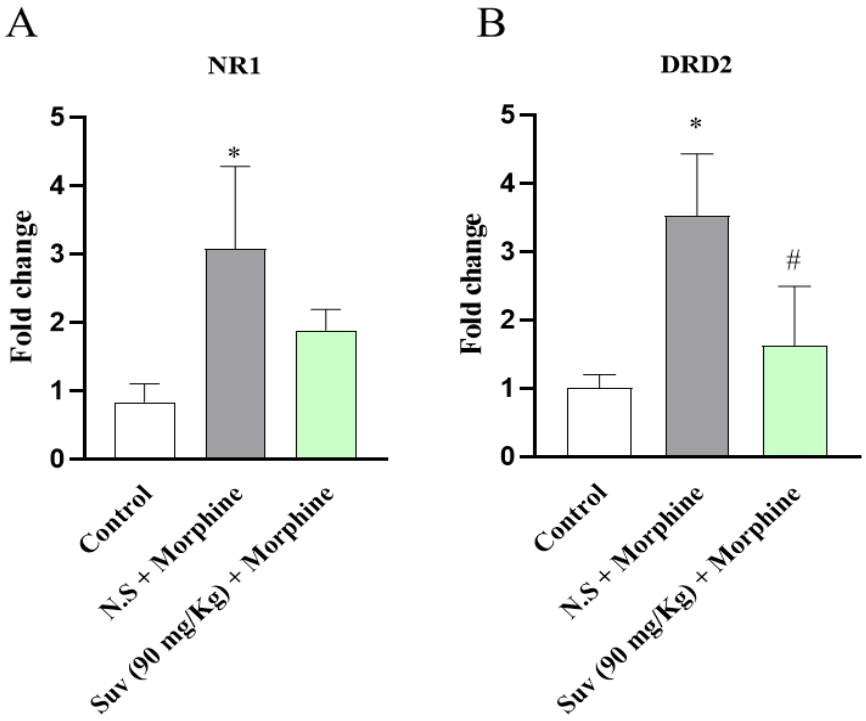


Figure 4. Effect of suvorexant (SUV) on DRD2 and NR1 gene expression. (A) Relative expression of the NR1 gene. (B) Relative expression of the DRD2 gene. mRNA levels were quantified by qPCR, and data were analyzed using the Livak method ($2^{-}\Delta\Delta Ct$). Statistical evaluation was conducted with one-way ANOVA followed by Tukey's post hoc test (n = 4 per group). * P < 0.05 compared with the control group. # P < 0.05 compared with the morphine group. Mor: Morphine, N.S: Normal saline, Suv: Suvorexant (**Prepared by Authors, 2025**).

4. Discussion

Opioids are commonly used in clinical settings to manage both acute and chronic pain (23). Nevertheless, a significant challenge associated with the extended therapeutic use of opioids like morphine is the emergence of tolerance, which diminishes their pain-relieving efficacy over time (24). The mechanisms behind morphine tolerance remain a topic of debate among researchers, and this uncertainty has hindered the development of effective treatments to preserve morphine's analgesic benefits (24). While substantial evidence supports the role of OXR antagonists in reducing morphine-induced dependence and withdrawal symptoms, limited research has explored their impact on morphine tolerance (4). Given this rationale, this research was structured to examine the influence of SUV on the progression of morphine tolerance and its possible regulatory effects on DRD2 and NR1 gene (in the mouse brain).

Our data reveal that repeated morphine injection markedly shortened tail-flick latency relative to controls, confirming the induction of tolerance. This outcome validates the experimental model employed to induce morphine tolerance and aligns with findings reported in previous studies (19, 22). Additionally, morphine administration significantly decreased locomotor activity relative to the control group. Consistent with earlier research, opioids have been shown to either enhance or suppress motor activity, depending on factors such as dosage and the duration of treatment. For instance, chronic opioid use often results in tolerance to these effects (25-28). Brady and Holtzman (29) also observed in their study that locomotor activity in dependent animals increased with low doses of morphine but decreased with higher doses (29).

