INTRODUCTION

The regulation of body temperature

One of the most beautiful example of the circadian rhythms is the physiological regulation of body temperature. Peripheral warm triggers arrive via the C-fibres, while the cold triggers arrive via the C and Aδ-fibers to the central thermoregulatory areas. Regarding the function of these central brain areas there have been a lot of controversies. Nowadays the most plausible explanation for the operation of the CNS thermoregulatory areas is by the „set-point" theory. The preoptic area of the hypothalamus and a part of the anterior hypothalamus can be selectively triggered by central or peripheral therma stmuli that will result in compensatory thermoregulatory responses. In particular, if small thermodes are applied to warm the preoptic area, immediate and profound sweating is observed along with vasodilation all over the body. Synchronously with this, some thermogenetic processes will be inhibited. As a result of this, in humans 0.1-0.2 ^{o}C deflection form the set point will trigger thermoregulatory responses allowing an interthreshold range of the temperature regulation about 0.2-0.4 ^{o}C largely independent of gender, but increasing with age.

Characterization of circadian rhythms

Such rhythms showing about a 24 hours cyclicity are called daily rhythms, when an external cue such as light/darkness is present. If this daily rhythm is endogenously generated (approximately 24 hr) we call it a circadian rhythm. The duration of the rhythms might be longer or shorter than 24 hours, but the environmental factors set their rhythmicity exatly to 24 hr. The rhythm is ultradian if is repeated within 24 hours, and infradian if its duration exceeds one day. Under steady environmental conditions these rhythms „free run", meaning that their periodicity is more or less 24 hour. Circadian rhythms can be characterized with the amplitude, period, acrophase and the mesor. These chacteristics are depicted on Figure 1. The aforementioned preoptic area has some connections with the suprachiasmatic nucleus (SCN). The activity of this structure is required for the development of the circadian temperature oscillation. There is a ventrolateral (core) and a dorsolateral (peripheral) region in the SCN. The neurons of the ventrolateral region, transmitting with GABA and VIP do not possess intrinsic activity, while the dorsomedial part exhibits rhythmic activity and the transmitters here are GABA and AVP. The sensory triggers to the ventrolateral region project to the dorsomedial part. Regarding the function of the SCN, it seems to be the main „zeitgeber" (time giver), with a period time (τ) slightly longer than 24 hrs in humans

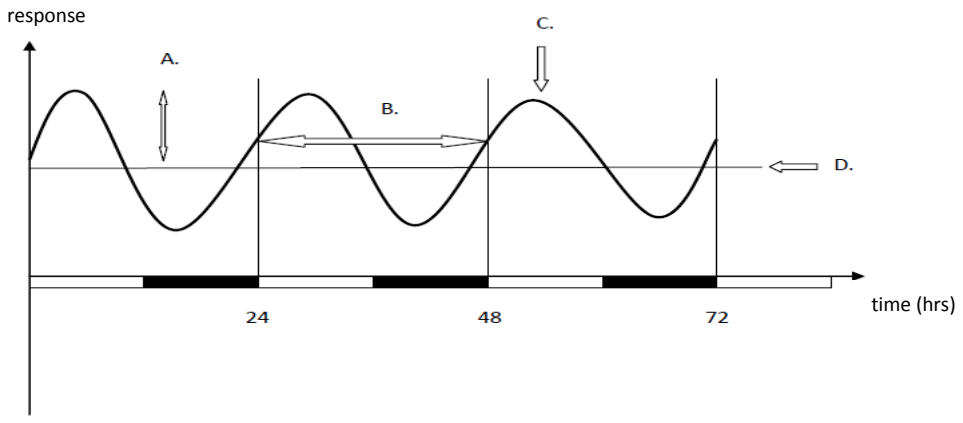

Figure 1. General characteristics of circadian rhythms. Amplitude (Ax2), period (B), acrophase (C) amd mesor (D) are depicted.

The role of the clock genes

The mammal circadian clock was studied in detail is now believed to form the physiological and biochemical background of the human circadian activity. The RNA, produced by the expression of the „clock-genes" is processed further via posttranslational steps. The mRNA produced by these steps induces the synthesis of different proteins, that acting together and having agonist and antagonist effects set up the oscillation of the endogenous clock. These proteins are named as CLOCK, BMAL1, ROR and REV-ERB.

Effects of surgical anaesthesia on the thermoregulation.

Surgical anaesthesia, let it be general or neuraxial, always results in loss of some heat in most patients. Under general anaesthesia due to the administered drugs there is a 1-1.5 ^{o}C decrease in core temperature. The main cause of this hypothermia is heat redistribution that arises from the direct vasodilatatory effects of anaesthetics and also from fall of the thermoregulatory threshold below the core temperature during anaesthetic procedures.

In human surgical anaesthesia the first exponential phase is followed by the linear phase that is more or less associated with the second hour of the anaesthesia and results in a slower decrease of body temperature than that of the exponential phase. This is probably due to a significant decrease in body energy metabolism.

The third, or plateau phase starts at the 3rd and 4th hour of anaesthesia. This can be active, or passive depending on the efficiency of compansatory mechanisms. During the passive plateu phase the thermoregulatory counter-mechanisms are not activated and can be observed only if the duration of the operation is not too long and if due attention is paid to artificial heat conservation.

During neuraxial anaesthesia heat loss is increased below the level of the block, due to vasodilation, but the paralysed nerves will not conduct this signal to the brain. The cold blood from the lower body will mix with the warm blood cooling the body and causing shivering without feeling the cold. This phenomenon is called paradoxical shivering.

