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EFFECT OF MELATONIN ON BODY TEMPERATURE IN THE RABBITS

(With 3 Fig.)

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تأثير الميلاتونين على درجة حرارة الجسم في الأرانب

امتثال مصطفى ، ابتسام المليجى
ممدوح أنور

أحدث الحقن الوريدى للميلاتونين بجرعات ١ر٠ – ١ مجم/كجم من وزن الجسم فى ذكور الارانب البالغه انخفاضاً معنوياً فى درجة حرارة الجسم المقاسه عن طريق الشرج . وتم الحصول على أقصى تأثير (حوالى ٩ر٠ م) بعد ١٥ دقيقه من حقن أعلى جرعه وهى ١ مجم/كجم . وبالاضافه الى ذلك قاوم الميلاتونين الارتفاع فى درجة الحراره المحدث بواسطة البروستاجلاندين – F2α .

وكان تأثير الميلاتونين الخافض للحراره فى الأرانب مرتفعة الحراره أوضح منه فى الارانب ذات درجة الحراره الطبيعيه . ولم يضاد الاتروبين والهيدرجين والبروبرانولول تأثير الميلاتونين الخافض للحراره .

ونستخلص من ذلك أن الميلاتونين يخفض درجة حرارة الجسم فى الأرانب ذات درجة الحراره الطبيعيه وكذلك فى الارانب مرتفعة الحراره ، وأن تأثير الميلاتونين الخافض للحراره ليس عن طريق مستقبلات الادرينالين أو مستقبلات الاستيل كولين . ويحتمل أن يكون عن طريق التأثير المباشر الباسط لجدار الاوعيه الدمويه أو يعمل مركزياً بمنع تخليق واطلاق البروستاجلاندين .

SUMMARY

Intravenous administration of melatonin at doses of 0.1-1 mg\kg BW in mature male rabbits decreased the rectal temperature. The maximum effect, about 0.90 °C, was reached with the highest dose (1 mg/kg) at 15 min after injection of melatonin. In addition, melatonin antagonized the prostaglandin F2α (PGF2α)-induced hyperthermia. The hypothermic effect of melatonin in hyperthermic rabbits was more marked than that in animals with normal body temperature. Atropine, hydergine and propranolol did not antagonize the hypothermic effect of melatonin. It can be concluded that melatonin decreases the body temperature in normal rabbits as well as in rabbits with hyperthermia. These results suggest that the hypothermic effect of melatonin is not mediated through the cholinergic or adrenergic receptors and may be due to its direct relaxant effect on the wall of the blood vessels. Also, melatonin may act centrally through inhibition of PG synthesis and release.

Keywords: Melatonin, body temprature and rabbits.

INTRODUCTION

The circadian nature of the body temperature rhythm in animals exposed to natural photoperiods is essentially an endogenous phenomenon *(ASCHOFF, 1963)*.

There is evidence suggesting that the pineal gland may be involved in modulation of photic stimuli. The pineal gland of different species is firmly established as a photosensitive transducer (*HANYA and NIWA, 1970 and HISANO* et al., *1972)*, and in mammals this gland has been assigned the role of an indirectly photosensitive, neuroendocrine transducer *(WURTAM and ANTONY-TAY, 1969 and KAPPERS, 1971)* receiving signals generated by light and dark and transmitting information to centers in the brain that mediate and synchronize biological rhythms. One such rhythm, that of core temperature, may be modulated by the photic environment through a neural path that includes the pineal organ *(BINKLEY* et al., *1971 and UIRICH* et al., *1974)*.

In house sparrows, for instance, the pineal structure has been implicated in thermoregulation as well as regulation of the circadian rhythm of body temperature *(BINKLEY* et al., *1971)*.

VISWANATHAN and JOHN, (1986) suggested that melatonin brings about thermoregulatory adjustments necessary for hibernation in Syrian hamster.

The present study was made on the effect of melatonin on rectal temperature in the unanesthetized unrestrained male rabbits as well as in rabbits with induced hyperthermia. Further study on the possible mechanism of action of melatonin was done.

MATERIAL and METHODS

Mature male rabbits 6 months old, 1-1.5 kg BW were maintained under controlled conditions of temperature and illumination, with a lighting schedule of 14h light and 10h darkness. Animals were caged individually and provided free access to food and water. Rabbits were divided into groups, 6 animals each.

