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Research Article

Impact of Oxycodone Hydrochloride on Cognitive Performance in Wistar Rats: Behavioral and Hormonal Aspects

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ABSTRACT

Introduction: Oxycodone hydrochloride is a semi-synthetic opioid widely prescribed for chronic pain management. Beyond its analgesic properties, growing evidence suggests that prolonged exposure to oxycodone may adversely affect cognitive functions and neuroendocrine homeostasis through suppression of the hypothalamic-pituitary-gonadal (HPG) axis. **Objective:** This study aimed to evaluate the impact of oxycodone hydrochloride on cognitive performance and hormonal profile in Wistar rats by jointly assessing behavioral and endocrine parameters. **Materials and Methods:** Thirty adult Wistar rats of both sexes (100-300 g) were randomly assigned into three groups (n = 10/group): a control group receiving distilled water (5 mL/kg), and two treatment groups receiving oxycodone hydrochloride orally at doses of 5 mg/kg and 10 mg/kg for 30 consecutive days. Cognitive functions were assessed using the Y-maze and Novel Object Recognition (NOR) tests. Serum hormonal levels were measured by ELISA. Statistical analyses included Student's t-test, one-way ANOVA, and Tukey's post hoc test, with significance set at $p < 0.05$. **Results:** Oxycodone hydrochloride induced dose-dependent impairments in cognitive performance in Wistar rats, with significantly reduced spontaneous alternation in the Y-maze and decreased discrimination in the novel object recognition test. It also significantly altered hormonal profiles, decreasing testosterone in males and reducing FSH, LH, and progesterone in females. **Conclusion:** Chronic oxycodone administration induces significant cognitive deficits associated with HPG axis dysregulation. These findings suggest the existence of an integrated neuroendocrine mechanism linking opioid exposure to cognitive and reproductive dysfunction.

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INTRODUCTION

Oxycodone hydrochloride is a semisynthetic opioid [1,2]. It binds to mu (μ), delta (δ), and kappa (κ) opioid receptors in the brain and spinal cord. It acts at these receptors as an opioid agonist without antagonistic effects. Oxycodone hydrochloride acts as an analgesic and sedative and is commonly used for the management of chronic pain [1,2,3]. In addition to these uses, oxycodone hydrochloride is prescribed in oncology, for postoperative care, for certain psychiatric conditions, and for the treatment of cough [4,5]. Its mechanism of action involves binding to μ -opioid receptors (MORs), particularly in the hypothalamus, leading to inhibition of the pulsatile secretion of gonadotropin-releasing hormone (GnRH) [6,7]. This inhibition leads to suppression of the hypothalamic-pituitary-gonadal axis, thereby affecting hormonal regulation [6,7,8]. Today, the rise in oxycodone prescriptions [9,10], combined with misuse [9,10], dependence [9,10], and overdose-related mortality [9,10], has transformed its initially intended therapeutic role into a major public health problem [9,10]. Concerns have been raised regarding its potential to cause adverse effects beyond its analgesic action, particularly on cognitive functions and the neuroendocrine system [7]. Oxycodone hydrochloride can disrupt the functioning of the central nervous system and impair other physiological systems, such as the endocrine system [7,11]. Cognitive performance, mood regulation, and hormonal balance may be affected as a result of chronic exposure to opioids. Hormonal axes, such as the hypothalamic-pituitary-gonadal axis, play a role in homeostatic regulation and may be vulnerable to opioid-induced suppression [7,11,12]. Given these established potential adverse effects, the interactions between neurobehavioral or cognitive dimensions and endocrine function have sparked interest in the behavioral and hormonal

consequences of prolonged exposure to oxycodone hydrochloride. The objective of the study was to evaluate the impact of oxycodone hydrochloride on cognitive performance and the hormonal profile in Wistar rats by jointly analyzing behavioral and endocrine parameters.

MATERIALS AND METHODS

Animals and Treatments

Thirty adult Wistar rats of mixed sex (15 males and 15 females), weighing between 100 and 300 g, obtained from the animal facility of the Faculty of Health Sciences, were used. They were housed in their natural enclosures with free access to water and food. The various products were administered orally at different doses for thirty days. For the study, three groups were formed, each containing ten adult male and female Wistar rats ($n = 10/\text{group}$; 5 males and 5 females per group). The rats were bred to prevent mating and treated as follows:

- The first group served as the control group and received distilled water at a dose of 5 ml/kg;
- The second group was treated with oxycodone hydrochloride at a dose of 5 mg/kg;
- The third group was treated with oxycodone hydrochloride at a dose of 10 mg/kg.

