

# Role of Testosterone in Swimming Exercise-induced Analgesia in Rats

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## ABSTRACT

**Objective:** “Feel good effect” of exercise is well known. Activation of pain inhibitory mechanisms after exercise is also well documented. Swimming is considered as a beneficial exercise as well as health-promoting sport. The significance of testosterone in swimming exercise-induced analgesia is yet to be understood. Therefore, it is worthwhile to investigate the significance of testosterone in swimming exercise-induced analgesia.

**Materials and Methods:** The basal tail flick latencies of all animals were recorded by using tail flick analgesiometer. In order to observe the effect of testosterone on swimming exercise-induced analgesia, testicles of animals of some groups were surgically removed. Then animals were subjected to swimming sessions of different patterns. After swimming, tail flick latencies were measured. **Results:** Swimming sessions resulted in increase in pain thresholds of all animals. Castration negatively affected the degree of analgesia achieved in rats. However, daily treatment of testosterone propionate (500 $\mu$ g/kg, s.c.) improved swim-induced analgesia in castrated rats. Moreover, daily administration of naloxone hydrochloride (1mg/kg, i.p.) fifteen min prior to swimming suppressed testosterone therapy resulted in an increase in swim-induced analgesia in castrated animals. **Conclusion:** We concluded that testosterone plays a significant role in swimming exercise-induced analgesia in male Wistar albino rats and this positive effect of testosterone on pain threshold might be mediated through its probable effect on the endogenous opioid system.

**Key words:** Castration, Swimming exercise, Pain threshold, Testosterone, Endogenous opioids.

## INTRODUCTION

Pain is a problematic issue worldwide.<sup>1</sup> It is one of the most common reasons for which patients require medical care.<sup>2</sup> Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”.<sup>3</sup> Sometimes surprisingly, troopers or warriors wounded in battlefield report that they do not experience lousy pain during the war.<sup>4</sup> Some of the habitual runners experience acute states of euphoria during or after running exercise.<sup>5</sup> Research studies on animals indicate multiple endogenous analgesia systems.<sup>6</sup> Various endogenous opioid peptides and endocannabinoids

are well reported to have analgesic properties.<sup>7,8</sup> A planned, repetitive physical activity in order to maintain and/or improve physical fitness is said to be exercised.<sup>9</sup> Exercise significantly increases serum  $\beta$ -endorphin levels as compared to its resting values.<sup>10</sup> Exercise elevates the pain threshold by triggering the release of endogenous opioids, which activate nociceptive inhibitory mechanisms.<sup>11</sup> It is a well-known fact that swimming is a good exercise. Swimming exercise significantly minimized the number of acetic acid-induced pain responses in mice when compared with the non-exercised group.<sup>12</sup> It has been previously

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reported that naloxone significantly attenuates swim-induced anti-nociceptive effects in adult rats.<sup>13</sup> Testosterone is a primary male sex hormone mainly secreted by testes.<sup>14</sup> It has been found that testosterone intensifies analgesia, cognitive performance and decreases anxiety in rats.<sup>15</sup> Low dose transdermal testosterone therapy is reported to increase angina threshold in human subjects.<sup>16</sup> At an identical level of pain intensity, a higher degree of  $\mu$ -opioid system activation has been observed in anterior thalamus, ventral basal ganglia and amygdala of men than in women.<sup>17</sup> It has been documented that testosterone may increase the sensitivity of adult male rats to  $\mu$  and  $\kappa$  opioid anti-nociception.<sup>18</sup> In a study, testosterone deficient men were found more likely to suffer from irritability, anxiety, insomnia, poor memory, low libido and reduced muscle and bone mass.<sup>19</sup>

In this study, we explored the effect of castration on swim-induced analgesia in male Wistar rats. We also investigated whether the role of testosterone therapy in restoring swim-induced analgesia in castrated rats is mediated through the endogenous opioid system.

## MATERIALS AND METHODS

### Animals

Adult male Wistar albino rats having an average body weight of  $225\text{g} \pm 10\%$  were housed in a controlled temperature of  $22 \pm 2^\circ\text{C}$  with 12:12 h light-dark schedule. All animals were fed on standard chow diet (wheat flour 22.5%, roasted Bengal gram powder 60%, skimmed milk powder 5%, casein 4%, refined oil 4%, salt mixture with starch 4% and vitamin and choline mixture 0.5%) and provided water *ad libitum*. All the experimental procedures were performed in accordance with the approval of the Institutional Animal Ethical Committee (1260/PO/Ere/S/09/CPCSEA/IAEC/2015/P.Col./R4) under strict compliance of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. Further, the experiments were conducted in accordance with the principles of laboratory animal care (National Research Council US Committee for the Update of Guide for the Care and Use of Laboratory Animals).

