

Differential Effects of α_2 -adrenoceptors in the Modulation of the Thermoregulatory Response in Mice Induced by Meperidine

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Background: Meperidine proved to be more effective in treatment of shivering than equianalgesic doses of other opioids, especially pure μ -agonists. Further, meperidine has well known nonopioid actions including agonistic effects at α_2 -adrenoceptors *in vitro*. Accordingly, the authors investigated nonopioid receptor-mediated effects of meperidine on thermoregulation using a mice model of nonshivering thermogenesis. To differentiate conceivable α_2 -adrenoceptor subtype specific interactions the authors analyzed wild-type mice and knock-out mice with deletion of the α_{2A} , α_{2B} , or α_{2C} -adrenoceptor.

Methods: Ten mice per group (n = 60) were injected with saline, meperidine (20 mg/kg), saline plus naloxone (125 μ g/kg), meperidine plus naloxone, fentanyl (50 μ g/kg) plus naloxone, or meperidine plus atipamezole (2 mg/kg) intraperitoneally. Each mouse was subjected to the six different treatments. Then they were positioned into a plexiglas chamber where rectal temperature and mixed expired carbon dioxide were measured while whole body cooling was performed. Maximum response intensity and thermoregulatory threshold temperature of nonshivering thermogenesis were analyzed.

Results: Meperidine decreased the thermoregulatory threshold temperature in wild-type mice and α_{2B} - and α_{2C} -adrenoceptor knock-out mice. This effect ended after injection of the α_2 -adrenoceptor antagonist atipamezole. In wild-type and α_{2B} -adrenoceptor knock-out mice, the decrease of thermoregulatory threshold was not reversible by administration of the opioid receptor antagonist naloxone. In contrast, in α_{2A} -adrenoceptor knock-out mice, no decline of thermoregulatory threshold following meperidine injection was detectable. Maximum response intensity of nonshivering thermogenesis was comparable in all groups.

Conclusions: The authors' results suggest a major role of α_2 -adrenoceptors, especially the α_{2A} subtype, in the mediation of thermoregulatory effects caused by meperidine in mice.

POSTANESTHETIC shivering is characterized by involuntary muscle activity, especially during the early postoperative period, and can be treated pharmacologically with opioids or α_2 -adrenoceptor agonists. Though the underlying mechanisms of shivering are not completely understood, a major contributing factor is perioperative

hypothermia mediated by anesthetic-induced inhibition of thermoregulation.^{1,2}

Previous studies have revealed that meperidine seems to be more effective in treatment of shivering than equianalgesic doses of other opioids, especially μ -opioid agonists.³ Possibly, meperidine's ability to also stimulate κ -opioid receptors may contribute to this effect.⁴ However, meperidine is known to also initiate nonopioid receptor-mediated effects in clinically relevant concentrations, e.g., activation of α_2 -adrenoceptors.^{4,5} On the other hand, α_2 -adrenoceptor agonists such as clonidine or dexmedetomidine proved to be even more effective in treatment of postanesthetic shivering than meperidine.^{6,7} Laboratory investigations in mice confirmed a pivotal role of α_2 -adrenoceptors in thermoregulation and have revealed the α_{2A} -adrenoceptor as primary mediator of hypothermic effects of α_2 -adrenergic agonists.^{8,9}

Therefore, the aim of our study was to analyze the effect of meperidine on α_2 -adrenoceptor-mediated thermoregulation in mice. Because rodents try to resist hypothermia by nonshivering thermogenesis, we focused on a mouse model of nonshivering thermogenesis that has been used by our group before.¹⁰ These experiments have revealed that meperidine mediates thermoregulatory effects *via* α_2 -adrenoceptors but did not investigate any α_2 -adrenoceptor subtype specifically. To evaluate the individual role of each of the three α_2 -adrenoceptor subtypes, we compared impact of meperidine using wild-type mice and mice with deletion of the α_{2A} , α_{2B} , or α_{2C} -adrenoceptor (knock-out mice). To differentiate between opioid receptor and α_2 -adrenoceptor-mediated effects, we also studied meperidine effects following administration of the opioid receptor antagonist naloxone and the α_2 -adrenoceptor antagonist atipamezole.