Melatonin (Sigma chemical company) and prostaglandin F2α(PGF2α) (supplied by Upjohn company) used to induce hyperthermia *(KARPPENEN* et al., *1979)*, were administered intravenously (iv).

The temperature was measured with a thermistor probe connected to a Washington 400 MD 4C oscillograph Biosciences Kent UK. The temperature was calibrated in a constant temperature bath at 36, 37, 38, 39, 40, 41, 42 and 43°C immediately before each experiment (The calibration curve).

Rabbits of group one were used to study the effect of melatonin (0.1, 0.5 and 1 mg/kg BW, iv injected) on the body temperature. Rectal temperature was measured at 0 min (control value) and after 1min, 5min, 10min and 15min post-melatonin administration. Since multiple doses of melatonin were used, a period of 30min was allowed to elapse before injection of the consequent dose of melatonin.

Rabbits of group 2 were used to study the effect of the maximal effective dose of melatonin on PGF2α-induced hyperthermia. PGF2α was administered iv in a dose of 0.5 mg/kg BW. 30 min after PGF2α, melatonin was iv injected in a dose of 1 mg/kg BW. Rectal temperature was measured before PGF2α, 30 min after its injection(which was considered to be the control value) and 1, 5, 10 and 15min post melatonin administration.

rabbits of group 3 were tested with 1mg/kg BW iv melatonin after receptor blockade treatment. Cholinergic blockade was performed with 3mg/kg iv atropine, alpha adrenergic blockade with 0.1mg/kg iv hydergine and beta-adrenergic blockade with 2mg/kg iv propranolol. Rectal temperature was measured at 0 min (control value) and 15min after melatonin injection.

All data were reported as mean ± standard error(SE). Comparisons of treatment effects were made with student t-test.

RESULTS

Effect of melatonin on rectal temperature (Fig 1).

Melatonin at the iv doses of 0.1, 0.5 and 1mg/kg induced a hypothermic effect. A nonsignificant reduction in mean rectal temperature was observed after 0.1mg/kg melatonin. A significant reduction in the mean rectal temperature was observed after 0.5 mg/kg melatonin from the control value of 40.35 ± 0.11°C to 39.93 ± 0.095°C (P<0.05) after 1min, to 39.87 ± o.11 °C (P<0.05) after 5 min and to 39.77 ± 0.09°C 10 min after melatonin injection. The maximum effect, about 0.58°C was reached 10 min post-injection. After 1mg/kg melatonin, the mean temperature was significantly reduced from the control value of 40.35 ± 0.11 °C to 39.73 ± 0.1°C (P<0.05), 39.63 ± 0.048 °C (P<0.01), 39.80 ± 0.12°C (P<0.05) and 39.45 ± 0.15°C (P<0.01)after 1, 5, 10 and 15 minutes respectively. The maximum effect, about 0.90°C was reduced at 15 min post injection.

Effect of melatonin on PGF2α -induced hyperthermia (Fig 2)

Intravenous administratin of PGF2α (0.5 mg/kg) induced hyperthermia. The mean temperature was significantly increased from a control value of 40.05 ± 0.15°C to 41.98 ± 0.23°C (P<0.001). Intravenous injection of melatonin (1mg/kg) in rabbits pretreated with PGF2α, partially antagonised the hyperthermic effect of PGF2α. the mean temperature was significantly decreased from a control value of 41.98 ± 0.23°C to 41.10 ± 0.20 (P< 0.05) and 40.47 ± 0.15°C (P< 0.05) after 5 and 10 min post injection of melatonin. The maximum effect, about 1.01°C was reached at 10 min post-injection.

Effect of melatonin after hydergin, propranolol or atropine pretreatment (Fig 3).

The hypothermic effect of melatonin was not significantly influenced by cholinergic receptor and alpha and beta-adrenergic receptor blockade.

DISCUSSION

Intravenous administration of melatonin at the doses of 0.1-1 mg/kg BW decreased the body temperature of adult malt rabbits. The maximum effect, about 0.90°C, was reached with the highest dose (1mg/kg) at 15 min post-injection. In addition, melatonin antagonized the PGF2α -induced hypothermia, The maximum effect, about 1.01°C, was reached at 10 min post-injection. The hypothermic effect of melatonin in hyperthermic rabbits was more marked than in animals with

normal body temperature. Atropine, hydergine and propranolol did not antagonize the hypothermic effect of melatonin.