Effects of surgical and fasting stress

Any surgical insult even with the most precise anaesthetics imposes a huge burden of stress to the body. It does not make a difference what kind of stress affects the organism, the response is universal. The extent of the response depends on the energy reserves of the body and also on the amount of stress exerted. The metabolic changes are adaptive aiming at the acceleration of the healing process. In the liver alanin originating from the striated muscles and gut is converted to glucose via gluconeogenesis, while other amino acids produce acute phase proteins which play pivotal role in the immune response of the body. Catecholamines secreted by stress will decrease insulin secretion together with a rise in plasma glucagon level. As a result of this, glycogenolysis, lipolysis, proteolysis will increase along with decreased tissue uptake of glucose that results in hyperglycaemia. Simultaneously, the level of corticotropin releasing factot (CRF) will increase resulting in the excretion of ACTH in the hypophysis. Along with this, plasma cortisol levels will increase which is accompanied by higher levels of plasma adrenalin and glucagon. Concomittantly,

the increase in the mineralocorticoid hormon levels will lead to sodium and water retention resulting in increased circulating blood volume. ADH will increase the reabsorption of water in the kidneys, together with increased vasoconstriction in the resistance vessels. The surgical wound can be perceived therefore as a large arteriovenous shunt with increased levels of circulating cytokines, resulting in an inflammatory response.

Fasting stress

Fasting stress develops rapidly during complete fasting, since the body does not receive any source of energy, but water and minerals is generally maintained. The duration of complete fasting is determined not only by the reserves of the body, but also by the ambient temperature or the simultaneous physical activity. Fasting stress has the same effects on regulatory mechanisms and metabolic pathways as surgical or traumatic stress.

AIMS

It is well known that in rodents with small body mass following insertion of a telemetric transmitter the daily circadian oscillation of body temperature will transiently cease. In our laboratory it was observed earlier in rats that after a second surgical stress the time required for the return of normal circadian rhythm is shortened compared to that period observed following the first procedure. Therefore in the first part of our experiments we analysed the pattern of the return of circadian rhythm and values of body temperature after standard surgical stress in mice. To study the physiological background we used melatonin and methylprednisolon supposing a causative role of sleep (melatonin) and stress (methylprednisolon) in this phenomenon.

In the second phase of our experiments we examined the effects of TRPV1 receptors on thermoregulation with a special interest in the energetic effects of the receptor. On one hand, in earlier stuides the the amplitude of daily oscillations in TRPV-1 KO mice was found to be larger compared to that of the wild types. On the other hand, it is known that the TRPV1 receptor is activated by supraphysiological heat stimuli and the heat resistance of the TRPV1-KO mice is deficient but thermoregulation against energy restriction in these mice have not been studied so far. Therefore, we analyzed the energetic responses of TRPV1-KO mice in the context of fasting heterothermia, comparing body temperature and locomotor activity responses of KO-mice animals with those of wild type mice possessing TRPV1 receptor.

In the third phase of our observations we looked into the changes of human circadian temperature rhythmicity after surgical stress. Patients undergoing major orthopaedic procedures were recruited and their parameters were compared with those of inpatients not having any surgical intervention. Since we have no data on long term analysis of body temperatures in patients undegoing major operation, the aim of this study was to see and characterize the supposed disappereance and reappearance of circadian rhythmicity over 5 postoperative days in a relatively homogenous patient group.

ANIMAL AND HUMAN STUDIES

Effects of repeated surgical stress on the daily changes of body temperature in mice

C57BL/6 mice were used with an initial body weight of 22-25 g, caged individually at an ambient temperutre of 23-25°C with a 12 hour light/dark cycle the light initiated at 06:00 AM. The animals had free access to normal rodent chow and tap water. The experimets were done under the regulation of Hungarian Law with the permission of the Ethical Committee of the University of Pécs.

Anaesthesia

The anaesthetic of the experimental animals were ketamin/xilazinin a dose of 78 mg/kg and 13 mg/kg, respectively. Injections were given intraperitoneally paying attention to cause minimal handling stress to the animals. The steady state of the anaesthesia was determined by the lack of response to a standard stimulus, i.e. pinching the abdominal skin with surgical forceps.

Operations

After adequate preparation a standard, median laparotomy was carried out. This was followed by the insertion of a telemetric radiotransmitter (ER-4000 model VMFH, Minimitter) to measure core temperature and horizontal locomotor activity. There was a 5-6 day of waiting for the stabilization of the body temperature in the experimental animals before further surgery was started. Repeated surgical stimuli were carried out four times at three day intervals. According to this, after the initial surgical stimulus each animal underwent another 3 laparotomies, as standard surgical procedures

Administration of melatonin

To assess the effect of melatonin on the return of circadian activity after repeated surgical stress situations the experimental, the animals received melatonin in a concentration of 40 μg/ml with the drinking water. According to their requirements, mice consumed daily 500-600 μg melatonin per 100 g body weight.

Administration of steroid (methylprednisolon)
To assess the steroid effect the experimental animals were given 600 mg/kg methylprednisolon intraperitoneally from the start of the surgical procedures. This meant 18 injections per experiments. According to the above four experimental groups were formed:

- ***L1:*** transmitter implantation along with the first laparotomy plus 6 days
- ***L2:*** second laparotomy plus 4 days
- ***L3:*** third laparotomy plus 4 days
- ***L4:*** fourth laparotomy plus 4 days

To assess the temporal effects of the laparotomies, ANOVA and Scheefe tests were carried out, while for the comparison of daily temperature amplitudes with control subjects the two-sampla T-test was used. For handling of telemetric data VitalView and ActiView softwares were used.

Results

As it is depicted on Fig. 2, five days were required in the control animals to stabilize their daily temperature amplitude after the implantation of the transmitters (L1). After repeated laparotomies

this period was shortened to 3, 2 and again 2 days (L2, L3, L4). Mice treated with melatonin exhibited a normal temperature oscillation on postoperative day 4.