### Drugs and chemicals

Testosterone Propionate (TP), an ester of testosterone was obtained from Sigma Aldrich Chemical Co. Testosterone propionate  $500\mu\text{g}/\text{kg}$  was dissolved in olive oil for subcutaneous (s.c.) administration.<sup>20</sup> Naloxone hydrochloride (Naloxone), an opioid antagonist was obtained from Sigma Aldrich Chemicals Co. Naloxone  $1\text{mg}/\text{kg}$  was dissolved in normal saline (0.9% sodium

chloride solution) for intraperitoneal (i.p.) administration<sup>21</sup> All drugs and chemicals used in the experimental study were of analytical grade and freshly prepared before use.

### Surgical castration

Animals were anesthetized by thiopental sodium  $40\text{mg}/\text{kg}$ , i.p.<sup>22</sup> The surgical castration was performed as discussed by Delev *et al.*<sup>23</sup> The skin was shaved prior to surgery. A 10mm long incision was made on scrotal skin apically. The incision was extended to a few mm of right and left sacs. Testes were pulled out gently. Vas deferens and blood vessels were ligated with silk thread. Both testicles were removed. The remaining tissue was carefully placed back in to the abdominal cavity. The incision was then closed using silk thread. The incisions were treated with topical neomycin sulfate powder (Nebasulf topical powder, Pfizer) for preventing microbial infection. For the purpose of healing, castrated rats were placed in individual cages with a free approach to food and water. Castrated rats were taken into the study after 6 weeks of castration providing time for the depletion of endogenous testosterone.<sup>24</sup>

### Experimental protocol

The animals were randomly assigned to eleven groups containing six rats ( $n=6$ ) per group. Animals were individually allowed to swim in water filled up to half of an open circular pool of diameter 160cm and depth 61cm. During swimming, the temperature of the water was maintained at  $25^\circ\text{C}$  to induce analgesia in rats.<sup>25</sup> After swimming, animals were dried gently by using a soft cloth.

**Group I: Normal control ( $n=6$ ):** Intact animals were not subjected to swimming exercise. Tail flick latencies were measured on a weekly interval for the assessment of pain threshold.

**Group II: Normal intact animals allowed to swim for 15 min for a single day only ( $n=6$ ):** Intact animals were allowed to swim for 15 min for a single day only; tail-flick latencies were measured on the same day and then on a weekly interval.

**Group III: Castrated rats allowed to swim for 15 min for a single day only ( $n=6$ ):** Castrated rats were allowed to swim for 15 min for a single day only; tail-flick latencies were measured on the same day and then on a weekly interval.

**Group IV: Normal intact animals allowed to swim every day for gradually increasing time period ( $n=6$ ):** Intact rats were allowed to swim in a manner given in Table 1 and tail flick latencies were measured on a weekly interval.

**Table 1: Swimming protocol for group IV.**

S.NO.	Duration of swimming (min)	Days
1.	3 min	(from Day 1 to Day 4)
2.	6 min	(from Day 5 to Day 8)
3.	9 min	(from Day 9 to Day 12)
4.	12 min	(from Day 13 to Day16)
5.	15 min	(from Day 17 to Day 20)
6.	15 min	(Day 20 onwards)

**Table 2: Swimming protocol for group V.**

S.NO.	Duration of swimming (min)	Days
1.	3 min	(from Day 1 to Day 4)
2.	6 min	(from Day 5 to Day 8)
3.	9 min	(from Day 9 to Day 12)
4.	12 min	(from Day 13 to Day16)
5.	15 min	(from Day 17 to Day 20)
6.	15 min per day	(Day 20 onwards)

**Group V: Castrated animals allowed to swim every day for gradually increasing time period (n=6):** Castrated rats were allowed to swim in a manner given in Table 2 and tail flick latencies were measured on a weekly interval.

**Group VI: Normal intact animals allowed to swim 15 min every day (n=6):** Rats were allowed to swim daily for 15 min and pain thresholds were measured on a weekly interval.

**Group VII: Castrated animals exposed to daily swimming for 15 min (n=6):** Castrated rats were allowed to swim daily for 15 min per day and tail flick latencies were measured weekly.

**Group VIII: Vehicle (olive oil) treated castrated animals allowed to swim daily for 15 min (n=6):** Castrated rats were daily given olive oil (1ml/kg, s.c.) and allowed to swim every day for 15 min. Pain thresholds were measured weekly.