In this study, administration of SUV (90 mg/kg) or CLO significantly increased pain response latency in animals relative to the morphine group, thereby counteracting the development of morphine tolerance. This result is consistent with previous reports (19). Evidence suggests that morphine tolerance arises from an adaptive process triggered by chronic morphine exposure. This process involves complex changes at molecular, cellular, synaptic, and circuit levels (30). Previous research has highlighted the critical role of NMDA receptors, a subtype of glutamate receptors, in mediating long-term potentiation (LTP) of synaptic plasticity —a mechanism strongly linked to the emergence of morphine tolerance (31, 32). Administration of NMDAR antagonists, such as MK-801, LY235959, and (+)-HA966, has been shown to delay the onset of morphine tolerance (33-35). Specifically, the NMDAR signaling pathway, activated by morphine, directly induces LTP, modulates Ca2+ levels, and triggers the CaMKII signaling pathway, ultimately leading to morphine tolerance (30). The NR1 subunit, integral to all functional NMDA receptor complexes, is fundamentally implicated in the processes underlying morphine tolerance. Previous studies have demonstrated that chronic morphine exposure induces region-specific alterations in NR1 gene expression, with a significant upregulation of NR1 mRNA in the striatum, contrasted by a marked downregulation in the prefrontal cortex (PFC). These divergent changes are thought to involve the activation of PKC (protein kinase C) signaling pathways and disruptions in glutamate homeostasis, leading to the removal of the Mg^{2+} block from NMDA channels, enhanced calcium influx, and subsequent activation of the nitric oxide signaling cascade. Collectively, these molecular adaptations play a critical role in the establishment of morphine antinociceptive tolerance (36-41).

On the other hand, the DRD2 has been identified as a key modulator in the control of pain perception and response mechanisms following the administration of morphine (42). Dopamine receptors belong to the G protein–coupled receptor family and are classified into two major subtypes, D1 and D2, based on their distinct pharmacological properties (43). Although DRD2 is associated with the analgesic effects of morphine (44), the precise pathways by which it contributes to the emergence of morphine tolerance are not yet fully understood (42). For instance, both DRD2 agonists and antagonists have been found to effectively counteract the emergence of morphine tolerance, as supported by multiple studies (45, 46).

Findings from this study demonstrated that repeated exposure to morphine produced a marked increase in the expression levels of the DRD2 and NR1 genes relative to the control group. While SUV administration did not significantly reduce the expression (relative) of the NR1 gene, it significantly decreased the relative expression of the DRD2 gene compared to the morphine group. Evidence (in animal models) suggests that orexin neurons are critical for the emergence of tolerance and dependence (47). Interestingly, research has shown that morphine stimulates neurons within the orexinergic system through direct activation of μ-opioid receptors (47, 48). Orexin has been identified as a key modulator that amplifies the presence of essential neurotransmitters, including glutamate and dopamine, within neural circuits, thereby influencing brain function and behavior (49, 50). Earlier research reported that administration of SUV in mice attenuates the development of morphine tolerance and physical dependence. They suggested that SUV may exert its effects by reducing CREB and p-ERK protein levels. Interestingly, their study showed no significant changes in NMDA protein levels, which aligns with our observations (19). Thus, it is likely that SUV's ability of to diminish tolerance to morphine's analgesic effects is mediated, at least in part, by its impact on reducing the relative expression of the DRD2 gene. Several limitations of this study should be recognized. The effects of Suvorexant were examined only over a short experimental period; therefore, its potential long-term impact on morphine tolerance and dependence remains uncertain. Moreover, this study focused solely on two molecular markers,

DRD2 and NR1; future investigations incorporating a wider range of signaling molecules may yield more profound insights into the underlying mechanisms. Addressing these aspects will be essential for validating and extending the present findings.

5. Conclusion

In this study, suvorexant at 90 mg/kg prolonged pain response latency in morphine-treated mice and suppressed the morphine-induced upregulation of DRD2 expression, while NR1 levels remained largely unchanged. These observations suggest a potential role for dopaminergic regulation in suvorexant's attenuation of morphine tolerance, although additional neural pathways are likely to contribute. Importantly, these findings are preliminary; dose–response analyses, long-term outcomes, and behavioral safety profiles were not addressed in this study. Taken together, our data suggest that suvorexant deserves further investigation as a potential modulator of opioid tolerance, particularly in contexts where dopaminergic dysregulation is implicated. Given that suvorexant is already clinically approved for insomnia, future translational studies in humans will be critical to determine whether it can be repurposed as an adjuvant therapy to improve opioid efficacy and reduce tolerance.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

This study was approved by the Ethics Committee of Kashan University of Medical Sciences (Ethics Approval No.:IR.KAUMS.AEC.1402.010). All procedures adhered to ethical guidelines.

6.3 Authors' Contributions

PESAA: gave the idea, designed, drafted, and edited the manuscript. AG: gave the idea, designed, drafted, edited the manuscript, and supervised the study. BA, ESH, and FH drafted and edited the manuscript. Authors read and approved the final manuscript.

6.4 Conflict of Interest

The authors have no conflict of interest.

6.5 Fund or Financial Support

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6.6 Using Artificial Intelligence Tools (AI Tools)

The authors declare that no artificial intelligence–based tools were used in the writing, data analysis, or preparation of this manuscript.

6.7 Availability of Data and Materials

All data and supplementary materials can be obtained from the respective author upon a reasonable request.

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