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Effect of μ-, κ-, and δ-Selective Opioid Agonists on Thermoregulation in the Rat

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HANDLER, C. M., E. B. GELLER AND M. W. ADLER. *Effect of μ-, κ-, and δ-selective opioid agonists on thermoregulation in the rat.* PHARMACOL BIOCHEM BEHAV 43(4) 1209–1216, 1992.—The effect of selective μ-, κ-, and δ-agonists on brain surface temperature (T_b), oxygen consumption (V_{o_2}), and heat exchange (Q) was studied in unrestrained, male Sprague-Dawley rats using whole-body calorimetry. Hyperthermia, produced by PL-017 (1.86 nM) given ICV, resulted from increased V_{o_2} and reduced Q during the first 15–45 min postinjection. T_b returned to control levels due to a combination of increased Q and reduced V_{o_2}. PL-017-induced hyperthermia was abolished by the μ-selective antagonist CTAP (0.75 nM). Dynorphin A_{1-17} (4.65 nM), a κ-selective agonist, reduced both V_{o_2} and Q, resulting in hypothermia that was blocked by the κ-selective antagonist nor-binaltorphimine (25 nM). The δ-selective agonist DPDPE (4.64 nM) caused no significant changes in T_b, V_{o_2}, *or* Q. The data indicate that central stimulation of the μ- and κ-opioid receptors affects both oxidative metabolism and heat exchange, which result in a change in T_b. These alterations can be prevented with selective opioid antagonist pretreatment.

Temperature regulation Oxygen consumption Heat exchange Selective opioid agonists Thermoregulation

THE endogenous opioid system serves several physiological functions in the body, including a role in temperature regulation. Three distinct opioid receptors—μ, κ, and δ—have been identified (28,29,34). Opioid agonists have been investigated in terms of their ability to alter body temperature (16,17,19,21), the response being dependent upon a number of factors including species, dosage, route of administration, restraint, ambient temperature, and receptor selectivity (3). Morphine, a predominantly μ-agonist, given SC to rats induces hyperthermia at low doses and hypothermia at high doses while ICV administration results only in hyperthermia. Naloxone, a general opioid antagonist, attenuates these effects (3). β-Endorphin alters body temperature in a manner similar to morphine, with modifications induced by dosage, restraint (44), route of administration, and ambient temperature (5,6,8). κ-Agonists, such as U-50,488H or dynorphin A_{1-17}, produce hypothermia (4,5,10,26,36). The role of the δ-receptor in temperature regulation, if any, is unclear (45).

Calorimetry allows not only measurement of changes in body temperature but also alterations in heat exchange and metabolic rate in response to different stimuli. Using calorimetric methods, we have examined the effects of three highly selective opioid agonists and their corresponding antagonists on both oxygen consumption (V_{o_2}) and heat exchange (Q), mechanisms that are the principal elements in the maintenance of body temperature. Tyr-Pro-*N*-MePhe-D-Pro-NH_2 (PL-017) is highly selective for the μ-receptor (12). Cyclic D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2 (CTAP), a somatostatin analog, acts as a selective μ-antagonist (25,35,42). The opioid peptide, dynorphin A_{1-17}, shows high affinity for the κ-receptor (13,14,22); nor-binaltorphimine (nor-BNI) is a selective κ-antagonist (37). Mosberg et al. (33) used the δ-selective agonist, cyclic (D-Pen^2-D-Pen^5)-enkephalin (DPDPE) to identify δ-receptors. Naltrindole is a δ-selective antagonist (1,9,38). The aim of the study was to use the selectivity of the ligands for each receptor to produce a change in T_b and examine the alterations in the patterns of metabolic response, correlating these to T_b, and thereby increasing our understanding of the role of the endogenous opioid system in thermoregulation.

METHOD

Male, albino Sprague-Dawley rats (Zivic-Miller) were housed four to five per cage in an animal room and maintained at 22 ± 2°C and 50 ± 10% relative humidity on a 12 L : 12 D cycle. Rats were fed standard rat chow with water available ad lib. Seven days prior to testing, a polyethylene cannula was implanted into the right lateral ventricle under pentobarbital anesthesia (60 mg/kg, IP). At the same time, a YSI thermistor (Yellow Springs Instruments, Yellow Springs, CO; resistance 2252 Ω at 25°C) was implanted on the surface of the left lateral cortex. Cannula and thermistor were secured to the cranium with stainless steel machine screws and dental acrylic. Animals were housed individually after surgery and

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weighed 250–300 g at time of testing. Cannula placement (approximately 93% correctly placed) was confirmed after testing and animals with incorrectly placed cannulae were not included in the results.