The doses used in the study correspond to therapeutic doses in clinical practice [9,10].

Behavioral Tests

Y-Maze

The Y-maze test was used to assess spatial working memory and exploratory behavior in Wistar rats [13,14,15]. The apparatus consisted of three identical arms arranged at 120° angles to one



another. Each rat was placed individually in the center of the maze and allowed to freely explore the three arms for 5 minutes. Spontaneous alternation was defined as successive entry into the three different arms of the maze. The total number of entries into the arms was also recorded as an index of locomotor activity. The apparatus was cleaned with a 70% ethanol solution after each animal's test to eliminate olfactory cues. The primary parameter analyzed was the percentage of spontaneous alternations, calculated using the following formula:

$$\% \text{ Spontaneous Alternation} = \left[\frac{\text{number of alternations}}{\text{total number of entries} - 2} \right] \times 100$$

Novel Object Recognition Test

The object recognition test was used to assess recognition memory [16]. After a habituation phase in the arena, each rat was exposed to two identical objects for 10 minutes (acquisition phase). Twenty-four hours later, one of the familiar objects was replaced by a novel object with a different shape and texture (retention phase). The time spent exploring each object was recorded over a 10-minute period. A high discrimination index value indicates better recognition memory. Recognition memory was assessed using the discrimination index (DI), calculated according to the formula:

$$\text{DI (\%)} = \left[\frac{\text{Time spent on new object} - \text{Time spent on familiar object}}{\text{Total exploration time}} \right] \times 100$$

Blood Collection

Blood was collected after anesthesia with ethyl ether via inhalation. The serum was decanted after centrifugation and used for biomedical analyses.

Hormone Levels

Testosterone and progesterone levels were measured using an enzyme-linked immunosorbent assay (ELISA) with the Cypress® kit.

Statistical Analysis

Results are expressed as mean \pm standard deviation. The treated animal groups were compared to the control group for each variable. Comparisons of non-time-dependent parameters were performed using Student's t-test and one-way ANOVA, followed by Tukey's test for comparisons among multiple experimental groups. Data were entered into Excel 2019. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 20. The significance threshold was set at a p-value < 0.05 .

Ethics

The study was conducted in accordance with Directive 2010/63/EU on the protection of laboratory animals [17].

RESULTS

Behavioral Tests

Y-Maze

Oxycodone hydrochloride was administered orally for 30 days at doses of 5 and 10 mg/kg to adult male and female Wistar rats. The effects observed on behavioral performance in the Y-maze test are presented in the table below.

Table I. Effects of oxycodone hydrochloride on behavioral performance in the Y-maze test

Parameters	ED 5 ml/kg	Oxy 5 mg/kg	Oxy 10 mg/kg
Spontaneous alternation (%)	90	60	40
Percentage of time spent in the new arm (%)	80	50	40



Novel Object Recognition Test

Oxycodone hydrochloride was administered orally for 30 days at doses of 5 and 10 mg/kg to adult

male and female Wistar rats. The effects observed on behavioral performance in the novel object recognition test are presented in the table below.

Table II: Effects of oxycodone hydrochloride on behavioral performance in the object recognition test

Parameters	ED 5 ml/kg	Oxy 5 mg/kg	Oxy 10 mg/kg
Discrimination Index (%)	80	65	50
Percentage of time spent exploring the new object (%)	80	40	30

Hormone Levels

Oxycodone hydrochloride was administered orally for 30 days at doses of 5 and 10 mg/kg to adult

male and female Wistar rats. The effects observed on hormonal parameters are presented in Table III.