**Group IX: Testosterone propionate treated castrated animals allowed to swim for 15 min per day (n=6)** Castrated rats were daily administered testosterone propionate 500µg/kg, s.c.<sup>20,26</sup> and allowed to swim daily for 15 min. Pain thresholds were measured weekly.

**Group X: Castrated animals treated with normal saline and olive oil were allowed to swim every day for 15 min (n=6):** Castrated rats treated daily with normal saline 1ml/kg, i.p. and olive oil 1ml/kg, s.c. were allowed to swim for 15 min per day. Pain thresholds were measured weekly.

**Group XI: Castrated animals treated with naloxone hydrochloride and testosterone propionate were exposed to swimming for 15 min per day (n=6)** Castrated rats were daily administered with naloxone hydrochloride (1mg/kg, i.p.) and testosterone propionate (500µg/kg, s.c.) and allowed to swim daily for 15 min. Naloxone was daily administered 15 min before swimming sessions. Pain thresholds were measured weekly.

### Assessment of pain threshold by measuring tail flick latencies

Tail flick latencies of the animals were considered as their pain threshold.<sup>27</sup> Pain threshold was measured by tail flick analgesiometer (Roxel, India). Animals showing basal tail flick latencies below 3 sec and above 5 sec were excluded from the experimental protocol. Current passing through naked nichrome wire was set at 3 ampere<sup>28</sup> to make the wire hot. A distance of about 1.5 cm was maintained between the heat source and tail skin to avoid tissue damage. About 1-2 cm portion of the tail tip was exposed to the heat source.<sup>29</sup> To avoid tissue damage, cut-off time was fixed as 10 sec. The time between placing the tail on exposure to heat and flick/withdrawal of tail was noted as tail flick latency. Tail flick latencies were measured at weekly interval.

### Statistical analysis

The results are presented as mean  $\pm$  SD (Standard Deviation). The data were analyzed using a two-way Analysis of Variance (ANOVA). The *p*-value <0.05 was considered statistically significant.

## RESULTS

Although in intact and castrated male rats, swimming in water at 25°C has been found to raise pain thresholds. This increase in latencies of the tail flick in castrated rats was not as high as normal rats. The peak tail-flick latencies were observed between 15 and 30 min after swimming sessions as previously reported.<sup>25</sup> This report presents data based on observed peak tail flick latencies.

### Effect of single day swimming session on pain threshold

Intact male rats who had a one-day swimming session of 15 min withdrew their tails later than the control group (group II vs. group I). After a single day swimming session of 15 min compared to intact rats (group III vs. group II), tail flick latencies were significantly lower in castrated rats. When the pain threshold was measured one week after this day of swimming, it was found that the analgesic effect of swimming in both groups was abolished. In addition, in comparison with intact male

rats (group III vs. group II), the pain thresholds of castrated male rats were significantly reduced. In addition, the measurement of tail flick latencies in the following weeks after the day of swimming revealed that the pain thresholds of castrated male rats were below their basic values, while intact animals withdrew their tails before swimming. (Figure 1A).

### Effect of swimming sessions of gradually increasing time durations on pain threshold

At the first week, the pain threshold was found increased but only up to a little extent in both castrated and non-castrated normal rats. With the gradual increase in the duration of swimming, latency in tail withdrawal from radiant heat source was found to be increased proportionally. The maximum peak of the pain threshold was noted on the 4<sup>th</sup> week. On exposure to swimming sessions of gradually increasing durations, elevation in tail flick latencies of castrated male rats was found to be significantly lesser than that observed in intact male rats (group V vs. group IV). Castrated male rats were observed to withdraw their tails significantly faster than intact rats (Figure 1B).

### Effects of daily swimming sessions of 15 min on pain threshold

Normal male rats allowed to swim for 15 min daily were observed to show significantly higher post-swimming analgesic responses in comparison of castrated animals exposed to daily swimming for 15 min (group VI vs. group VII). Maximum tail-flick latencies were observed on week 4 measurement. A significant difference in swim-induced delay in tail flick responses was detected in both VI and VII groups as compared to normal group (Figure 1C).

### Effect of testosterone replacement therapy on pain thresholds

Testosterone propionate administration to castrated animals significantly increased the pain threshold when compared to untreated castrated rats allowed to swim for 15 min (group IX vs. group VII). Tail flick latencies of testosterone propionate treated castrated animals exposed to daily swimming sessions of 15 min were found equivalent to intact swimming group. Vehicles treated castrated rats did not show any significant variation from vehicle untreated castrated male rats (Figure 1D).