Our data confirm and extend other researches demonstrating the hypothermic effect of melatonin in other species. Pharmacological doses of melatonin given during day light hours are hypothermic in the mouse *(ARUTYUNYAN et al., 1964)* and rat *(BARCHAS et al., 1964)*.

WEITZMAN et al., (1979), WEVER (1979) and *STRASSMAN et al., (1991)* found that melatonin secretion contributes to the lowering of core body temperature seen in the early morning in humans. They found that sleep deprivation in "nonbiologically" active light regularly raises rectal temperature in human by 0.2-0.3°C. *STRASSMAN et al., (1991)* measured rectal body temperature in normal men whose melatonin levels were suppressed by all-night sleep deprivation in bright-light and compared the values with those seen in sleep in the dark, sleep deprivation in dim-light and sleep deprivation in bright-light with an infusion of exogenous melatonin that replicated endogenous levels. Minimum rectal temperature, calculated from 2300 to 0515 h (36,64°C) was greater in bright-light sleep deprivation than in conditions of sleep deprivation in dim-light (36.06°C). An exogenous melatonin infusion in bright-light returned the minimum temperature to that seen in dim-lihgt sleep deprivation (36.34°C).

Removing circulating melatonin by pinealectomy decreased evaporated water loss and elevated core temperature in heat stressed rats, relative to intact animals *(HARLOW, 1987)*. In humans, both rectal temperature and plasma melatonin demonstrate a well established circadian rhythm. The temperature minimum occur in the early morning *(WEITZMAN et al., 1979)* similar to the timing of peak plasma melatonin levels *(STRASSMAN et al., 1987)*. *SHANAHAN and CHARLES (1991)* found that the time of the fitted maximum of the endogenous rhythm consistently preceded the fitted temperature minimum by a mean of ± SE of 1.8 ± 0.2 h. They also found that bright-light exposure induced substantial and equivalent phase shifts of the melatonin and temperature rhythm (mean ± SE difference in the phase shifting response, o.03 ± 0.32 h). Similar results was obtained by *CAGNACCI et al., (1992)*. They demonstrated that the time course and amplitude of nocturnal melatonin secretion were temporally coupled with the decline of core body temperature.

Core temperature is a result of counterbalancing effect of heat production and heat dissipation by central and peripheral mechanisms. Decrease in metabolic rate may be produced by beta-adrenergic receptor blockade. In addition heat loss may be

facilitated by peripheral vasodilatation induced by alpha-adrenergic receptor blockade *(HOFFMAN et al., 1986).*

WFNGER et al., (1976) and STEPHENSON et al., (1984) demonstrated that thresholds for sweating and vasodilatation/ cutaneous blood flow which mediate much of the heat loss from the extremities were lowest at 0400 h, when core temperature is lowest in humans.

Our results indicate that cholinergic receptor and alpha and beta adrenergic receptor blockade did not attenuate the hypothermic effect of melatonin. It might be concluded that the hypothermia produced by melatonin was not mediated through cholinergic nor adrenergic mechanisms. This indicate that melatonin may act directly on the smooth muscle causing vasodilatation. Melatonin induced vasorelaxing effect on rabbit bassilar artery *(SHOJE et al., 1989),* rabbit aorta *(SATAKE et al., 1991)* and rat aorta *(BRUCE, 1991).*

Another possible mechanism of the action of melatonin on body temperature is that melatonin may inhibit the synthesis and release of PGF2α. The present results showed that melatonin antagonized the hyperthermic effect of PGF2α. The maximum effect, about 0.90 C, was reached at 15 min post melatonin injection in normal rabbits, versus 1.01C reached at 10 min after its injection in rabbits with PGF2α -induced hyperthermia. Prostaglandin of E and F series are highly active hyperthermic agent in the brain *(MILTON, 1976; SPLAWINSKI et al., 1978 and HOFFMAN et al., 1986). LEWINSKI and PAWLIKOWSKI (1986)* found that melatonin alter PGF2α synthesis. *MOHAMED and EMTETHAL (1990)* concluded that melatonin has some similar effect to that of indomethacin on PGs. *EMTETHAL (1990)* suggested that the suppressive effect of melatonin on the local vascular permeability in rat skin was through the inhibition of PG synthesis.