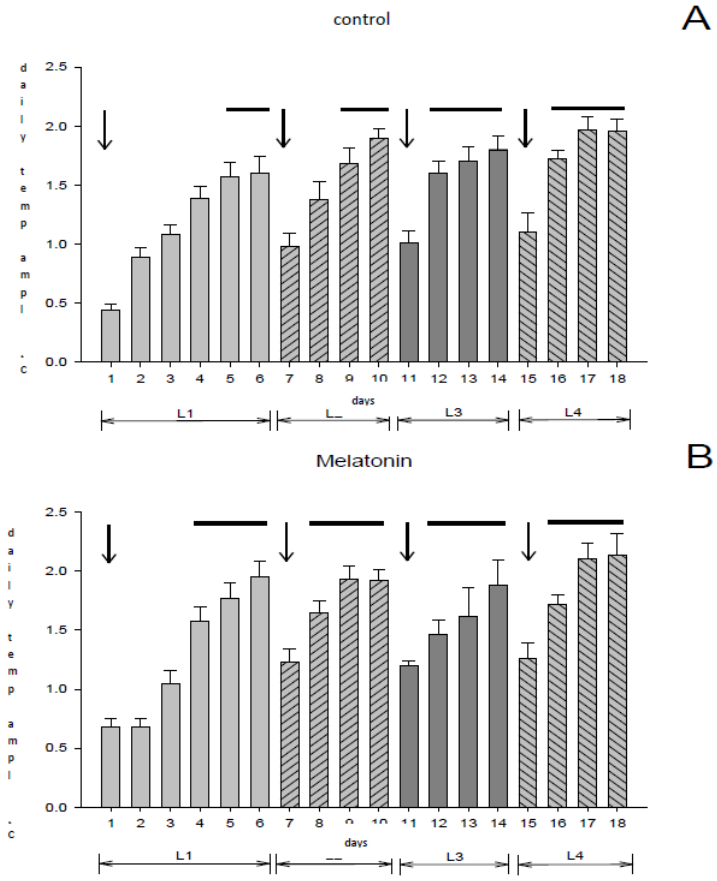

Figure 2. Changes of body temperature in control mice consuming tap water (A, n=10) and those receiving melatonin (B, n=13). Arrows refer to the days of laparotomies. The vertical lines above the columns show the stability of the temperature amplitude in the post-laparotomy period (L1-4).

The process was similar during the second laparotomy: the daily temperature change stabilized one day earlier and following the third and fourth laparotomies we did not find any change in regard to the circadian temperature changes (Fig. 3). Those mice treated chronically with methyl-prednisolon and injected with pyrogen free saline intraperitoneally required only three days to develop a steady rhythm of temperature (Fig. 3 part A) – unlike the animals having had no injections and requiring 5 days for the restituion of normal circadian temperature activity – which can be due to the stress inducing effect of the injections. It is important to emphasize that control mice treated with pyrogen free saline required 2 days for the restitution of normal temperature changes afetr the repeated laparotomies (Fig. 3 part A). As a result of the daily methylprednisolon treatment the daily temperature amplitude normalized in a gradulal manner, compared with the values registered in the control animals (Fig. 3 L1/A vs. L1/B). After methylprednisolon it seemed that - unlike melatonin - the restitution of the daily temperature amplitude did not accelerate: on the contrary, following the second and fourth laparotomies, the process rather decelerated. It is remarkable that the amplitude of the first post-laparotomy temperature change doubled after the surgical interventions (see the

arrows on Figs. 2 and 3) either in the control, or in the group of tretaed animals (day 1 vs day 7) and stayed similarly high following the last two laparotomies (day 7, 11, 15 both on A and B).

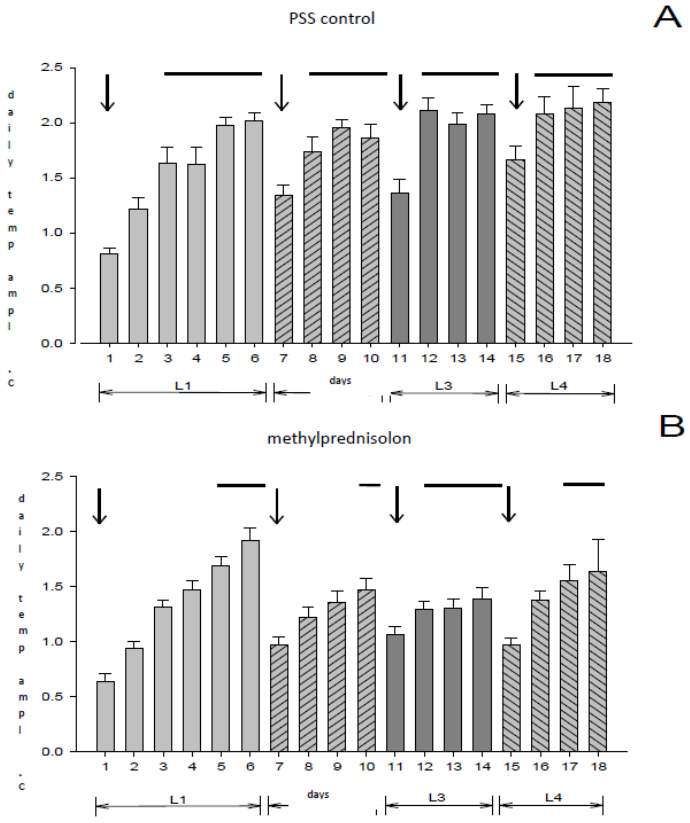

Figure 3. Changes of body temperature in control mice consuming tap water (A, n=10) and those receiving intraperitoneal methylprednisolon (B, n=13). Arrows refer to the days of laparotomies. The vertical lines above the columns show the stability of the temperature amplitude in the post-laparotomy period (L1-4).

As shown by Fig. 4, the daily temperature amplitude of animals treated with melatonin (A) and methylprednisolon (B) were similar to respective values of the untreated animals. It can also be seen that there was no change after the administration of melatonin compared with the controls (A), while the daily core temperature amplitude decreased significantly after methylprednisolon treatment and this trend was seen throughout the experimets (L3 and L4 in B).