A gradient-layer calorimeter was flushed with air (20% O_2) and brought to testing temperature (20 ± 0.5°C). Measurements were made at the same time each day, during the 12-h light portion of the cycle, eliminating diurnal variation (32). V_{o_2}, Q, and T_b [output measured in V; (18)] were recorded using a MacLab™ and MacClassic™ computer and stored on diskette. Data were continuously recorded for 180 min prior to injection, with the last 60 min constituting a preinjection control for comparisons with continuous recordings 180 min postinjection.

Doses of drugs were selected from full dose–response curves for each agonist using rectal temperature as the end point (5,7,20,24,27). The dose of PL-017 was selected because it induced distinct hyperthermia with side effects limited to sedation and a slight exopthalmia. The dose of dynorphin A_{1-17} was chosen because it produced a robust hypothermia but was not accompanied significant behavioral side effects (such as barrel-rolling) other than sedation. There were no significant changes in T_b at any of the doses of DPDPE (< 100 μg) tested; therefore, the dose used in this study is in the more δ-selective portion of the dose–response curve. Animals given DPDPE did not appear to be sedated.

PL-017 (Peninsula Labs, Belmont, CA), dynorphin A_{1-17} (Bachem Labs, Torrance, CA), and DPDPE (Peninsula) were dissolved in pyrogen-free saline (0.9%) and injected ICV in a volume of 5 μl, followed by a 3-μl saline flush. CTAP (Peninsula), nor-BNI [Research Biomedicals, Inc. (RBI), Natick, MA] and naltrindole (RBI) were dissolved in pyrogen-free saline and injected ICV 30 min (CTAP) or 15 min (nor-BNI and naltrindole) prior to injection of the agonist in a volume of 3 μl with a 3-μl saline flush. Results are reported as ΔT_b (°C), ΔV_{o_2} (ml O_2/g body wt/h), and ΔQ (cal/g body wt/h) from baseline controls for each time interval. These changes were analyzed for each agonist or agonist/antagonist combination using a one-way analysis of variance (ANOVA) with a repeated-measure variable of time, followed by a posthoc Fisher's test. An unpaired Student's t-test was used to evaluate treatment differences at specific time intervals. Results are reported as means of each measured variable ± SEM. Levels of significance were $p \leq 0.05$.

RESULTS

μ-Selective Agonist

As shown in Fig. 1, 1.0 μg (1.86 nM) PL-017 caused a sustained increase in T_b ($p \leq 0.05$), beginning 15–30 min postinjection and lasting for about 1.5 h. V_{o_2} increased (1.57 ml O_2/g/h; $p \leq 0.05$) during the early postinjection period and there was an initial decrease in Q (−0.80 cal/g/h) followed by an increase in Q (+0.80 cal/g/h; $p \leq 0.05$) over preinjection control levels at the time when T_b was returning to control levels. The changes were blocked by 30-min pretreatment with 1 μg (0.75 nM) CTAP, which had no effect of its own. The ratio of Q to V_{o_2}, representing the relationship between the modulatory arms of thermoregulation, decreased sharply prior to PL-017-induced periods of hyperthermia (Table 1). Changes seen in Q/V_{o_2} were absent following CTAP pretreatment.

κ-Selective Agonist

Dynorphin A_{1-17} (10 μg, 4.65 nM) resulted in a significant decrease in T_b ($p \leq 0.05$) and a significant decrease ($p \leq 0.05$) in V_{o_2} for 60–75 min post injection. These decreases were accompanied by significant decreases ($p \leq 0.05$) in heat loss, with recovery beginning 75 min postinjection (Fig. 2). Nor-BNI (25 nM), which had no effect when injected ICV followed by saline, blocked these changes. Q/V_{o_2} increased prior to dynorphin-induced hypothermia (Table 1).

δ-Selective Agonist

DPDPE (3 μg; 4.64 nM) produced no statistically significant changes in T_b, V_{o_2}, *or* Q during the postinjection period (Fig. 3). Naltrindole (1 nM, 15-min pretreatment), a δ-selective antagonist, alone or in combination with DPDPE had no significant effect on any of the measures and Q/V_{o_2} was not changed (Table 1).