Materials and Methods

Permission for this study was received from the local Animal Care Committee at the Ministry for Agriculture and Environment, Kiel, Germany, before the initiation of work. The generation of mouse lines lacking a single α_2 -adrenoceptor (α_{2A} , α_{2B} , or α_{2C} -adrenoceptor knock out) has been described previously.^{11,12} The knock-out mice were obtained from L. Hein (Freiburg, Germany), and maintained in a specified pathogen-free facility at our institution where all experiments were performed. Also, wild-type mice (129S2/SvHsd) were analyzed as a control group.

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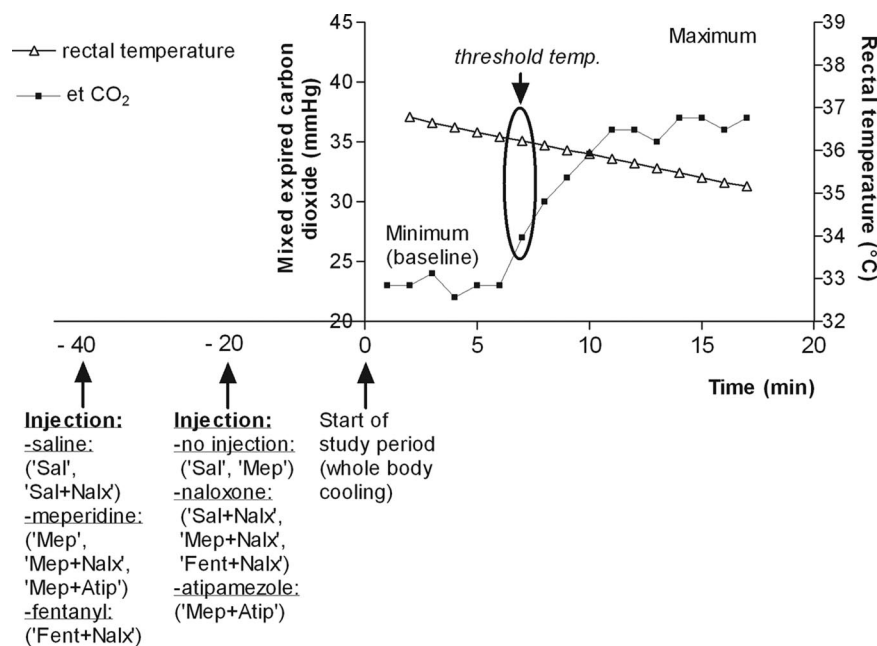


Fig. 1. Experiment design and data analysis: rectal temperature (Δ) and mixed expired carbon dioxide (\blacksquare) as a function of time. The maximum response intensity of nonshivering thermogenesis is defined as the ratio between the maximum and the minimum (baseline) level of mixed expired carbon dioxide. The thermoregulatory threshold temperature is defined as the temperature at which a sustained increase of mixed expired carbon dioxide is detectable. Fent+Nalx = fentanyl plus naloxone; Mep = meperidine; Mep+Atip = meperidine plus atipamezole; Mep+Nalx = meperidine plus naloxone; Sal = saline; Sal+Nalx = saline plus naloxone.

Ten mice of each group weighing 26–35 g were investigated. Mice were housed 3–4 animals per cage and maintained on a 12-h light-dark cycle with free access to water and food. All experiments were performed between 09:00 and 16:00 h. The animals were weighed before the experiments. In a first set of experiments, animals received saline or meperidine (20 mg/kg) (Dolantin; Sanofi-Aventis, Frankfurt, Germany), respectively. To rule out that a possible effect of meperidine is mediated *via* opioid receptors, in a second set of experiments, the opioid receptor antagonist naloxone hydrochloride (125 μ g/kg) (Naloxon Curamed; Curamed Pharma, Karlsruhe, Germany) and the α_2 -adrenoceptor antagonist atipamezole (2 mg/kg) were injected 20 min after the injection of saline/meperidine.