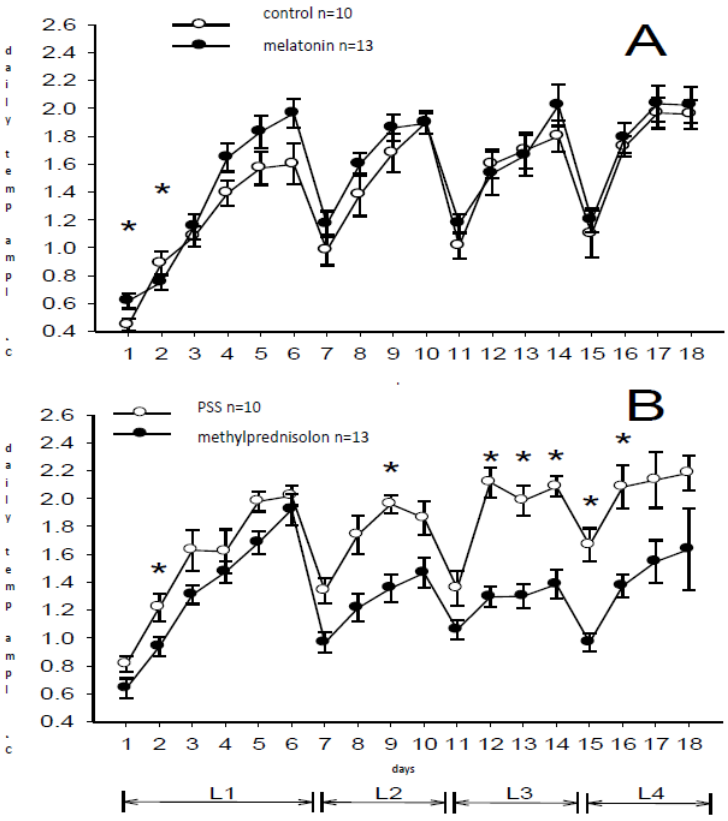

Figure 4. Differences of daily temperature amplitudes in mice treated with melatonin, undergoing repeated laparotomies compared with control untreated, but laparotomized mice (A). Changes of body temperature in methylprednisolon treated mice compared with control, saline treated mice (B). Asterisks depict significant differences.

Energetics of fasting heterothermia in TRPV1-KO and wild type mice

Fourteen C57BL/6 (wild type) and TRPV1-KO mice each with an initial body weight of 22-26 g were used in these experiments . Animals were held individually in plastic cages either at 27-28 °C ambient temperature, being slightly under the thermoneutral zone of mice and also at 23-24 °C cool environment with a light/dark cycle of 12 hrs light starting at 06:00 AM.

Apart from the fasting period, the animals had free supply of chow and tap water. Complete rest was provided for them during fasting, even refeeding was so cautious not to disturb them. The experimets were done under the regulation of Hungarian Law with the permission of the Ethical Committee of the University of Pécs.

The anaesthetic procedures and the implantation of the biotelemetric transmitters were exactly the same as outlined above.

After the implantation of the biotelemetric transmitters we waited a week for the return and stabilization of normal daily temperature changes . After these mice were exposed to complete fasting starting at 09:00 AM. Depending on the ambient temperature, fasting lasted for 3 (T_{amb}: 27-28 °C) or for 2 (T_{amb}: 23-24 °C) days. The duration of the observation on the former temperature made it possible to analyze the energetic processes in higher details, and at the same time the body mass decrease was not bigger than that of the animals kept on lower ambient temperatures but for a shorter period of time. The fasting cycle was stopped by refeeding at 09:00 AM, when both core temperature or activity decreased otherwise characteristic to nocturnal species. Temperature and activity readings were recorded every five minutes and the further analysis of data was achieved with the aforementioned VitalView and ActiView softwares. Before statistical analysis data were processed by an averaging of 1 and 2 hours, except the activity where the original sampling periods were applied. ActiView software enables us to observe any shifts in temperature or activity resulting from fasting. The two-sampled T-test was applied to assess the temperature and activity changes caused by fasting and refeeding in wild type and TRPV1-KO mice.

Results

Fasting for 2 or 3 days in cool and thermoneutral environment resulted in the progressive decrease of the daily minima, while maxima stayed the same or approached those of the values measured before fasting (Figs. 5 and 6). Locomotor acitivity was similar to those of temperature values both day and night, but refeeding resulted in an immediate increase in temperature while activity increased only slightly or did not even change. Comparing the 2 day fasting of wild type and TRPV1-KO mice, no significant difference was found. On day 2 core temperature of the wild type mice became significantly lower than the core temperature of the TRPV1-KO mice; it decreased below 30 °C in the former group. Concomittantly, on fasting day 2 core temperature maxima of the wild type mice became lower than those of the TRPV1-KO, not even reaching normothermia (Fig. 5). Over the three days of fasting on near thermoneutral temperature, similar changes were observed in the two groups. Core temperature decrease on day 2 and 3 observed in the TRPV1-KO group was not as high as that in the wild type mice, where minima progressively decreased during the 3 day fasting (Fig. 6). By day 3 not only the tempreture values differed significantly, but also activity did: activity was significantly higher in the TRPV1-KO mice than in wilde type ones (Fig. 7). Activity during 3 days fasting in TRPV1-KO mice increased progressively, but this could not be observed in the wild type group (Fig. 8). In connection with the timing of the increase in activity and temperature, an other phenomenon was observed. In TRPV1-KO mice the increasing phase of the two parameters happened simultaneously just before the beginning of the dark period. Core temperature and activity increases in the wild type mice started well before the dark period, with a distinctive and progressive entrainment: the cyclicity of the fed animals was 23-25 hours, while it changed to 17 hours on the 3rd day of fasting, but only in wild type mice. This advance of the daily rhytms was not obeserved in TRPV1-KO mice.