In conclusion, results here indicate that melatonin decreases the body temperature in normal rabbits as well as in rabbits with hyperthermia. The hypothermic effect of melatonin may be due to its direct relaxant effect on the wall of the blood vessels. Also, melatonin may act centrally through inhibition of PG synthesis and release.

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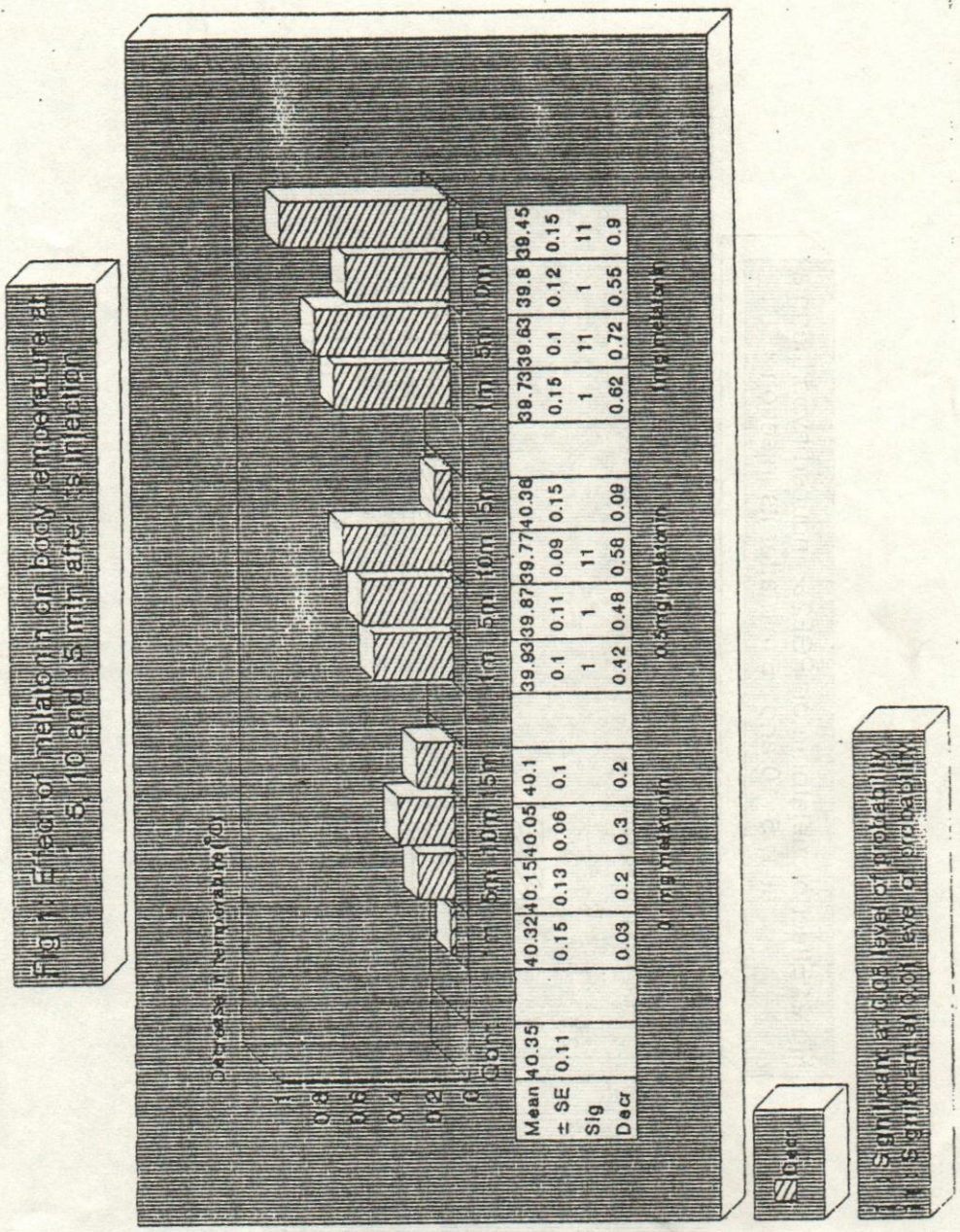
Fig 1: Effect of melatonin on body temperature at 1, 5, 10 and 15 min after i.v injection
Decrease in temperature (C)
1
0.8
0.6
0.4
0.2
0
1m 5m 10m 15m
0 mg melatonin
0.5mg melatonin
Mean 40.35 40.32 40.15 40.05 40.1 39.93 39.87 39.77 40.38 39.73 39.63 39.8 39.45
± SE 0.11 0.15 0.13 0.06 0.1 0.1 0.11 0.09 0.15 0.15 0.1 0.12 0.15
Sig 1 1 11 1 11 1 1
Decr 0.03 0.2 0.3 0.2 0.42 0.48 0.58 0.08 0.62 0.72 0.55 0.9
1mg melatonin
Decr
Significant at 0.05 level of probability
Significant at 0.01 level of probability

