# THE ROLE OF ENDOGENOUS OPIOIDS IN THE THERMOREGULATORY CAPACITY OF AGED RATS

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*SUMMARY: It has been shown that endogenous opioids are involved in the adaptive mechanisms related to stress. The adaptive competence of an organism is known to decline with age. In this experiment, age related changes in the thermoregulatory capacity of rats and the role of endogenous opioids in this mechanism were studied using the ice-water immersion test. Young (7-8 month old) and old (16-18 month old) rats were used. Opioid activity was evaluated indirectly using the specific opiate antagonist naloxone. Restoration of body temperature was significantly slower in old rats ($p<0.05$). Following naloxone administration, there was an increased drop in rectal temperature and a decreased rate of recovery in old rats ($p<0.05$). This indicated that the thermoregulatory response was significantly impaired in old rats when compared to young rats. It is concluded that a naloxone-reversible opioid activity plays a role in thermoregulatory competence. This role appears to be more critical with increased age.*

*Key Words: Endogenous Opioids, aging, naloxone, thermoregulatory competence.*

## INTRODUCTION

The ability to overcome various types of stress and show adaptation to changes in the environment decreases with age (15). One of the mechanisms known to play a part in the response of an organism to stress is activation of the endogenous opioid system (5,10). Endogenous opioid peptides (EOP) are substances which are produced in the body and take part in various functions as hormones or neuromodulators. There are studies showing that the opioid system also undergoes age related changes. The concentrations of beta endorphin, dynorphin and the enkephalins in the hypophysis, hypothalamus and certain other regions of the brain, and the concentration and affinity of the opioid receptors in various regions of the brain of young and aged experimental animals have been reported to show significant differences (4,9,11,12,16).

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One of the functions in which the opioid peptides play a role is the regulation of body temperature (1). Thermoregulatory capacity is known to decrease to some extent with aging (13). The aim of this study was to investigate the change in thermoregulatory response and adaptation capacity with aging in experimental animals and to determine the role of endogenous opioid peptides in these changes.

## MATERIALS AND METHODS

In our experiment 7-8 month old (206.8 ± 4.46 gr) and 16-18 month old (335.5 ± 11.58 gr) Swiss albino rats were used. Each age group consisted of 10 rats.

The thermoregulatory compensatory capacity was measured by three minute whole body immersion in ice water (13). The rectal temperature was recorded and 0.5 cc saline or naloxone hydrochloride (Du Pont Pharmaceuticals, 5 mg/kg) was injected intraperitoneally prior to the start of the experiment. Each rat was

placed in a plastic cage and immersed in ice water. The animal was removed three minutes later and placed in a straw-filled box. The rectal temperature was measured every three minutes for the first 15 minutes, then every 10 minutes until the initial temperature was reached. The experiments were carried out between 9.00 and 13.00, at a room temperature of 18-21°C. The animals were given food and water *ad libitum*.

Rectal temperature measurements were carried out with the Yellow Springs Instruments (YSI) Telethermometer. A type 302 thermistor probe was inserted 6 cm into the rectum, and the temperature was recorded after 30 seconds. Temperature changes were expressed as mean ±SEM. Statistical analyses were made using the Student t test.

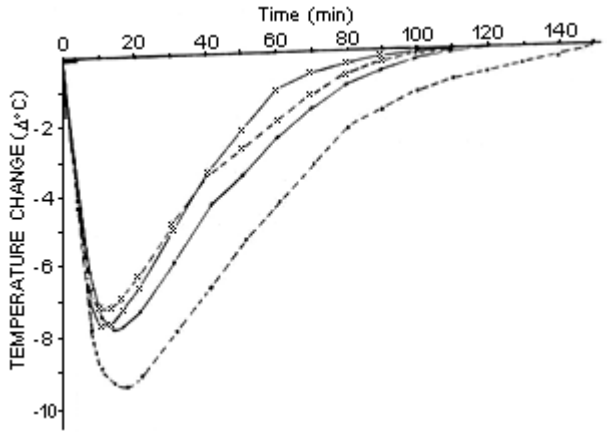


Figure 1: Differences in body temperature changes in young and old rats following 3 min whole body ice-water immersion. Rats were immersed in ice-water at 0 time, and removed 3 minutes later (—).

.—. old, salin x — x young saline
.------. old, naloxone x-----x young, naloxone

RESULTS

Measurement of body temperature following ice-water immersion showed an initial drop followed by a return to initial levels in both young and old rats. The changes in rectal temperature are given in Figure 1. Starting from the 3rd minute, the body temperatures in all the groups showed a significant difference compared with the initial level ($p<0.001$). In the young group this difference became insignificant at the 70th minute and in the old group at the 110th minute. After naloxone administration this difference became insignificant in the young group at the 90th minute and in the old group at the 140th minute ($p>0.05$).