Refeeding completely changed the parallel behaviour of core temperature and activity, that was observed before and after fasting. After refeeding core temperature started to increase immediately and reached a normal value independent of the actual core temperature measured on the last morning of fasting. Contrary to this, as can seen on Figs. 7 and 8, no increase in activity was observed

in any group following an increase in core temperature. The speed of temperature increase was very quick (30-40 mins, see the Figs.) supposing an increased heat producion in the background that was obviously independent of physical activity.

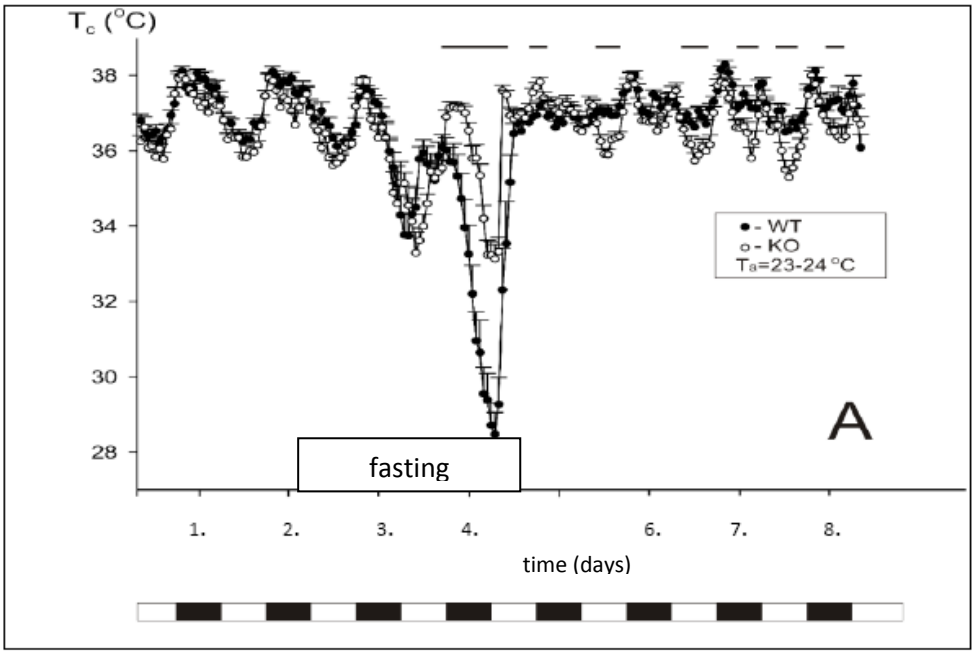

Figure 5. Changes of abdominal temperature in wild type (thin line) and TRPV1-KO (thick line) before and after fasting of two consecutive days. Significant results are labelled with horizontal lines.

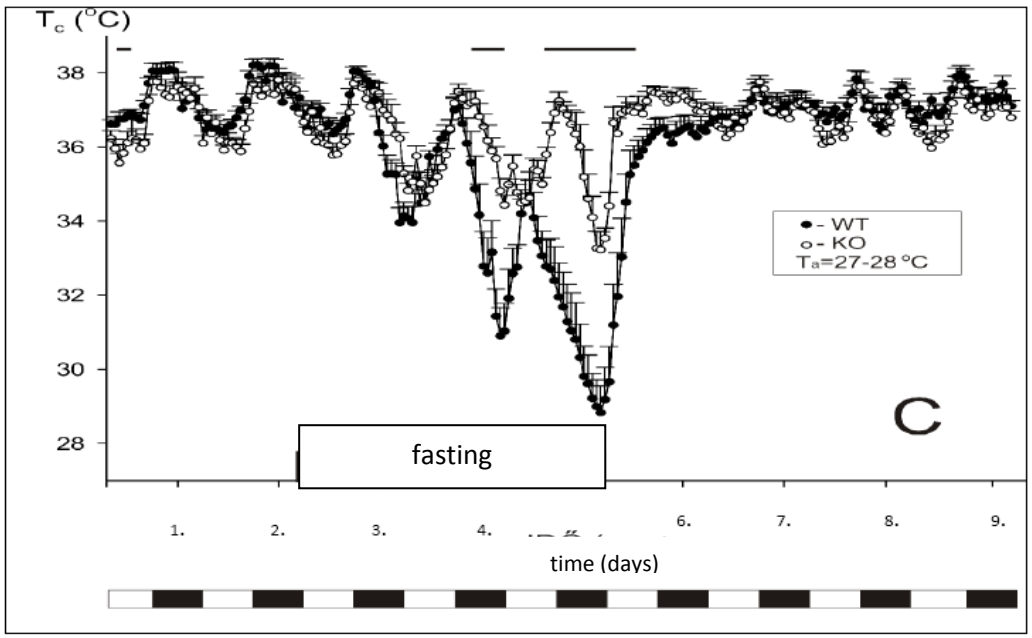

Figure 6. Changes of abdominal temperature in wild type (thin line) and TRPV1-KO (thick line) before and after fasting of three consecutive days. Significant results are labelled with horizontal lines.

