INFFLUENCE OF TESTOSTERONE ON MORPHINE ANALGESIA INALBINO RATS

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Summary : Pain threhshold for thermal stimulus after morphine, naloxone alone and naloxone in combination with morphine was studied in male rats before and after three days treatment with testosterone. It was also determined 15 days after gonadectomy and administration of testosterone in such rats.

There was significant reduction in morphine analgesia after administration of testosterone and also after gonadectomy. Naloxone increased the pain threshold in gonadectomised rats and it enhanced morphine induced analgesia instead of antagonising it. Naloxone, however, had no effect on morphine analgesia in testosterone treated control rats and gonadectomised rats.

Key words : morphine testosterone thermal stimulus naloxone gonadectomy

INTRODUCTION

Mangat *et al.* (2) reported that testosterone administration in conscious monkeys caused inhibition or potentiation of evoked responses like stimulation of skin, abdomen and nipples in a specific manner. Genitosensory motor cortex under such circumstances exhibited potentiation of evoked responses. Accordingly they proposed genital afferent input as playing a selective role in facilitation of E.E.G. activity in venteromedial nucleus and anterior hypothalamic nucleus.

It has also been observed that there is a significant reduction in pain threshold after testosterone administration to male albino rats and a marked increase in pain threshold after castration. This increase disappeared after administration of testosterone to castrated rats (3), Encephalins and endorphins affect appreciation of pain besides subserving a variety of other cerebral functions, They mimic the actions of opiates, In view of these considerations a study was undertaken to investigate if morphine analgesia is influenced by pr esence of testosterone.

MATERIAL AND METHODS

Male albino rats (100-180 *gm*) were used for the study in groups of 10. Tail withdrawl time on thermal stimulus was determined following the method of Bonnycastle (1) using analgesiometer (Techno Electronics, Lucknow). Three readings were taken at 30 min intervals daily for 3 consecutive days. Mean of such 9 readings was considered Rats showing marked variation in withdrawl time were replaced by those showing consistent withdrawl time.

It was found in the preliminary experiments that the influence of morphine started within half an hr, reached its peak value at 1-3 hrs and lasted for 4 hrs after im injection. All the observations were therefore made between 1-3 hrs after the injection of morphine (300 *µg/kg*) and the tail withdrawl time was noted at 1,2 and 3 hrs. The tail withdrawl time was determined in the same rats on 4th day after three days treatment with testosterone (*1 mg/kg*, im) and after injecting morphine 300 *µg/kg* (im).

Seven days after the last testosterone injection gonadectomy was performed under ether anaesthesia. Sham operation was done in animals of control group. Sixteen days later tail withdrawl time was again determined before and after injection morphine (300 *µg/kg*). After a lapse of seven days naloxone (1 *mg/kg*, im) was injected in the gonadectomised animals and the same procedure repeated. Statistical analysis was done using Student's 't' Test.

RESULTS

The results are presented in Table I. There was a significant increase in tail withdrawl time after morphine injection in normal rats but it was decreased after castration as well as after testosterone treatment in the same rats. Testosterone treatment in castrated rats, however, restored it to the precastration level. Naloxone (1 *mg/kg*) antagonised the morphine-induced increase in tail wthdrawl time in control, testosterone-treated and testosterone-treated castrated rats. Naloxone did not antagonise morphine induced increase tail withdrawl time in castrated rats. Naloxone caused increase in tail withdrawl time in castrated rats who did not receive additional testosterone treatment and potentiated morphine induced increase in tail withdrawl time.

TABLE I : Effect of morphine and naloxone on tail withdrawl time of male albino rats ± S.D.

Treatment	*Mean tail withdrawl time (sec. ± S.D.)*		
	Control	*Morphine 300 µg/kg*	*Naloxone+Morphine (1 mg/kg)*
1. Nil (Control)	6.6±0.5	15.8±0.61**	8.3±0.52
2. Testosterone	5.2±0.78*	10.5±0.5*	8.5±0.92
3. After Castration	13.6±0.84**	10.5±0.8*	19.8±1.34**
4. Castration+Testosterone as in (2)	6.4±0.61*	14.2±0.81**	9.8±0.92**

There were 10 animals in each group. Comparisons were made between 1 and 2, 1 and 3 and 3 and 4 (*$P<0.05$; **$P<0.01$ t-test).

DISCUSSION

Morphine increased tail withdrawl time on application of thermal stimulus to control rats. This increase was reduced if the rats were either treated with testosterone or castrated i.e. in presence of higher level of testosterone and in absence of testosterone. This raises the question of role of this hormone in morphine analgesia and hormonal effect on the sensitivity of opiate receptors. endogenous peptides, pain pathways and pharmacokinetics of morphine

Castration *per se* increases the pain threshold and testosterone administration restores the pain threshold to precastration level (3). After administration of morphine it plunges to a level lower than one obtained afrer castration.

Hyperalgesia in place of analgesia is produced by morphine in testosterone defecient rats. It is for consideration if in such rats morphine antagonises endogenous opiates or leads to production of a compound which decreases pain threshold or to altered sensitivity of receptors.

In control rats naloxone prevented the increase of tail withdrawl time by morphine. In gonadectomised rats naloxone further increased the tail withdrawl time by morphine, Naloxone enhanced the action of morphine in gonadectomised rats as opposed to antagonism seen in control rats.

Naloxone, however, had no effect on morphine analgesia in testosterone treated control rats as well as castrated rats. This could be due to high testosterone levels.

Naloxone has been reported to augment nociceptive responses and produce hyperalgesia in both rats and mice in a variety of experimental models employing thermal, mechanical, electrical and chemical stimuli (4). There is a reversal of action of morphine and naloxone in testosterone defecient rats. Naloxone however had no effect on morphine analgesia in normal rats treated with testosterone; this could be due to hormonal level being higher than normal. The influence of testosterone on response to noxious stimulus and action of morphine and naloxone seems to be complex.

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