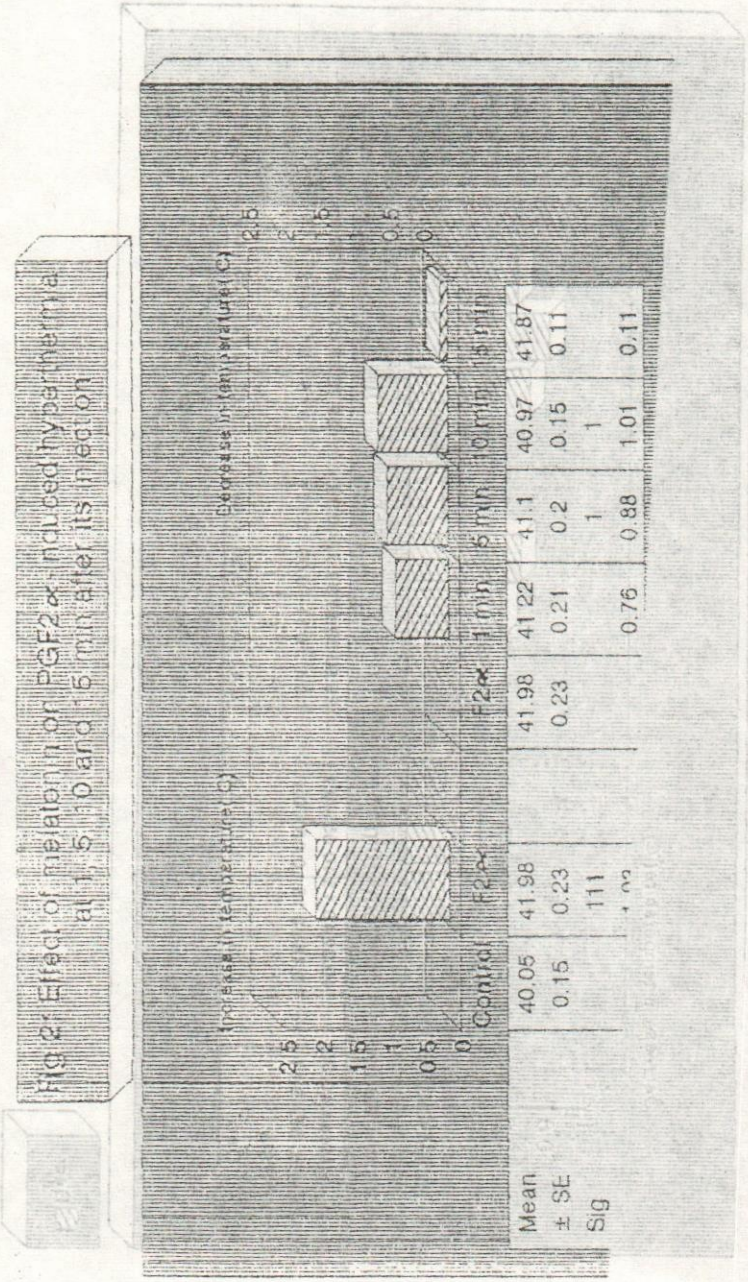
Fig 2: Effect of relaxin on PGF2α induced hyperthermia at 1.5 ug and 5 min after its injection
Increase in temperature (C)
2.5
2
1.5
1
0.5
0
Control
F2α
1 ug/ml
5 ug/ml
10 ug/ml
15 ug/ml
Mean
± SE
Sig
40.05
0.15
41.98
0.23
41.98
0.23
41.22
0.21
0.76
41.1
0.2
0.88
40.97
0.15
1.01
41.87
0.11
0.11