Table III. Effects of oxycodone hydrochloride on hormonal parameters

Parameters	Sex	ED 5 ml/kg	Oxy 5 mg/kg	Oxy 10 mg/kg
FSH	Male	0,32±0,08	0,39±0,16 ^{ns}	0,32± 0,12 ^{ns}
LH		0,47±0,34	0,82±0,41 ^{**}	0,80±0,37 ^{**}
Testosterone		1,48 ± 0,35	0,41± 0,13 ^{**}	0,29 ± 0,10 ^{***}
FSH	Female	11,82 ± 1,96	3,16 ± 0,15 [*]	2,91 ± 0,11 [*]
LH		14,33 ± 1,94	1,26 ± 0,22 [*]	1,16±1,08 [*]
Progesterone		45,21 ± 1,29	18,87 ± 7,86 ^{**}	10,27 ± 0,48 ^{***}

The results are expressed as mean ± standard deviation. Statistical differences were analyzed using Student's t-test, one-way ANOVA, and Tukey's post-hoc test. (*) : p<0.05; (**) : p<0.001; (***) : p<0.0001; NS (not significant). ED : Distilled water; Oxy : Oxycodone hydrochloride.

DISCUSSION

Oxycodone hydrochloride is a semisynthetic opioid that acts as an agonist at the μ , δ , and κ receptors, with a predominant affinity for μ -opioid receptors (MORs) located primarily in the central nervous system, particularly the hypothalamus. Through this mechanism, it inhibits the pulsatile secretion of GnRH, leading to suppression of the hypothalamic-pituitary-gonadal axis and disruption of hormonal homeostasis [18]. It is used in clinical practice, in oncology, and in the postoperative setting for the treatment of chronic pain. Its increasing use and potential for abuse

make it a major public health concern, particularly due to its neurobehavioral and endocrine effects [19]. The objective of this study was to evaluate the impact of oxycodone on cognitive performance and hormonal profile in Wistar rats after 30 days of oral administration at therapeutic doses. Memory performance was assessed using the Y-maze and NOR tests, while hormone levels were measured by ELISA. The results reveal a dose-dependent impairment of cognitive functions associated with significant endocrine disturbances.

The results of this study highlight a clearly dose-dependent deleterious effect of oxycodone hydrochloride on the cognitive performance of Wistar rats following 30 days of chronic administration. The observed impairments jointly involve spatial working memory, behavioral flexibility, and recognition memory, reflecting an overall impairment of mnemonic functions that

depend primarily on the hippocampus and the prefrontal cortex [11,19,20].

In the Y-maze test, control animals exhibited optimal performance, characterized by a strong capacity for spontaneous alternation and efficient exploration of the novel arm, indicating the functional integrity of the fronto-hippocampal circuits [11,19,20]. In contrast, rats exposed to oxycodone showed a progressive and significant deterioration in these parameters, proportional to the administered dose [11,19,20]. This gradual decline in performance reflects an impairment in spatial working memory as well as a deficit in cognitive flexibility, suggesting a disruption of the neurobiological mechanisms involved in exploratory decision-making [11,19,20,21]. Taken together, these changes suggest a possible alteration of the neural networks connecting the prefrontal cortex to the hippocampus, structures that are essential for working memory and novelty-seeking behavior [11,19,20,21]. However, since no neurobiological investigations were performed in the present study, the involvement of these brain regions remains hypothetical.

The results obtained in the object recognition test are consistent with previous findings. Control animals retained a clear preference for the novel object, indicating intact recognition memory, normal encoding capacity, and memory consolidation [11,21,22]. In contrast, chronic exposure to oxycodone was accompanied by a significant decrease in this preference, revealing a progressive impairment of recognition memory. This deficit may suggest the involvement of brain regions associated with recognition memory, particularly the hippocampus and related cortical structures, as well as a possible alteration of long-term memory consolidation mechanisms [11,21,22,23]. Nevertheless, these interpretations

should be considered with caution because no direct assessment of brain function was conducted.

From a mechanistic standpoint, several non-exclusive processes may be involved. Oxycodone, through its prolonged action on μ -opioid receptors, induces inhibition of neuronal excitability in key cognitive structures, notably the hippocampus and the prefrontal cortex. This chronic inhibition is likely to disrupt synaptic plasticity, particularly long-term potentiation, a fundamental mechanism of learning and memory [23,24].

Furthermore, experimental data suggest that prolonged exposure to opioids may contribute to increased oxidative stress, persistent neuroinflammation, and dysregulation of the hypothalamic-pituitary-adrenal axis, all of which may exacerbate cognitive dysfunction [7,25,26]. Although these mechanisms were not directly investigated in the present study, they may partly explain the behavioral alterations observed following chronic oxycodone administration.