To investigate possible effects of different opioids on the thermoregulatory threshold temperature that can be reversed by naloxone, we also analyzed fentanyl (50 μ g/kg) (Fentanyl-Janssen; Janssen-Cilag, Neuss, Germany) plus naloxone (125 μ g/kg) as an additional control.

To rule out that 125 μ g/kg naloxone was not sufficient to completely reverse opioid receptor-mediated effects, a control group of 10 α_{2C} -adrenoceptor knock-out mice received meperidine plus different naloxone doses (125 *vs.* 1250 μ g/kg). All drugs were administered intraperitoneally (0.1 ml/10 g body weight).

Each animal was analyzed with all six different drug regimens (saline, meperidine, saline plus naloxone, meperidine plus naloxone, fentanyl plus naloxone, and meperidine plus atipamezole) and therefore served as its own control. Before a new experiment was started, animals had at least 2 weeks to recover from injections of pharmaceuticals. After injection of saline or meperidine, the animals were returned to their cages until

starting the measurements 40 min later. In a second set of experiments, 20 min after injection of saline (for saline plus naloxone experiment), meperidine (for meperidine plus naloxone or meperidine plus atipamezole), or fentanyl (for fentanyl plus naloxone) as the first drug, mice were injected with naloxone or atipamezole as the second drug and immediately returned to their cages until start of measurements 20 min later (fig. 1). To prevent an inappropriate decline of body temperature, cages were warmed by a heating lamp.

Forty minutes after injection of the first drug, mice were positioned in a gas-tight plexiglas chamber (internal diameter, 4 cm; length, 7 cm). A constant oxygen flow of 100 ml/min was delivered to the chamber. Mixed expired carbon dioxide was recorded continuously by capnography (Phasein Multigas sensor; Armeda Medizintechnik, Hannover, Germany). Body temperature was measured and recorded continuously by a rectal temperature probe (Sirecust 402; Siemens, Danvers, MA). Ice was positioned around the plexiglas chamber to provoke a thermoregulatory response by whole body cooling. No animal was allowed to get colder than 32°C. According to previous studies in rats,¹³ the thermoregulatory threshold was defined as the temperature (°C) at which a sustained increase in expiratory carbon dioxide can be measured (fig. 1). The maximum response intensity of nonshivering thermogenesis was calculated as the ratio of the maximum and minimum carbon dioxide plateau during cooling.

Statistical and Data Analyses

To determine the thermoregulatory threshold, plots of mixed expired carbon dioxide (mmHg) as a function of time were analyzed by three blinded observers and the median value of the three observers was taken for fur-