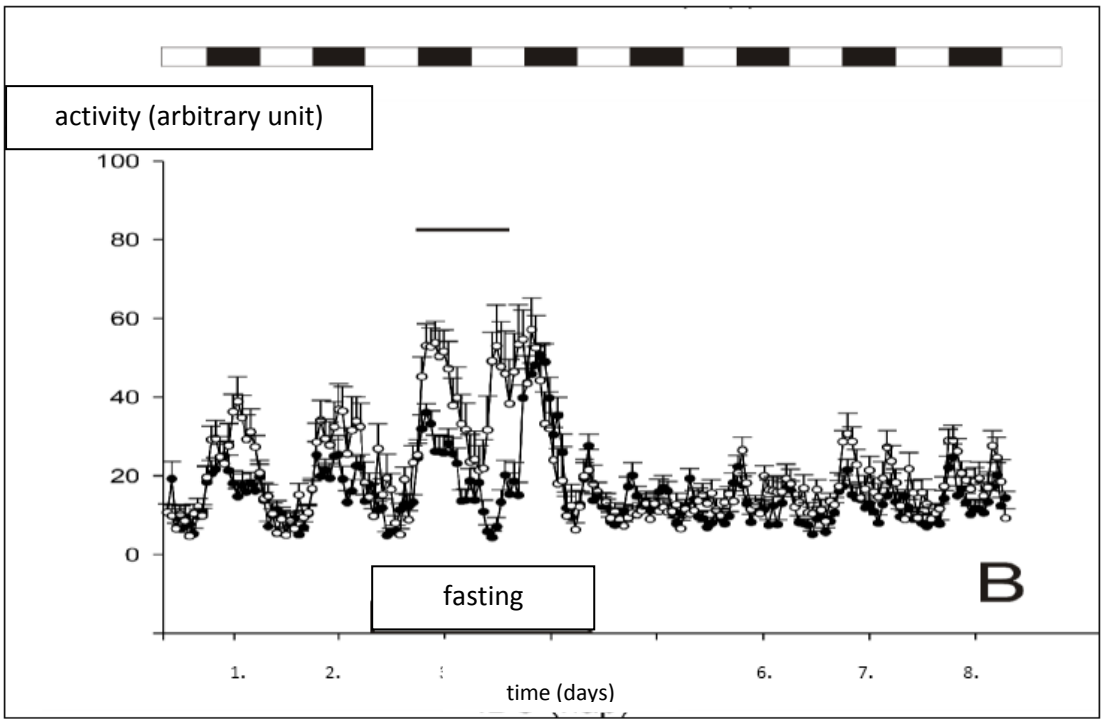

Figure 7. Locomotor activity in wild type (thin line) and TRPV1-KO (thick line) before and after fasting of 2 days. Significant results are labelled with horizontal lines.

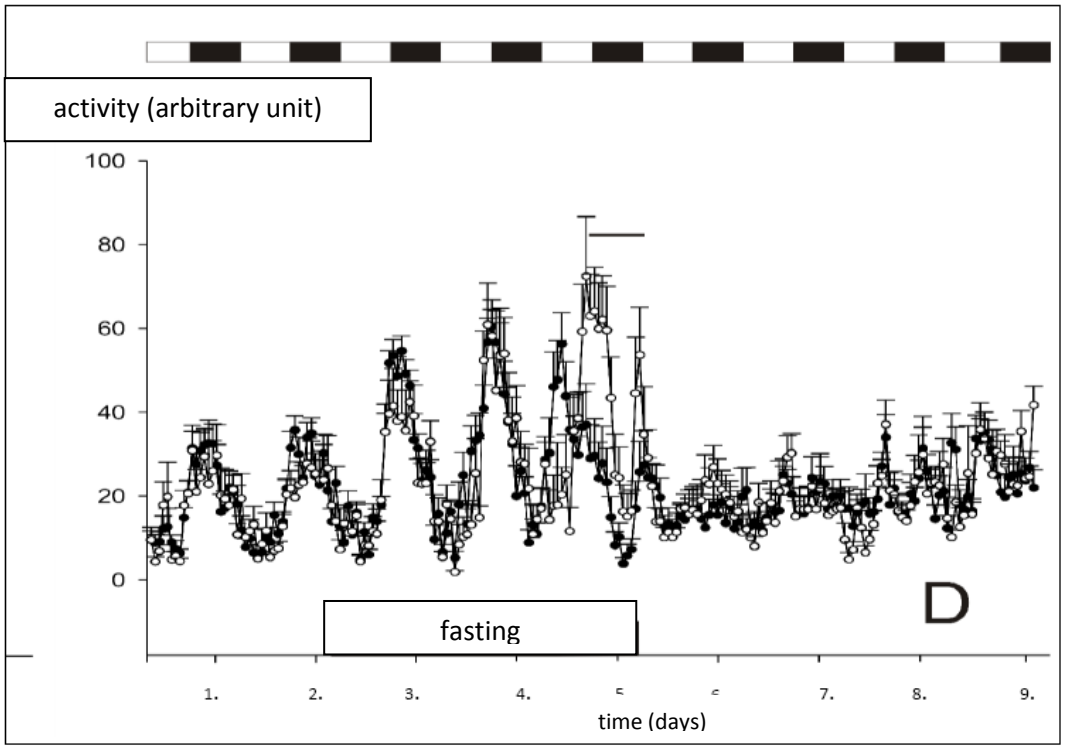

Figure 8. Locomotor activity in wild type (thin line) and TRPV1-KO (thick line) before and after fasting of 3 days. Significant results are labelled with horizontal lines.

HUMAN OBSERVATIONS. CHANGES OF CORE AND AXILLARY TEMPERATURES AFTER MAJOR ORTHOPAEDIC PROCEDURES.

After approval of the Ethical Committee of the University of Pécs, Medical Faculty, thirty-two ASA 1 and 2 patients awaiting total hip replacement were enrolled in the study after signing informed consent. Patiens were free to withdraw their consent at any time during the study. There were 16 male and 16 female patients with the average age of 62 (41-80) years. Exclusion criteria were patient refusal, ASA 3 status, operation with a duration longer than 2.5 hours, major blood loss (> 20 % of circulating blood volume), evidence of thyroid disease, and any medication that might interfere with temperature regulation. Patients were admitted the day before the operations and their tympanic membrane (T_{tm}) and axillary temperatures (T_{ax}) were measured by using a tympanic membrane (Omron Gentle Temp MC-510-E) and axillary (Omron O-Temp-II, MC-204-E) thermometer, respectively, with an accuracy of 0.1 ºC which has been a well accepted method in other clinical studies . All surgical procedures were done under spinal anaesthesia given by an anaesthetist other than the authors. With routine monitoring of blood pressure, heart rate and peripheral O_2 saturation was monitored continuously and a 16 G intravenous line was inserted for fluid replacement. Spinal anaesthesia was given in the sitting postion aiming at the lumbar 2/3 interspinal space and routinely a 25 gauge pencil point needle with an introducer or a 22 gauge sharp needle was used in difficult cases. According to patient height an average of 16 (14-20) mg heavy bupivacaine was injected into the spinal space. After development of anaesthesia patients were positioned supine with a sandbag under the operated site. Using the tympanic membrane thermometer patient parameters were