DISCUSSION

The functional role of the opioid receptors and their ligands in thermoregulation most certainly involves interaction with other neurotransmitter and neuropeptide systems. Increased evidence (46) points to the G-proteins as the intracellular second messenger system stimulated or inhibited by opioid agonists. Cavicchini et al. (11) demonstrated that pertussis toxin, known to have an uncoupling effect on G-proteins through adenosine diphosphate (ADP) ribosylation, attenuated the hypothermic effect of dynorphin A but did not alter behavioral effects. The long-recognized ability of opioids to alter body temperature has led to attempts to determine the mechanisms involved. Using partial calorimetric methods, Lin and Su (30) have shown a dose-dependent hypothermia in rabbits after injecting morphine or β-endorphin at 2 and 22°C. Hypothermia at 2°C resulted from a reduction in metabolic heat production, while at 22°C an increased peripheral flow as well as reduced metabolic rate contributed to the hypothermia. Using whole-body calorimetry, Lynch et al. (31) and Zwil et al. (47) measured metabolic rate and heat exchange as well as body temperature after administration (SC and ICV) of morphine, methadone, and U-50,488H in rats. A low dose of morphine (4 mg/kg, SC) produced hyperthermia, accompanied by increases in oxygen consumption (V_{o_2}) and heat exchange (Q). Hypothermia from a high dose of morphine (64 mg/kg, SC) or from U-50,488H (SC) was accompanied by decreased metabolic rate, although there were distinct differences in the pattern of recovery from the hypothermia between the two drugs. Recovery from morphine-induced hypothermia was characterized by a sharp increase in V_{o_2} while Q increased but lagged behind T_b and V_{o_2}. T_b began an exponential recovery that lasted 30–60 min. Recovery from U-50,488H-induced hypothermia was characterized by a recovery pattern for T_b lasting for several hours. Increases in V_{o_2} were small and steady while heat loss remained low and stable, representing an active conservation of heat that, in turn, produced the slow recovery of T_b (Lynch, personal communication).

In our laboratory, we have found that the ratio of Q to V_{o_2} represents a useful indicator of the direction of temperature change. In addition, we have found that while body temperature may return to control levels after drug treatment Q and V_{o_2}, either one or both, may remain altered, actively regulating T_b. Of the two metabolic regulators we studied, Q is often the slowest to return to preinjection levels and may be the more active regulator. These changes in regulatory mechanisms influence the direction of change in body temperature and are consistent with the hypothesis that μ- and κ-opioid agonists shift set point, leaving the ability to thermoregulate intact (3,15). The concept of set point is an integral part of thermal