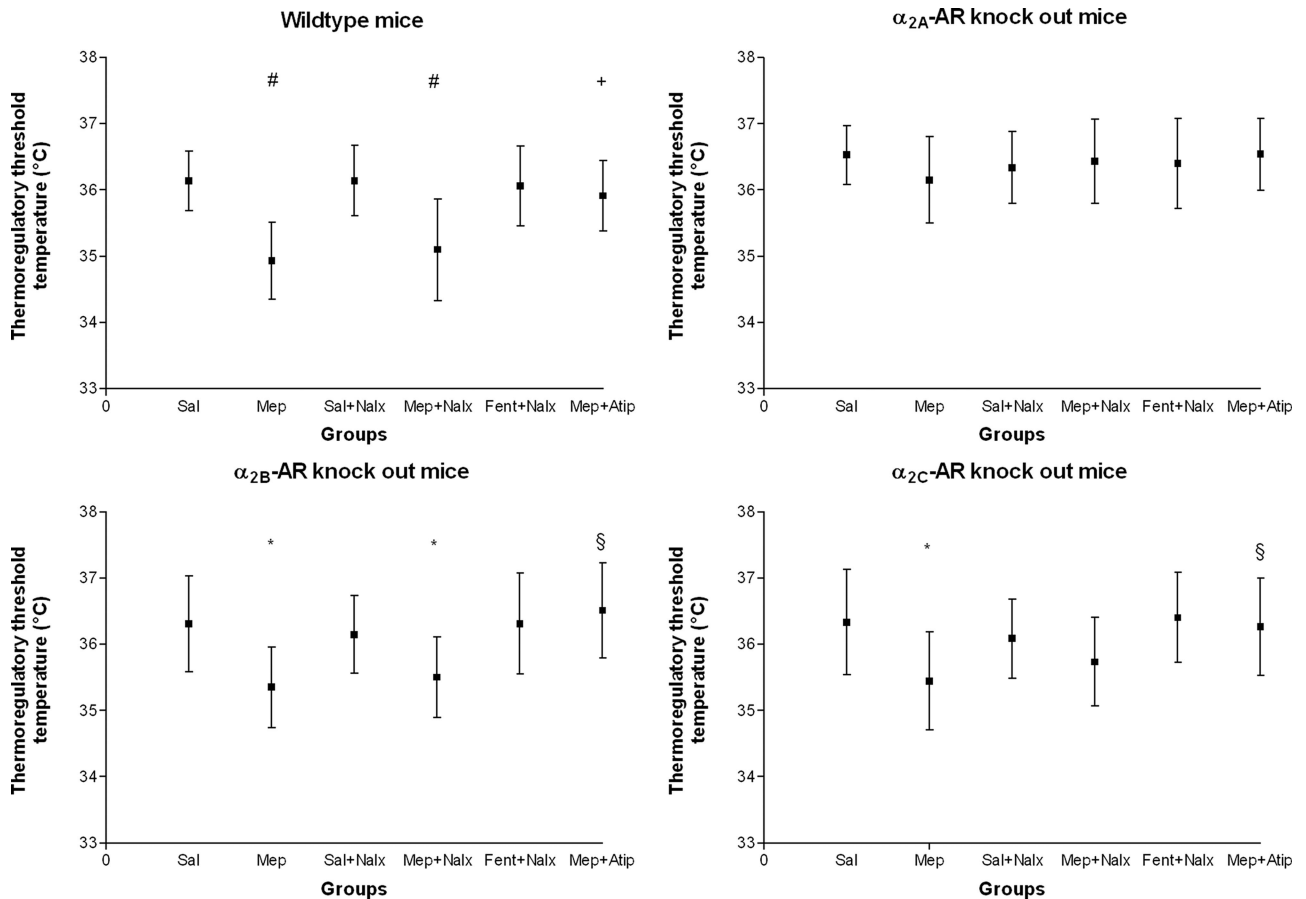


Fig. 2. Thermoregulatory threshold temperatures after administration of saline (Sal), meperidine (Mep), saline plus naloxone (Sal+Nalx), meperidine plus naloxone (Mep+Nalx), fentanyl plus naloxone (Fent+Nalx), and meperidine plus atipamezole (Mep+Atip) in wild-type, α_{2A} -, α_{2B} -, and α_{2C} -adrenoceptor knock-out mice (n = 10 per group). Data are presented as mean \pm SD. # $P < 0.01$; * $P < 0.05$ vs. saline; + $P < 0.01$; § $P < 0.05$ vs. meperidine.

ther analysis. Within-group data were analyzed using repeated-measures ANOVA, with Dunnett test for comparison to control (precooling baseline values). Differences between the treatment groups were evaluated using one-way ANOVA followed by Bonferroni correction for multiple comparisons. To analyze differential effects between different genotypes, a 4×6 ANOVA was performed. Results are presented as mean \pm SD; $P < 0.05$ was considered significant. GraphPad Prism 5.0 (GraphPad Software, San Diego, CA) was used to perform statistical analyses.

Results

Baseline body temperatures before and after intraperitoneal injection were neither significantly different between mice of all groups, nor between wild-type and α_2 -adrenoceptor knock-out mice.

In wild-type mice receiving saline, the thermoregulatory threshold temperature was $36.3 \pm 0.4^\circ\text{C}$. Additional injection of naloxone did not change threshold temperature significantly ($36.2 \pm 0.5^\circ\text{C}$). After administration of meperidine, the thermoregulatory thresh-

old decreased to $35.0 \pm 0.6^\circ\text{C}$ ($P < 0.01$). This effect could not be abolished by additional administration of naloxone ($35.2 \pm 0.7^\circ\text{C}$) (fig. 2).