Table 1: Interval between initation of cold application and return to initial rectal temperature-Recovery Time (min ±SE).

| | Saline | Naloxone | P |
|---|---|---|---|
| Young | 74.00 ± 6.00 | 80.00 ± 9.57 | > 0.05 |
| Old | 102.50 ± 5.54 | 134.50 ± 13.28 | < 0.05 |
| P | < 0.05 | < 0.05 | |

Table 2: Time taken to reach the lowest rectal temperature (mean±SE).

| | Saline | Naloxone | P |
|---|---|---|---|
| Young | 9.90 ± 0.46 | 10.20 ± 0.66 | > 0.05 |
| Old | 12.90 ± 0.64 | 13.50 ± 0.50 | > 0.05 |
| P | < 0.05 | < 0.05 | |

Table 3: Rate of fall in rectal temperature to lowest level (ΔT°C/min ± SE).

| | Saline | Naloxone | P |
|---|---|---|---|
| Young | 0.789 ± 0.040 | 0.709 ± 0.709 | > 0.05 |
| Old | 0. 614 ± 0.062 | 0.704 ± 0.025 | > 0.05 |
| P | < 0.05 | > 0.05 | |

The greatest drop in temperature was 7.63±0.44°C in the 9th minute in the young group, while in the old group this drop was 7.70±0.44°C in the 12th minute. The differences between temperatures of the two age groups at the 9th and 12th minutes were statistically insignificant ($p>0.05$). After naloxone administration the drop in temperature in the young group was 7.17±0.96°C in the 9th minute, and in the old group 9.32±0.23°C in the 15th minute. On comparison of the changes at the 9th, 12th and 15th minutes it was seen that the difference in temperature between the two age groups became progressively greater, and was statistically significant at the 15th minute ($p<0.05$).

The time required for restoration of normal body temperature from the initiation of cold immersion is called the Recovery Time. The comparison of the Recovery Time in old and young rats is given in Table 1. It is seen that this value is greater in old rats. Naloxone did not affect the Recovery Time in young rats, but caused a significant increase in old rats.

Comparison of the heat loss in the two age groups shows that the rate of temperature drop is slower in old rats, and that the drop continues for a longer time (Tables 2,3). Naloxone had no effect on these parameters in either age group.

Table 4: Interval between lowest rectal temperature and return to initial temperature (min±SE).

| | Saline | Naloxone | P |
|---|---|---|---|
| Young | 64.10 ±5.72 | 69.80 ±9.30 | > 0.05 |
| Old | 89.60 ±5.41 | 121.00 ±12.98 | < 0.05 |
| P | < 0.05 | < 0.05 | |

Table 5: Rate of rise in rectal temperature from the lowest temperature to the initial value ($\Delta T^{o}C$/min±SE).

| | Saline | Naloxone | P |
|---|---|---|---|
| Young | 0.125 ± 0.007 | 0.105 ± 0.004 | < 0.05 |
| Old | 0.088 ± 0.007 | 0.086 ± 0.009 | > 0.05 |
| P | < 0.05 | > 0.05 | |

The interval between the lowest rectal temperature and return to initial temperature was significantly longer in old rats (Table 4). The rate of return of body temperature from the lowest level to the initial value was found to be significantly lower in old rats (Table 5). The time interval for this rise in temperature was unchanged by naloxone, while the rate of rise of temperature was significantly decreased in young rats (Tables 4,5). As seen in Figure 1 this decrease developed especially after the 40th minute. In old rats, this time interval was significantly greater, while the rate of rise in temperature was unchanged by naloxone.

## DISCUSSION

Segal and Timiras reported that the ability to maintain body temperature was reduced and the recovery mechanism was disturbed with age (13). This finding is accepted as a sign of physiologic aging (15). The longer Recovery Time in old rats in our study is in agreement with this report. The significantly lower rate of return of body temperature from the lowest value and the longer interval for this return in old rats suggest that activation of mechanisms responsible for heat gain and prevention of heat loss is delayed and that thermoregulatory competence declines with aging.

EOP's play a role in the response of the organism to various stress conditions of even a few minutes duration (10). Although there is some disagreement about the tonic activity of the opioid system in the thermoregulatory mechanism, it is accepted that this system is involved in circumstances requiring regulation of body temperature (1,6,14). In our study, the depressant effect of naloxone on the Recovery Time in old rats indicates a role for the EOP's in the thermoregulatory response.

The effects of naloxone during the rising phase of the temperature changes suggest that the effect of EOP's is seen in the homeostatic mechanisms involved in the return of body temperature to normal levels. This is in agreement with reports that EOP's are involved in adaptation to cold and that naloxone has a hypothermic effect in cold due to its inhibitory action on the heat gain mechanism (1,14). In addition, the release of stress activated endogenous opiodis has a hyperthermic action which can be blocked by naloxone (2,3).

Aging has been shown to produce changes in opioid concentration and receptor density in the brain (4,11,16). Other studies report findings of decreased endogenous opioid activity in analgesia, feeding and immune mechanisms with aging (7,8,12). The changes in the receptors and distribution of EOP's may be responsible for this decrease in opioid functions. In our study it was found that the naloxone reversible heat-gaining opioid activity was greater in old rats than in young rats. In rats activation of the mu receptors which are located primarily in the brain causes increased heat gain. In contrast, activation of kappa receptors, which are outside the brain, produces heat dissipation (1). Furthermore it has been reported that, even though the total receptor number may not change with age, there is a change in the receptor type, and mu receptors increase (12). In addition, the decrease in the effectiveness of other stress-responsive neuroendocrine mechanisms may underlie an increased need for opioid activity. While young rats require the opioid response less and at a later stage, it may be possible that old rats make maximum use of this response. It is clear that further studies are necessary on this subject.

In conclusion our experiments suggest that endogenous opioid peptides play a role in the recovery mechanism in rats following ice-water immersion and that opioid activity is more important in old rats than in young rats.

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