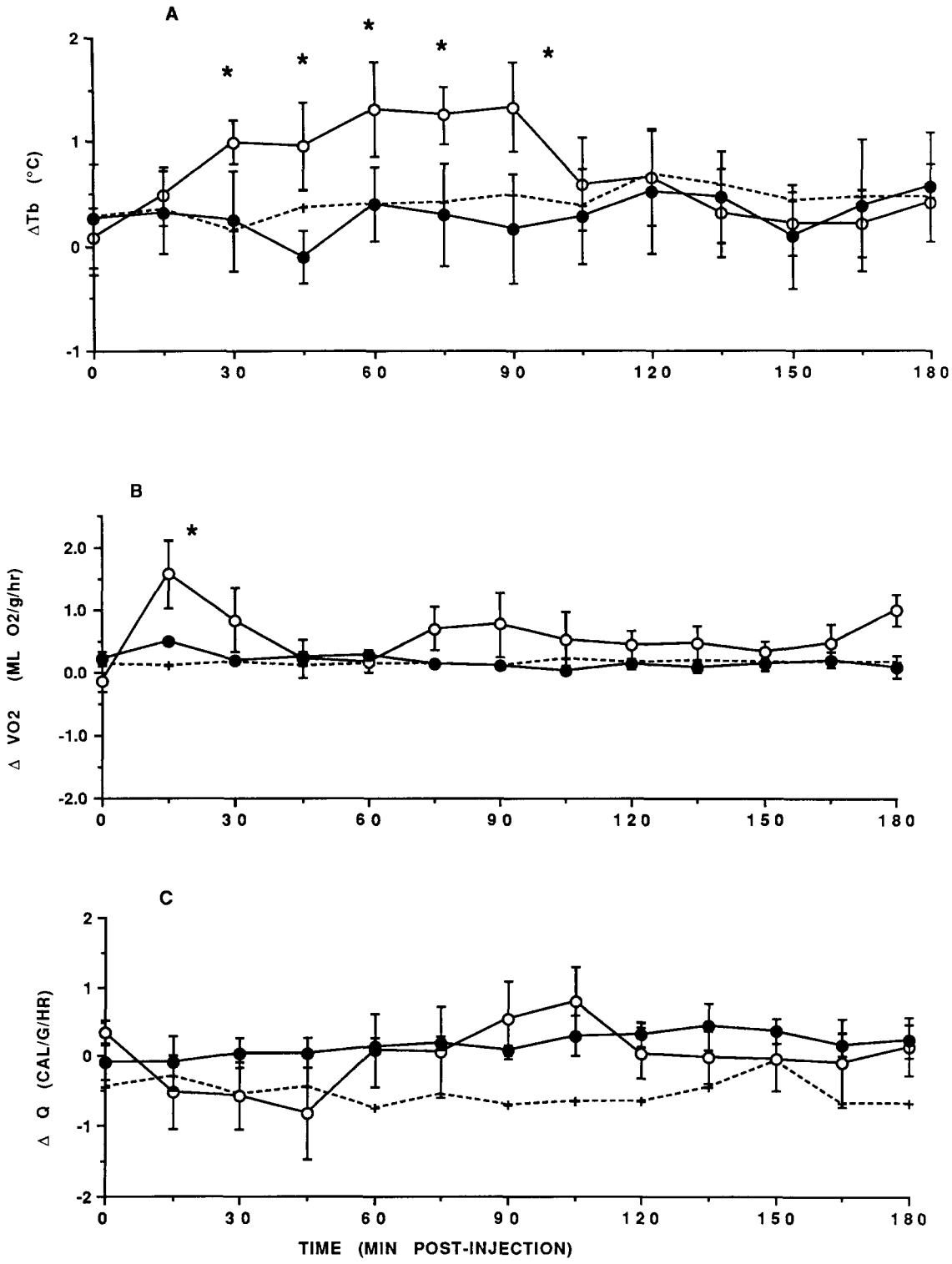

FIG. 1. Effect of PL-017 (1 μg, 1.36 nM, ICV) on the change in brain surface temperature (A), oxygen consumption (B), and heat exchange (C) at 20°C. Saline (----), PL-017 (○), and PL-017 + CTAP (●) are reported at 15-min intervals postinjection. Each point represents the mean of at least six animals ± SEM. *$p \leq 0.05$.

TABLE 1

PERCENT CHANGE IN Q/VO_2 FOR SELECTIVE μ-, κ-, AND Δ-AGONISTS

	PL-017 (%)*		Dynorphin (%)*		DPDPE (%)*	
Time (min)†	$\Delta Q/VO_2$	ΔT	$\Delta Q/VO_2$	ΔT	$\Delta Q/VO_2$	ΔT
0	109	±	114	−	116	±
15	39	±	138	−	122	±
30	55	±	161	−	114	±
45	81	+	191	−	112	±
60	97	+	155	−	109	±
75	65	+	124	±	108	±
90	67	+	115	±	112	±
105	80	±	113	±	116	±
120	77	±	128	±	117	±
135	74	±	135	±	114	±
150	82	±	144	±	109	±
165	73	±	148	±	114	±
180	56	±	136	±	124	±

+, significant increase in temperature; −, decrease in temperature; ±, no change in temperature.
*Change from preinjection control.
†Minutes postinjection.

physiology. Set point is the temperature that is subject to regulation within narrow limits, the sum of all effectors being zero (41). In simplest terms, the set-point model holds that the regulation of body temperature results from an active process of adjustment of the levels of body temperature to the level prescribed by the set point (39). Drugs, as well as other nonthermal factors, such as fever, sleep, and circadian rhythm, may alter set point. Alternatively, a drug may impair the ability to thermoregulate, causing a drift toward heterothermy (3,23). The precise control of body temperature, characteristic of homeotherms, results from the multilayered integration of sensory input into a multilevel response (40).