In α_{2B} - and α_{2C} -adrenoceptor knock-out mice, the thermoregulatory threshold temperature after injection of saline was comparable ($36.3 \pm 0.7^\circ\text{C}$ vs. $36.3 \pm 0.8^\circ\text{C}$). No significant changes could be detected in both groups after additional injection of naloxone. Administration of meperidine decreased the threshold temperature to $35.3 \pm 0.6^\circ\text{C}$ (α_{2B} -adrenoceptor knock out) ($P < 0.05$) and $35.4 \pm 0.7^\circ\text{C}$ (α_{2C} -adrenoceptor knock out) ($P < 0.05$), respectively. In α_{2B} -adrenoceptor knock-out mice, the additional administration of naloxone after meperidine was followed by a minimal and not significant increase of threshold temperature ($35.5 \pm 0.6^\circ\text{C}$). In α_{2C} -adrenoceptor knock-out mice meperidine plus naloxone administration resulted in an alleviated decline of threshold temperature, which was not significant compared with saline administration anymore (fig. 2).

In contrast, in α_{2A} -adrenoceptor knock-out mice, meperidine application alone did not result in a significant decline of the thermoregulatory threshold temperature ($36.2 \pm 0.6^\circ\text{C}$ vs. $36.5 \pm 0.4^\circ\text{C}$ in the saline control

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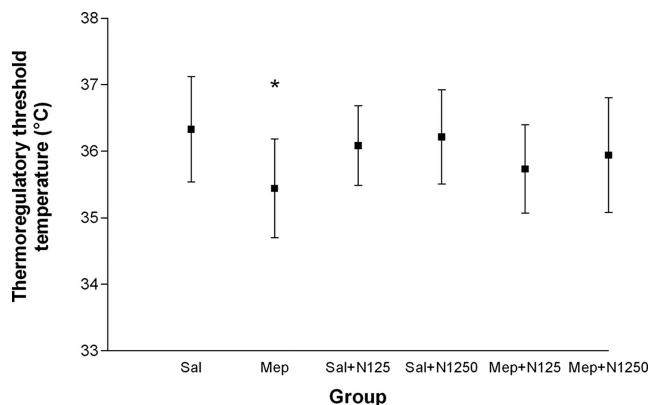


Fig. 3. Effects of different naloxone doses in α_{2C} -adrenoceptor knock-out mice. Thermoregulatory threshold temperatures after administration of saline (Sal), meperidine (Mep), saline plus 125 $\mu\text{g}/\text{kg}$ naloxone (Sal+N125), saline plus 1,250 $\mu\text{g}/\text{kg}$ naloxone (Sal+N1250), meperidine plus 125 $\mu\text{g}/\text{kg}$ naloxone (Mep+N125), and meperidine plus 1,250 $\mu\text{g}/\text{kg}$ naloxone (Mep+N1250) in α_{2C} -adrenoceptor knock-out mice ($n = 10$). Data are presented as mean \pm SD. * $P < 0.05$ vs. saline.

group). No significant differences could be detected between threshold temperatures of α_{2A} -adrenoceptor knock-out mice in all analyzed groups (fig. 2).

In wild-type, α_{2B} , and α_{2C} -adrenoceptor knock-out mice, the thermoregulatory threshold after meperidine plus atipamezole injection was significantly higher than after meperidine alone, whereas atipamezole had no effect in α_{2A} -adrenoceptor knock-out mice. There also was no significant difference between saline control and meperidine plus atipamezole in wild-type, α_{2B} , and α_{2C} -adrenoceptor knock-out mice. This indicates that atipamezole abolished the effects of meperidine in wild-type and α_{2B} and α_{2C} -adrenoceptor knock-out mice (fig. 2).

The application of fentanyl plus naloxone had no significant effect on the thermoregulatory threshold temperature in wild-type and α_{2} -adrenoceptor knock-out mice compared with saline control.

An extraordinarily high dose of 1250 $\mu\text{g}/\text{kg}$ naloxone compared with 125 $\mu\text{g}/\text{kg}$ following saline or meperidine injection had no significant effect on the thermoregulatory threshold temperature in α_{2C} -adrenoceptor knock-out mice (fig. 3).