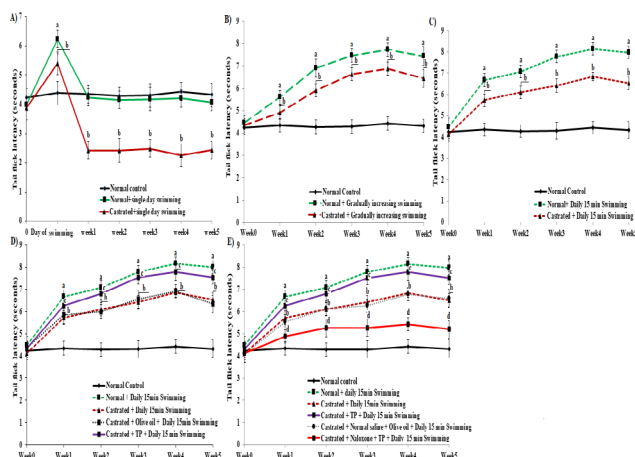
### Effect of naloxone on pain thresholds of rats receiving testosterone propionate therapy

Animals receiving both naloxone and testosterone propionate withdrew their tails significantly faster

than animals receiving the testosterone propionate therapy alone (group XI vs. IX). In addition to this, it was observed that castrated animals receiving vehicle treatment exhibited the same degree of swim-induced increase in pain threshold as shown by castrated animals not getting any drug/vehicle treatment (Figure 1E).

## DISCUSSION

In our study, we found that swimming in water at a temperature of 25°C induces analgesia in male Wistar rats, which is consistent with previous findings.<sup>25</sup> During the study, we observed that all types of swimming protocols (single day swimming session, daily swimming with the gradual increase in duration and daily swimming of fixed duration i.e. 15 min) resulted in the elevation of pain thresholds in male Wistar rats which support the previous reports regarding swim-induced antinociception in rodents.<sup>12</sup> A comparatively lesser degree of swim-induced analgesia in castrated male rats indicates the importance of testosterone in intrinsic pain reducing mechanisms. As depicted in Figure 1A, we observed that tail flick latencies were elevated only on the day of swimming, while on weekly assessment of pain threshold after that single day swimming session of 15 min, elevated pain threshold was found to be reduced which indicated towards time limited activation of pain reducing mechanisms in the body. Animals subjected to gradually increasing daily swimming pattern (Figure 1B) were found to exhibit higher pain thresholds than animals exposed to a single day swimming (Figure 1A). The reason behind this progressive increase in pain threshold might be the up-regulation of  $\mu$  opioid receptors in the Ventral Tegmental Area (VTA) male rat's brain.<sup>30</sup> There is a high possibility of involvement of VTA in pain sensation as the intra-VTA infusion of morphine significantly reduced pain in male rats.<sup>31</sup> Expectedly, rats exposed to swimming for 15 min per day since starting achieved highest pain threshold (Figure 1C) which supports the previous finding that swim session of 15 min produces more profound anti-nociception than a shorter session.<sup>32</sup> For further exploration, we choose groups that were acquiesced to swimming for 15 min per day. Castration resulted in significantly lesser swim-induced analgesia when compared to intact animals although it was regained by testosterone propionate therapy (Figure 1D) which supports the previously documented findings that removal of testes (primary source of testosterone) has been observed to result in decreased pain threshold which was regained after testosterone supplementation,<sup>20</sup> gonadectomized male rats treated with testosterone were found to have



**Figure 1:** A) Effect of single day swimming session of 15 min duration on pain threshold.  $a=p<0.05$  vs. normal control,  $b=p<0.05$  vs. normal single day swimming; B) Effect of swimming sessions of gradually increasing time duration on pain threshold.  $a=p<0.05$  vs. normal control,  $b=p<0.05$  normal + daily gradually increasing swimming; C) Effect of daily swimming sessions of 15 min duration on pain threshold.  $a=p<0.05$  vs. normal control,  $p= p<0.05$  vs. normal daily 15 min swimming; D) Effect of testosterone replacement therapy on swimming exercise-induced analgesia in male castrated rats.  $a=p<0.05$  vs. normal control,  $b= p<0.05$  vs. normal daily 15 min swimming,  $c=p<0.05$  vs. castrated + daily 15 min swimming and olive oil treated castrated rats + daily 15 min swimming; E) Effect of naloxone on testosterone replacement therapy resulted increase in swimming exercise-induced analgesia in male castrated rats.  $a=p<0.05$  vs. normal control,  $b=p<0.05$  vs. normal daily 15 min swimming,  $c=p<0.05$  vs. castrated + daily 15 min swimming and normal saline, olive oil treated castrated rats + daily 15 min swimming,  $d=p<0.05$  vs. castrated + testosterone + daily 15 min swimming. All values are expressed in mean  $\pm$  Standard Deviation (S.D.).