In the present study, the μ-selective agonist PL-017 induced a hyperthermia of 1.33°C 30–90 min postinjection. This increase in T_b was preceded by a 142% increase in V_{O_2}, as well as a decrease in Q, representing an increase in the quantity of available metabolic heat and a conservation of that generated heat, both of which contributed to the rise in T_b and regulation at the new temperature. These changes were mirrored by a Q/V_{O_2} decrease during this period, preceding the rise in T_b. Spencer et al. (43) found that the μ-agonist DAMGO (0.3 μg, ICV) produced hyperthermia in conjunction with the behavioral selection of a warm (31°C) ambient temperature in a thermocline during the rising phase of hyperthermia and a shift to cooler ambient temperatures during the return to basal levels. Mean time to reach peak hyperthermia was 59.7 min with a range of 40–80 min. Our data, along with the work of Spencer, indicate that μ-selective opioid agonists, given ICV at low doses, act to shift thermoregulatory set point.

Dynorphin $A_{1\text{-}17}$, a κ-selective agonist, induced a decrease in T_b, primarily as the result of a decrease in metabolic rate. There were corresponding decreases in Q that probably represent a thermoregulatory reaction to the lower quantity of generated metabolic heat. Overall, the Q/V_{O_2} ratio showed an increase. Thus, there was a relative decrease in the amount of available heat and a resultant drop in T_b. Changes in heat gain/loss also appeared to be responsible for the return of T_b to baseline. Nor-BNI, the highly selective κ-antagonist, blocked the changes in V_{O_2} and Q, thus preventing a change in T_b. Cavicchini et al. (10) reported similar changes in T_b with dynorphin A (5 and 10 nM, ICV) that were blocked with verapamil and MR 1452 but not naloxone or naltrexone. Spencer et al. (43) found that 100 μg of the κ-agonist U-50,488H resulted in a small degree of hypothermia in conjunction with behavioral selection of cool (13°C) ambient temperatures during the falling phase of hypothermia (first 25 min postinjection). Adler et al. [(4) and unpublished results] were unable to obtain similar changes in T_b with ICV administration of U-50 (doses < 100 μg), although higher doses and SC injection did produce dose-related hypothermia that was attenuated by naloxone. Other κ-selective agonists, such as U-69,593 and spiradoline, given ICV, also produced hypothermic effects that were antagonized by nor-BNI (2). Our data and that of others point toward a κ-agonist-induced shift in set point, although the results are not as clear when compared to the μ-agonist changes.

Our results demonstrate that DPDPE, the δ-selective agonist, produces no significant changes in T_b or in the metabolic parameters that support it. Likewise, naltrindole, a δ-selective antagonist, had no effect on T_b, V_{O_2}, *or* Q. In our laboratory, doses of up to 38 μg DPDPE given ICV have produced no significant changes in T_b (2) although Spencer et al. (43) demonstrated a small hypothermia (<1°C) in conjunction with selection of cool ambient temperatures during hypothermia using doses of 30 μg. The hypothermia was not blocked by naloxone (3 and 10 mg/kg, SC) or the δ-selective antagonist ICI 174,864 (1 and 3 μg, ICV), indicating that the hypothermia was a non-opioid-receptor-mediated effect.

The data presented in this study extend the findings on SC and ICV morphine administration in rats reported by Lynch et al. (31) and Zwil et al. (47). Changes in V_{O_2} and Q may be induced by μ-selective agonists acting on central receptors. Prior to hyperthermia, there is an abrupt increase in V_{O_2}. The heat generated by the increase in peripheral oxidative metabolism is initially conserved (a decrease in heat loss, $-\Delta Q$). These sequential events produce an increase in body temperature. Regulation at the increased temperature represents a change in set point. Return to baseline levels is the result of a