The dose-dependent effect observed in both behavioral paradigms strongly supports the hypothesis of a causal link between oxycodone exposure and cognitive impairment [23,24,25,26]. The simultaneous impairment of working memory and recognition memory suggests a widespread neurobiological alteration, extending beyond a simple localized functional deficit to reflect a global imbalance in cognitive circuits [27,28]. Taken together, the results indicate that chronic exposure to oxycodone hydrochloride induces a significant, progressive, and systemic impairment of cognitive performance in Wistar rats, the severity of which is closely correlated with the administered dose.

In parallel with the cognitive impairments, this study highlights a profound disruption of the hypothalamic-pituitary-gonadal (HPG) axis, the



expression of which varies according to sex and the intensity of exposure [7,29,30].

In males, the administration of oxycodone is associated with a significant decrease in testosterone, reflecting impaired gonadal steroidogenesis. Although opioids are generally known to suppress hypothalamic GnRH secretion and consequently reduce gonadotropin release, the increase in LH observed in the present study suggests the activation of a compensatory pituitary feedback mechanism in response to reduced testosterone levels [7,12,29,30,31]. This endocrine profile may therefore indicate not only central neuroendocrine dysregulation but also a possible peripheral impairment of testicular function, particularly at the level of Leydig cells [7,12,29,30,31].

In females, endocrine disturbances are more profound and widespread. The marked decrease in pituitary gonadotropins reflects a clear central inhibition of the HPG axis, accompanied by a significant drop in progesterone. Taken together, these findings indicate a major impairment of ovarian function, which may correspond to inhibition of ovulation, luteal insufficiency, or a general disruption of the hormonal cycle [7,32,33].

Comparative analysis highlights an increased sensitivity of the female neuroendocrine system to oxycodone. This difference could be explained by a more pronounced modulation of GnRH pulsatility, or by complex interactions between opioids and the central neuromodulatory networks involved in the regulation of reproduction [7,32,33].

From a pathophysiological perspective, these observations fit within the well-established framework of opioid action on the reproductive axis. Activation of μ -opioid receptors in the hypothalamus leads to inhibition of GnRH release,

which in turn induces a decrease in LH and FSH secretions [7,30,32,33,34].

Beyond the reproductive axis, these hormonal disturbances appear to be closely linked to the observed cognitive deficits. Sex hormones play an essential role in synaptic plasticity, the modulation of hippocampal circuits, and the maintenance of memory functions [7,35]. Consequently, oxycodone-induced gonadal hypofunction may represent one of the mechanisms contributing to impaired cognitive performance, although the present study does not allow the establishment of a direct causal relationship between hormonal disturbances and memory deficits [7,35].

The present study has some limitations that should be acknowledged. First, locomotor activity was not specifically assessed; therefore, a potential contribution of opioid-induced sedation to the behavioral outcomes cannot be completely excluded. Second, no histological, neurochemical, or molecular investigations were performed to confirm the involvement of specific brain regions or signaling pathways. Finally, although cognitive and endocrine alterations were observed simultaneously, the study design does not permit the establishment of a direct causal relationship between hormonal dysregulation and memory impairment.

Oxycodone hydrochloride appears to be a neuroactive agent with multidimensional deleterious effects, capable of inducing both a significant impairment in cognitive performance and a profound dysregulation of the hypothalamic-pituitary-gonadal axis. Taken together, these results support the existence of an integrated neuroendocrine mechanism at the intersection of hormonal, synaptic, and cognitive functions, whose progressive disruption may underlie the behavioral deficits observed in Wistar rats.



CONCLUSION

Chronic administration of oxycodone hydrochloride for 30 days induces a dose-dependent impairment of cognitive performance in Wistar rats, affecting spatial working memory and recognition memory. These behavioral changes are associated with significant disruptions in the hormonal profile, characterized by decreased levels of sex hormones and alterations in gonadotropins. The results suggest an association between the observed cognitive deficits and the endocrine disturbances induced by oxycodone, although they do not establish a direct causal link. Further studies are needed to better understand the neurobiological mechanisms involved.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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