registered, but not revealed in this study. The average duration of the operations were 94 (50-135) minutes. A 30 % or higher decrease in the blood pressure compared to the initial values was treated with 5 mg increments of ephedrine and increments of Hartmann's solution or gelofusine infusion. No critical bradycardia or hypotension was reported in any of the cases. Each patient received a single dose of cefuroxime 1.5 g as antibacterial prophylaxis. Twelve patients needed blood transfusion with an average amount of 1.47 units. Packed red blood cells were warmed through a warming coil during transfusion. There were no pyrogenic reactions observed due to blood administration. Postoperative pain relief was achieved by intermittent nalbuphine administration (10 mg 4 hourly, up to a maximum of 40 mg/24 h) and 1g of metamizole as needed up to a maximum of 4 g/24 hr. For deep venous thrombosis prophylaxis 20 mg Enoxaparine was given. Core temperatures of the patients were taken by using the tympanic membrane thermometer, axillary temperatures were measured by the digital thermometer (manufacturer's details as above). Measurements started at 12:00 on the first preoperative and were finished on the end (18:00) of the fifth postoperative day. A reading was taken at 06:00, 12:00, 18:00 and 22:00 hours. To ensure uninterrupted sleep the last measurement was not taken 6 hours after the 18:00 reading but fours hours later. Ambient temperature in the operating theater and in wards were within the comfort zone usual in surigal facilities and wards, respectively. Illumination was not following any cyclic pattern although there was an 8 hour dark cycle from 22:00 till 06:00.Tympanic membrane and axillary temperature values were compared with those of twelve inpatients not having any surgical interventions, establishing a control group. These patients had no major circulatory, respiratory and endocrine derangements, the group mostly comprised of hypertensive inpatients on blood pressure adjustments and those of ischaemic heart disease (NYHA II). The axillary and tympanic membrane temperatures were registered in the same fashion as with the surgical patients. Anybody receiving such treatment that could have affected temperature regulation or heat balance was excluded from the control group. The average age of the control patients was 55 years (17-78). Data were analyzed by using the independent samples t-test (for the two group's means, i.e. T_{tm} and T_{ax}) for the parametric and the Mann-Whitney test for nonparametric distribution.

Results

There was a significant drop in the tympanic membrane and a non-significant decrease in the axillary temperatures of the patients during and after the procedures despite the standard warming techniques using warming mattress and warm-air blankets. Tympanic membrane temperature was 36.25 (±0.132) °C before and 35.49 (±0.102) °C after the operations while axillary temperature decreased in a nonsignificant manner from 36.06 (±0.109) °C to 35.97 (±0.097) °C. Tympanic membrane temperature had a tendency to increase on the first postoperative day (Table 1) We started measurements on day 1 at noon to give the patients time to settle after the hardships of the first postoperative morning. On day 2 a circadian pattern developed in the tympanic membrane temperature which persisted throughout our study. Significant differences were registered for the rest of the days except at 06:00 on day 4. It is important to note that the mesor of the circadian temperature showed a constant decrease, but the daily differences remained significant even on day 5 (figure 9.). Axillary temperature showed a very similar pattern, but significant difference was registered even at 22:00 on day 1 that appeared to be invariable throughout the measurements except at 12:00 on day 4 (Table 2). The daily differences of axillary temperature were greater than

those of tympanic membrane temperature, but again, the mesor decreased by the end of the observation (figure 10.) and – as in the case of the tympanic membrane temperatures - the differences remained also significant.

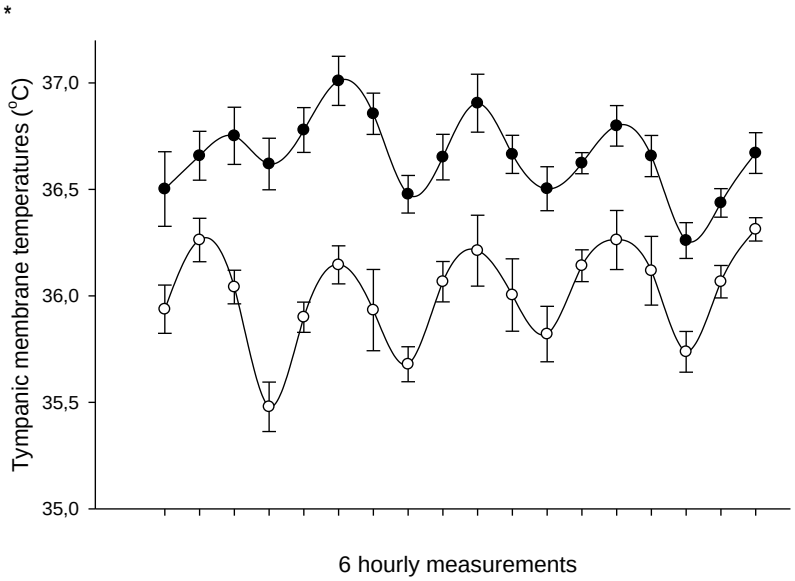

Figure 9. Changes of tympanic membrane temnperatures over 5 days following hip replacement in operated (●-●) and control (○-○) patients