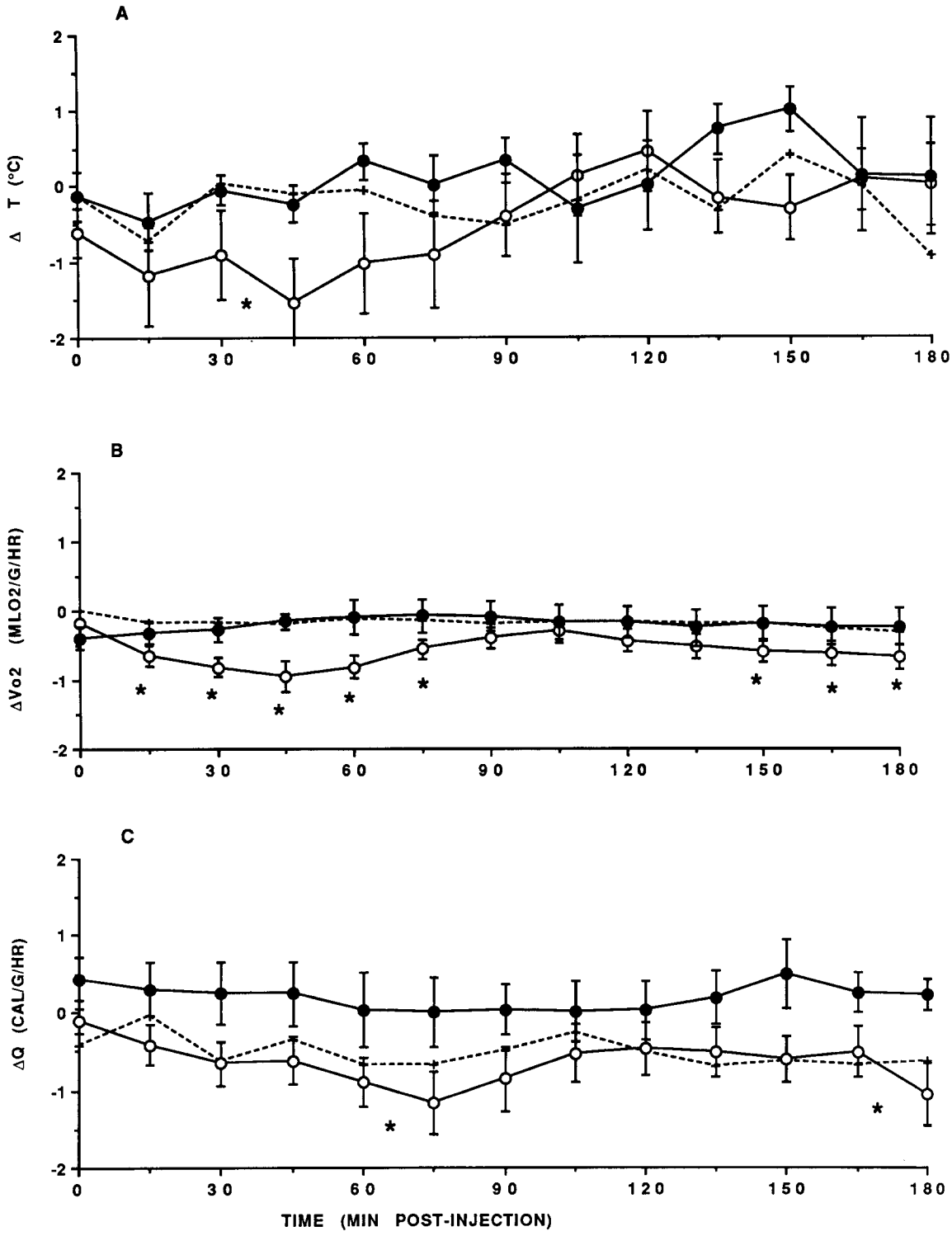

FIG. 2. Effect of dynorphin $A_{1\text{-}17}$ (10 μg, 4.65 nM, ICV) on the change in brain surface temperature (A), oxygen consumption (B), and heat exchange (C) at 20°C. Saline (-----), dynorphin $A_{1\text{-}17}$ (○), and dynorphin $A_{1\text{-}17}$ + nor-BNI (●) are reported at 15-min intervals postinjection. Each point represents the mean of at least seven animals ± SEM. *$p \leq 0.05$.