The maximum response intensity of nonshivering thermogenesis did not show any significant differences between the analyzed groups. Maximum response intensity

also was comparable between wild-type and α_{2} -adrenoceptor knock-out mice (table 1).

Finally, the analysis of a differential effect by a 4×6 ANOVA revealed no significant interaction between both drugs applied and mice genotype (interaction term, $P = 0.2986$).

Discussion

The main findings of our study are as follows:

1. Meperidine decreased the thermoregulatory threshold temperature in wild-type and α_{2B} and α_{2C} -adrenoceptor knock-out mice. This effect was not abolished by additional administration of the opioid receptor antagonist naloxone but by additional administration of the α_{2} -adrenoceptor antagonist atipamezole.
2. Naloxone had no effect on meperidine-induced decrease of thermoregulatory threshold in wild-type and α_{2B} -adrenoceptor knock-out mice, but did in α_{2C} -adrenoceptor knock-out mice.
3. In contrast, in α_{2A} -adrenoceptor knock-out mice, meperidine had no significant effect on thermoregulatory threshold temperature. Furthermore, naloxone administration did not show any effect.
4. The maximum intensity of nonshivering thermogenesis was comparable in wild-type and α_{2} -adrenoceptor knock-out mice.

The underlying mechanisms of meperidine's impact on thermoregulation, including the thermoregulatory threshold temperature, remain to be elucidated. In fact, meperidine is more effective in treatment of postanesthetic shivering than equianalgesic doses of other opioids, especially specific μ -opioid receptor agonists.^{3,14,15} It has been suggested, that additional κ -opioid receptor activation by meperidine was responsible for this effect.^{4,16} However, even high-dose naloxone expected to block κ -opioid receptors did not completely reverse the antishivering action of meperidine in volunteers.⁴

In addition to its agonistic effects at opioid receptors, meperidine shows local anesthetic activity and anticholinergic properties,^{17,18} but this does not fully explain meperidine's special antishivering action.¹⁹

Table 1. Maximum Response Intensity of Nonshivering Thermogenesis

	Saline	Meperidine	Saline + Naloxone	Meperidine + Naloxone	Fentanyl + Naloxone	Meperidine + Naloxone
Wild type	2.4 \pm 0.6	2.2 \pm 0.8	2.4 \pm 0.8	2.3 \pm 0.5	2.5 \pm 0.7	2.6 \pm 0.6
α_{2A} -adrenoceptor knock out	2.7 \pm 0.5	2.4 \pm 0.3	2.2 \pm 0.7	2.6 \pm 0.4	2.4 \pm 0.6	2.6 \pm 0.5
α_{2B} -adrenoceptor knock out	2.1 \pm 0.7	2.4 \pm 0.4	2.4 \pm 0.5	2.6 \pm 0.9	2.3 \pm 0.7	2.5 \pm 0.4
α_{2C} -adrenoceptor knock out	2.0 \pm 0.4	2.6 \pm 0.5	2.3 \pm 0.7	2.3 \pm 0.6	2.6 \pm 0.8	2.3 \pm 0.6

Maximum response intensity of nonshivering thermogenesis in wild-type, α_{2A} , α_{2B} and α_{2C} -adrenoceptor knock-out mice after injection of saline, meperidine, saline plus naloxone, meperidine plus naloxone, fentanyl plus naloxone, and meperidine plus atipamezole ($n = 10$ per group). Data are presented as mean \pm SD.

On the other hand, α_2 -adrenoceptor agonists such as clonidine or dexmedetomidine have demonstrated their potency in treatment of shivering and their ability in decreasing both the shivering and the vasoconstriction threshold.²⁰ A previous study from our group demonstrated that meperidine decreased the thermoregulatory threshold temperature in wild-type mice. According to our present results, this effect was abolished by administration of the α_2 -adrenoceptor antagonist atipamezole, indicating an involvement of α_2 -adrenoceptors in the mediation of meperidine actions.¹⁰ This conclusion is supported by the fact that meperidine acts as an agonist at α_2 -adrenoceptors *in vitro* in clinically relevant concentrations, showing highest affinity to the α_{2B} -adrenoceptor subtype (α_{2B} , $8.6 \pm 0.3 \mu\text{M}$; α_{2C} , $13.6 \pm 1.5 \mu\text{M}$; α_{2A} , $38.6 \pm 0.7 \mu\text{M}$).⁵