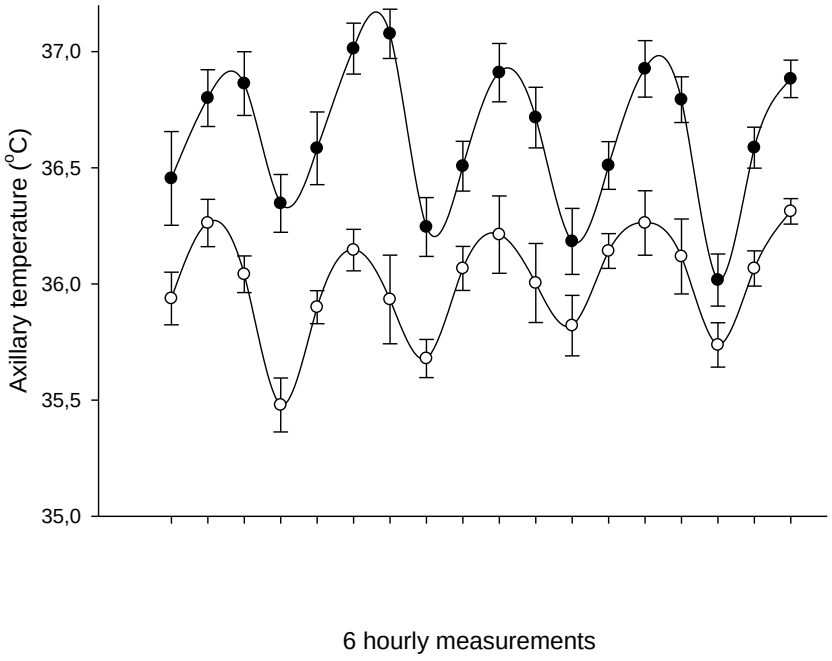

Figure 10. Changes of axillary temnperatures over 5 days following hip replacement in operated (●-●) and control (○-○) patients

Summary and discussion

The aim of our human observations and animal studies was to assess how does the delicately controlled process of thermoregulation change stress situations. The complicated mechanisms of fasting and surgical stress can affect thermoregulation on numerous occasions. It is highly important to consider the above role of stress factors in the anaesthetic practice, too. A requirement of preoperative fasting of 6 hours is well known to all anaesthetists. It may well be a safety measure but at the same time in the clinical practice it is a much longer period. This is a realistic problem especially in paediatric anaesthesia, resulting in an imbalance of metabolic processes in kids. Obviously it is not only the outcome of the operation that depends on the stress free anaesthetic, but the general state of the patients, the duration of hospital admission and psychological reactivation. The main cause of postoperative fatigue is the lack of sleep, the disturbance of one of our most strikingly circadian activity. More and more clinicians focus on the stress induced sleep disturbances. The lack of this circadian activity may result in serious cardiovascular and respiratory complications, furthermore the mortality of those with stress induced insomnia is higher. ITU patients were observed to cease the circadian secretion of melatonin, measured by decrease in urine 6-SMT (6-sulfatoxymelatonin), a metabolite of melatonin. Inpatients have a shortened REM sleep phase , whatsmore, REM can totally be abolished after surgical interventions. It is well known that the increased amount of ACTH and cortisol secreted in the postoperative phase inhibit the REM phase, but it is more likely that endogenous opiates – otherwise effective analgesics - are responsible for this process. The frequently observed oxygen desaturation in the postoperative period is most striking on postoperative day 2 and 3. The episodic desaturations can lead to the shortening of REM phase even in healthy individuals, and this is exaggerated in otherwise helathy, but operated patients. The process of temperature decrease caused by surgical and anaesthesiological stress was accelerated by administration of interleukin-6 antibodies, giving evidence of the involvement of citokines in stress activation. The details of derangements in circadian activity induced by stress need further evaluation.

The mice studies presented before shed light on how three molecules, acting at different levels of thermoregulation, affect caloric restriction, as stress factor. The alpha-blocker guanethidin (10 mg/kg) did not change the temporal (circadian) pattern of body temperature, but administration of the centrally acting muscle relaxant mephenesine (42 mg/kg/day) resulted in the deepening of hypothermia provoked by caloric restriction. The general opiate anatgonist naloxone (20 mg/kg/day) had similar effects to mephenesine. None of the three drugs above affected the speed of rise in core temperature induced by refeeding. Our investigations raise the quiestion whether the maintenence of core temperature in completely fasting mice is due to the increase in locomotor activity, or shivering thermogenesis plays also a pivotal role to keep the core temperature steady. The massive decrease in core temperature induced by naloxone points at the role of endogenous opiates in thermoregulation not only in normothermia but also during hypothermia.

NEW RESULTS

It was found that ***under surgical stress the return of the circadian temperature rhythm can be affected by melatonin and mathylprednisolon***. Melatonin accelerated the restitution of the circadian temperature rhythmicity, while methylprednisolone had somewhat opposite effect.

It was further shown ***that core temperatures of TRPV1-KO and wild type mice are showing the same characteristics on fasting day 1, but from day 2 the core temperature of TRPV1-KO mice is significantly lower thant those of their wild counterparts*** presuming the role of the capsaicin receptor in the development of fasting hypothermia.

In the present ***human studies we observed the daily changes of axillary and tympanic membrane temperatures and found that normal circadian temperature oscillation returns on postoperative day 1*** but the minima and maxima of the temperature are distributed around a higher set-point and this diffenerence can be observed even on day 5.

LIST OF PUBLICATIONS

List of publications related to the thesis:

First author papers in referred journals:

1. Kanizsai P, Garami A, Solymár M, Szolcsányi J, Szelényi Z: Energetics of fasting heterothermia in TRPV1-KO and wild type mice. Physiol Behav 2009, 96:149-54. (IF: 3.295)

2. Kanizsai P, Vámos Z, Solymár M, Garami A, Szelényi Z: Effects of repeated surgical stress on daily changes of body core temperature in mice. Acta Physiol Hung, 2010, (97), 203–210 (IF: 0.750)

First author papers in non-referred journals:

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