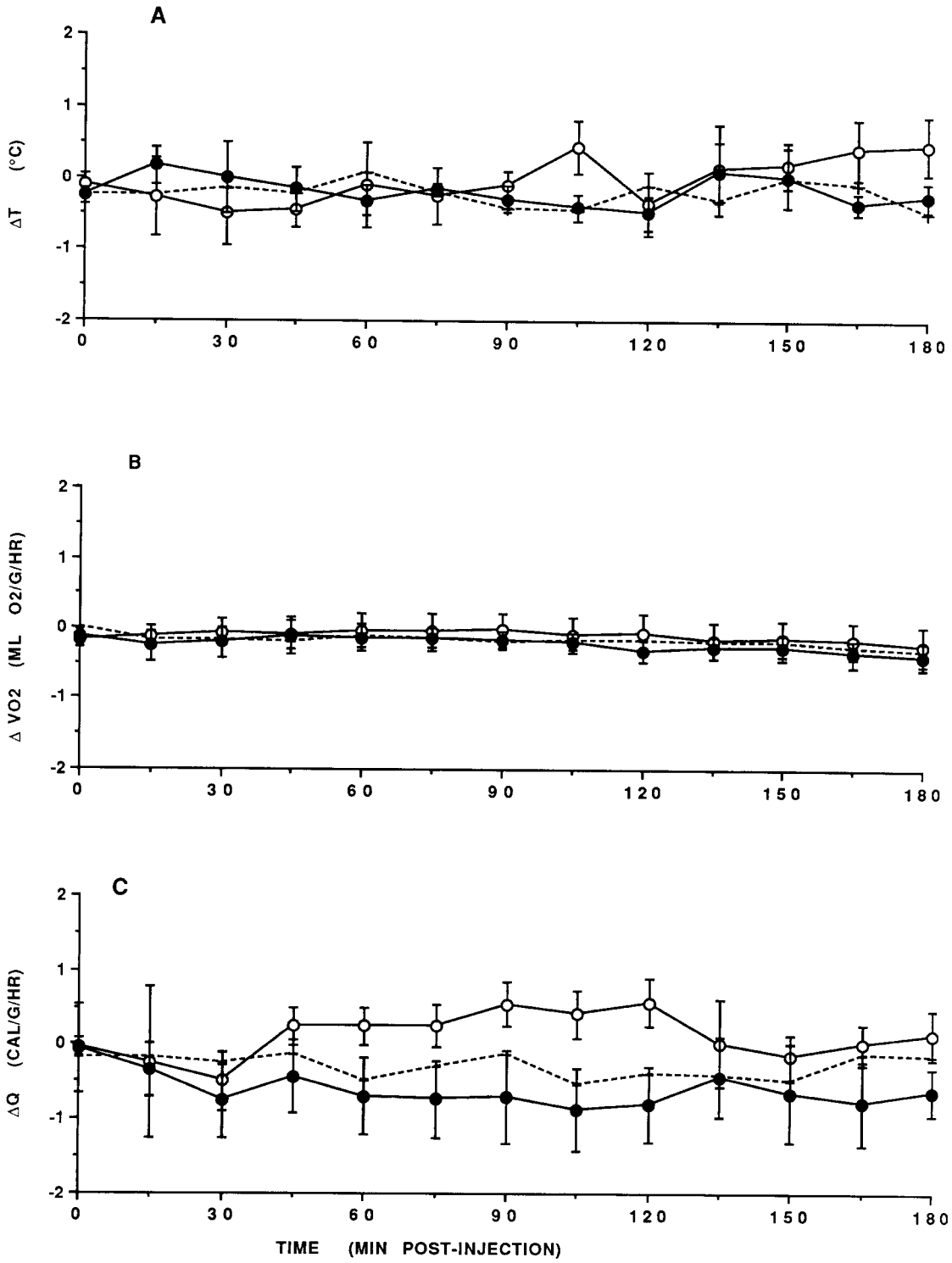

FIG. 3. Effect of DPDPE (3 μg, 4.64 nM, ICV) on the change in brain surface temperature (A), oxygen consumption (B), and heat exchange (C) at 20°C. Saline (-----), DPDPE (○), and DPDPE + naltrindole (●) are reported at 15-min intervals postinjection. Each point represents the mean of at least seven animals ± SEM. *$p \leq 0.05$.

decrease in V_{O_2} and an increase in heat loss. Hypothermia, induced by a κ-agonist, results from a decrease in V_{O_2} as well as a decrease in heat loss. Under these conditions, the reduced level of metabolic heat appears to be actively conserved over an extended period of time, returning body temperature to preinjection levels.

We have presented data that demonstrate that stimulation of central opioid receptors by selective μ- and κ-ligands results in changes in oxidative metabolism. The increase or decrease in metabolic rate is responsible for the quantity of heat that is available to regulate T_b through heat exchange mechanisms. These alterations in metabolic rate and heat exchange can be blocked with selective opioid receptor antagonist pretreatment. In addition, it would appear that oxidative metabolism is extremely sensitive to μ- and κ-opiate receptor stimulation and is the probable primary cause of altered T_b following μ- or κ-activation. Central stimulation of δ-receptors by DPDPE does not appear to have a direct effect on the metabolic parameters that support T_b. Studies of similar interactions promise to provide important new information on the mechanisms that homeotherms utilize to maintain a stable internal temperature needed for the optimal functioning of multiple systems in the body.

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