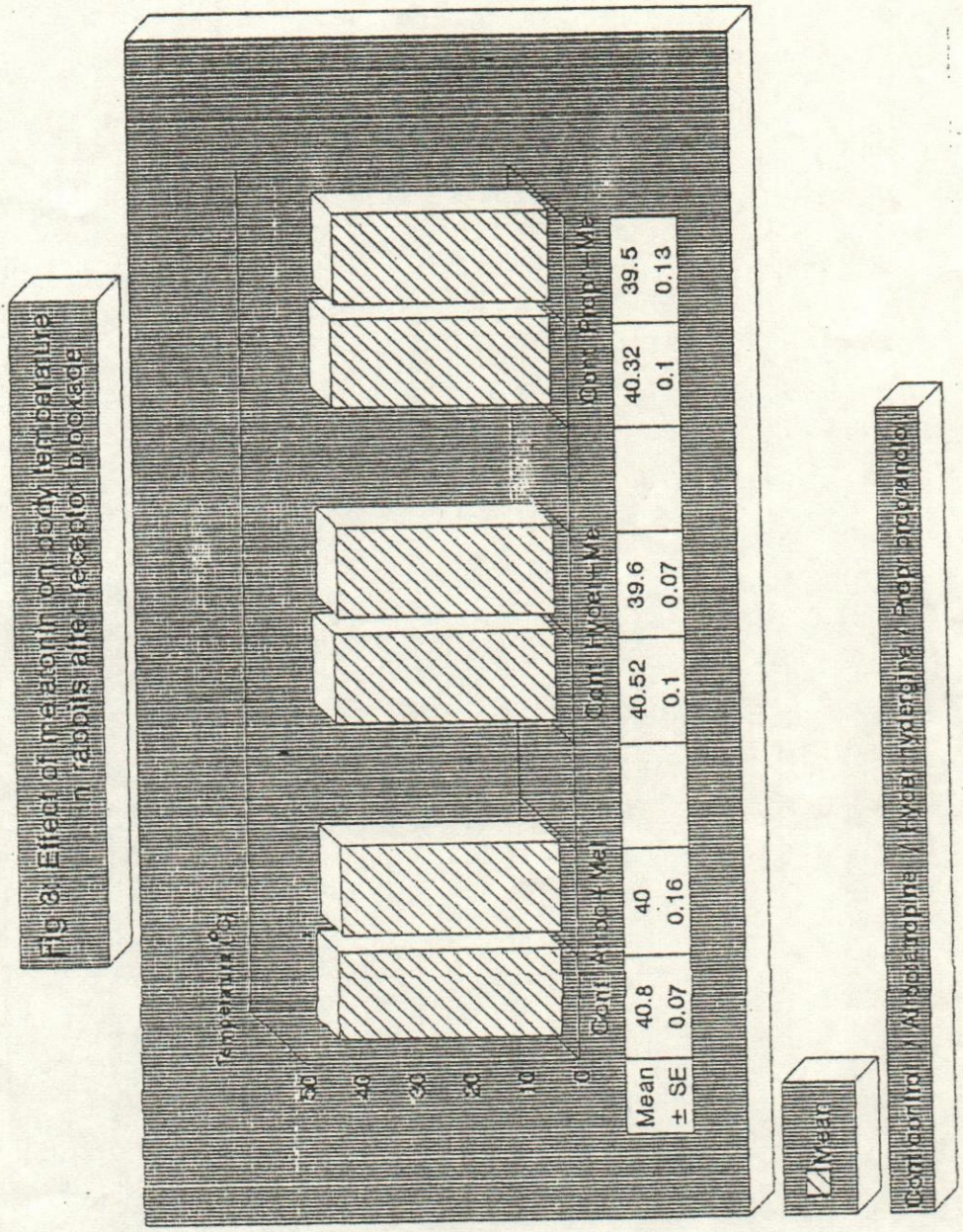

Fig 3: Effect of melatonin on body temperature in rabbits after receptor blockade

Mean ± SE
40.3 0.07
40 0.0
40.2 0.1
39.6 0.07
40.32 0.1
39.8 0.0