As a result of these *in vitro* binding studies, mice with modified α_2 -adrenoceptor genes have become important tools in elucidating α_2 -adrenoceptor subtype-specific functions. In agreement with our results with meperidine, Hunter *et al.*⁸ did not detect hypothermic effects in mice with a functional α_{2A} -adrenoceptor knock out in response to varying doses of dexmedetomidine. In contrast, in wild-type and α_{2B} - and α_{2C} -adrenoceptor knock-out mice, thermoregulation was influenced, whereas Salinen *et al.*²¹ reported a slight attenuation of the hypothermic response in α_{2C} -adrenoceptor knock-out mice. These results point to the α_{2A} -adrenoceptor as the primary mediator of the thermoregulatory effects of α_2 -adrenoceptor agonists, although the α_{2C} -adrenoceptor subtype also may be involved.⁹

In our study, in α_{2A} -adrenoceptor knock-out mice no significant decline of the thermoregulatory threshold temperature after meperidine administration could be detected, whereas the threshold temperature decreased in wild-type- and α_{2B} - and α_{2C} -adrenoceptor knock-out mice. The fact that this decrease in wild-type and α_{2B} -adrenoceptor knock-out mice was not abolished by naloxone but atipamezole administration indicates that non-opioid receptor pathways are involved.

To rule out that the high naloxone dose⁴ that we applied was too small and not capable of blocking all μ - and κ -opioid receptors, we compared the effects of 125 $\mu\text{g}/\text{kg}$ versus 1,250 $\mu\text{g}/\text{kg}$ naloxone without any significant difference. Average duration of our experiments from naloxone administration was 45 min, so a repetitive injection seemed unnecessary. On the other hand, meperidine plus naloxone injection led to a small increase of threshold temperature compared with meperidine alone in α_{2C} -adrenoceptor knock-out mice. In α_{2B} -adrenoceptor knock-out mice, this tendency also was detectable but not significant. This indicates that opioid receptors—possibly the κ -subtype—in addition are likely to be involved in the mediation of meperidine's effects.

From the current data, no change of the maximum response intensity of shivering as the ratio of the maxi-

mum and minimum carbon dioxide plateau during cooling could be observed. In agreement with our results, Ikeda *et al.*²² did not detect any changes in the maximum intensity of shivering after meperidine and also alfentanil application. However, both drugs proved to decrease the thermoregulatory threshold. This indicates that antishivering activity does not necessarily include both an effect on the thermoregulatory threshold and on the maximum intensity or gain (defined as incremental intensity increase) of shivering.

Our study may be criticized because of the relatively small number of animals investigated, resulting in a certain variability of the results. Furthermore, naloxone was initially administered in only one defined high dosage to block both μ - and κ -opioid receptors, according to previous studies in humans and mice.⁴ Small differences between meperidine and meperidine plus naloxone may not have been detected as result of the sample size. As a result, we cannot conclude that the effects of meperidine on thermoregulation in mice are mediated exclusively by α_2 -adrenoceptors. Furthermore, data from animal studies should be projected to humans with some limitations. Whereas adult humans use shivering as a defense against hypothermia and nonshivering thermogenesis plays only a small role, rodents use nonshivering thermogenesis as their primary mechanism to resist hypothermia. Therefore, it should be clearly stated that our results in mice have only very limited impact on the peri- or postoperative thermoregulation in humans.

In conclusion, the present data indicate that meperidine's ability to decrease the thermoregulatory threshold temperature in wild-type mice is not abolished by additional administration of the opioid receptor antagonist naloxone. In α_{2A} -adrenoceptor knock-out mice, meperidine administration had no significant effect on the thermoregulatory threshold temperature. This indicates an important role of the α_{2A} -adrenoceptor in the modulation of the thermoregulatory response induced by meperidine in mice.

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