longer tail withdrawal latencies in comparison of gonadectomized rats not treated with testosterone.<sup>18</sup> Our work revealed the significance of testosterone in swimming exercise-induced analgesia as the reduced analgesic effect of swimming exercise in castrated male rats was found to be restored with testosterone replacement therapy. When naloxone hydrochloride (a well-known opioid receptor antagonist) 1mg/kg was daily administered intraperitoneally (15 min prior to swimming session) to castrated rats receiving testosterone propionate therapy, a significant reduction in swim-induced analgesia (Figure 1E) was observed when compared to castrated animals treated merely with testosterone and exposed to swimming session daily for 15 min. This suppressing effect of naloxone indicated that the pain threshold enhancing the effect of testosterone in castrated male rats might be directly or indirectly mediated through endogenous opioid mechanisms. This contention is supported by some earlier documented reports such as testosterone treated

castrated male rats were found to have significantly higher levels of Proopiomelanocortin (POMC; precursor of  $\beta$  endorphins) mRNA signals in comparison of sham-treated castrated male rats and POMC mRNA signals in testosterone-treated castrated male rats were very similar to that of intact control rats,<sup>33</sup> castration decreased and testosterone increased anti-nociception produced by opioid agonists in male rats.<sup>18</sup>

## CONCLUSION

On the basis of the above discussion, it can be concluded that the regular swimming sessions might have proved to be beneficial in order to increase the pain threshold. In terms of increase in pain threshold, castrated male rats were found significantly less benefited by swimming sessions when compared to intact male rats. Treatment with testosterone propionate 500 $\mu$ g/kg/day s.c. was proved to be significantly effective in order to improve swimming exercise-induced an increase in pain threshold in castrated male rats. It indicated that the adequate existence of testosterone is required for the normal functioning of pain reducing mechanisms in the body. In addition to this, we came to the conclusion that the positive influence of testosterone on pain threshold might be mediated through its probable effect on the endogenous opioid analgesic system. In a nutshell, the deficiency of testosterone might have a negative impact on regular swimming exercise-induced increase in pain threshold of an individual. Though, it can be compensated by testosterone therapy.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

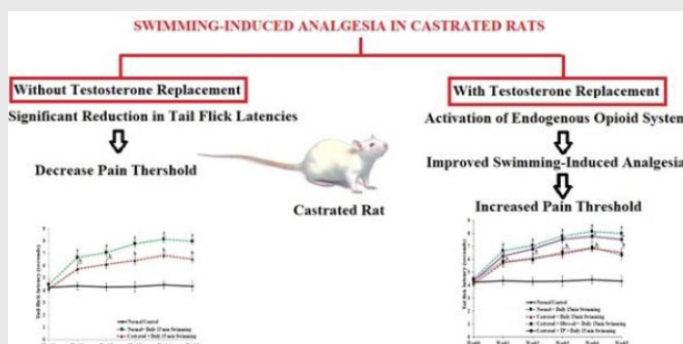
## ABBREVIATIONS

**CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals; **IAEC:** Institutional Animal Ethics Committee; **SD:** Standard Deviation; **TP:** Testosterone Propionate; **VTA:** Ventral Tegmental Area; **POMC:** Proopiomelanocortin.

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## PICTORIAL ABSTRACT



## SUMMARY

- Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.
- Exercise elevates the pain threshold by triggering the release of endogenous opioids, which activate nociceptive inhibitory mechanisms.
- It has been observed that testosterone may increase the sensitivity of adult male rats to  $\mu$  and  $\kappa$  opioid anti-nociception.
- Naloxone (a well-known opioid receptor antagonist) significantly attenuates swim-induced anti-nociceptive effects in adult rats.
- In our study, regular swimming sessions might have proved to be beneficial in order to increase the pain threshold. Castrated male rats were found significantly less benefited by swimming sessions when compared to intact male rats in terms of increase in pain threshold.
- Treatment with testosterone propionate 500 $\mu$ g/kg/day s.c. was proved to be significantly effective in order to improve swimming exercise-induced an increase in pain threshold in castrated male rats.
- The positive influence of testosterone on pain threshold might be mediated through its probable effect on the endogenous opioid analgesic system, which is confirmed by the intraperitoneal administration of naloxone. Concisely, the deficiency of testosterone could adversely affect regular swimming exercise-induced increase in pain threshold of an individual. Although, testosterone therapy can compensate for it.

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