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Opioid, cannabinoid CB_1 and NOP receptors do not mediate APAP-induced hypothermia in rats

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ABSTRACT

Acetaminophen (APAP) produces antinociception and hypothermia. Because the antinociceptive effect in rats is partially dependent on opioid and cannabinoid CB_1 receptor activation, we determined if activation of these receptors also contributes to the hypothermic effect of APAP. Rats injected with APAP (100, 250, 375 or 500 mg/kg, i.p.) displayed dose-related hypothermia. For combined administration, the hypothermic effect of APAP (400 mg/kg, i.p.) was not altered by pretreatment with: naltrexone (10 mg/kg, s.c.), a non-selective opioid antagonist; naltrindole (1 mg/kg, s.c.), a delta opioid antagonist; nor-binaltorphimine (10 mg/kg, i.p.), a kappa opioid antagonist; SR 141716A (3 mg/kg, i.m.), a cannabinoid CB_1 receptor antagonist; or JTC-801 (1 mg/kg, i.p.), a nociceptin/orphanin FQ peptide (NOP) receptor antagonist. The demonstration that APAP produces hypothermia independent of opioid, cannabinoid CB_1 or NOP receptor activation is contrary to its antinociceptive effect, which requires opioid and cannabinoid CB_1 receptor activation.

1. Introduction

The mechanism of action of acetaminophen (APAP) remains unclear 120 years after its original synthesis. It penetrates the brain following peripheral administration, and evidence suggests a central component to its mechanism of action (Björkman, 1995). Unlike traditional non-steroidal anti-inflammatory drugs, APAP does not significantly bind to the cyclooxygenase (COX) (prostaglandin H_2 synthase, PGHS) isozymes, COX-1/PGHS-1 or COX-2/PGHS2, at analgesic doses (Hinz and Brune, 2007). A major therapeutic use of APAP, in addition to relieving pain, is to reduce fever caused by bacterial and viral infections and by clinical trauma such as cancer or stroke (Oborilová et al., 2002; Prescott, 2000). A less recognized effect of APAP is its capacity to produce hypothermia in the absence of fever. For example, therapeutic doses of APAP cause hypothermia in humans (e.g., in febrile children or HIV or stroke patients) and high doses of APAP induce hypothermia in mice (Ayoub et al., 2004; Denes et al., 2004; Dippel et al., 2003; Li et al., 2008; Van Tittelboom and Govaerts-Lepicard, 1989; Walker et al., 1981). The mechanism of APAP hypothermia, especially in regard to the messengers and receptors which initiate the process, is poorly understood. APAP-induced hypothermia in mice is accompanied by a reduction in brain levels of prostaglandin E_2 (PGE_2), and (PGHS-1b) (COX-3) has been proposed to account for this hypothermic effect (Ayoub et al., 2004). However, there is no consistent evidence in the literature that central PGE_2 participates in the control of normal body temperature in any species, and a recent study demonstrated that APAP produces hypothermia in mice by a COX-3-independent mechanism (Aronoff and Romanovsky, 2007; Satinoff, 1972; Li et al., 2008).

One approach to elucidating the process of APAP hypothermia is to identify receptors which play a permissive role in the hypothermia. Two lines of evidence suggest a potential role for opioid and cannabinoid receptors. First, the antinociceptive effect of APAP in rats is partially dependent on opioid and cannabinoid CB_1 receptor activation (Bujalska, 2004; Ottani et al., 2006). Second, cannabinoid CB_1, kappa opioid or delta opioid receptor activation causes hypothermia in rats and mice (Rawls et al., 2002, 2005; Baker and Meert, 2002; Handler et al., 1992; Spencer et al., 1988; Geller et al., 1982). Thus, we hypothesized that cannabinoid CB_1, kappa opioid, or delta opioid receptor antagonism would reduce a significant proportion of APAP-induced hypothermia. We also investigated a role for nociceptin/orphanin FQ peptide (NOP) receptors in the hypothermia.

2. Methods

2.1. Animals

All animal use procedures were conducted in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Institutional University Animal Care and Use

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Committee. Male Sprague–Dawley rats (Zivic-Miller, Pittsburgh, PA, USA) weighing 225–250 g were housed 1 per cage for a minimum of 5 days before experimental use. Rats were maintained on a 12-h light/dark cycle and fed rat chow and water ad libitum. Each rat was used in a single experiment and then immediately euthanized.

2.2. Materials

Acetaminophen (N-acetyl-p-aminophenol) was purchased from Sigma (St. Louis, MO, USA) and dissolved in dimethylsulfoxide (DMSO). Drugs provided by the National Institutes on Health (Bethesda, MD, USA) were naltrexone hydrochloride, a nonselective opioid receptor antagonist; naltrindole hydrochloride, a delta opioid receptor antagonist; and SR 141716A (rimonabant) [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride], a cannabinoid CB_1 receptor antagonist. A kappa opioid receptor antagonist, nor-Binaltorphimine dihydrochloride (nor-BNI), was purchased from Tocris Biosciences (St. Louis, MO, USA). Naltrexone, naltrindole and nor-BNI were dissolved in distilled water. SR 141716A was dissolved in a 20% cremophor/80% distilled water solution. A NOP receptor antagonist, JTC-801 [N-(4-amino-2-methylquinolin-6-yl)-2-(4-ethylphenoxy-methyl)benzamide monohydrochloride], was a generous gift from Dr. Nurulain T. Zaveri (SRI International in Menlo Park, CA, USA). JTC-801 was dissolved in a 20% DMSO/80% distilled water solution. All drugs were administered in a volume of 1 ml/kg.

2.3. Experimental protocol

Body temperature experiments were conducted as described previously (Rawls et al., 2007). Rats were placed in an environmental room maintained at a constant temperature of 21 ± 0.3 °C and relative humidity of 52 ± 2%. Following a 2-h acclimation interval, baseline temperature measurements were taken with a thermistor probe, which was lubricated and inserted 6 cm into the rectum, and a digital thermometer. Prior to drug administration, body temperature was determined every 30 min during a 90-min baseline interval. Initially, we determined the dose- and time-related effects of APAP by itself on body temperature. Following the baseline period, graded doses of APAP (100, 250, 375 or 500 mg/kg, i.p.) were injected and body temperatures were determined 30, 60, 90, 120, 150, 180 and 210 min post-administration. Based on results obtained from this initial experiment, we selected a fixed, submaximal dose of 400 mg/kg of APAP for our combination experiments. In those experiments, rats pretreated with an opioid, cannabinoid CB_1 or NOP receptor antagonist were injected with 400 mg/kg of APAP and body temperatures were determined 30, 60, 90, 120, 150, 180 and 210 min post-injection (Table 1).

2.4. Data analysis

Three consecutive body temperature readings were averaged to establish a baseline (predrug) temperature prior to drug administration. Raw data were transformed into 'normalized ranks' to address non-normality and expressed as the mean ± S.E.M. of the change from baseline body temperature. For the experiment investigating the effects of APAP by itself, data were analyzed using a repeated measures, two-way analysis of variance followed by pair-wise multiple comparisons incorporating the Bonferroni correction at the different time points. For drug combination experiments, data were analyzed using a Student's *t*-test (APAP group compared to antagonist/APAP group) except for the naltrexone experiments, which were analyzed with repeated measures two-way ANOVA. Values of $P<0.05$ were considered to be statistically significant.

Table 1
Dosing paradigm for receptor antagonist/APAP experiments.

Antagonist	Dose (mg/kg)	Administration route	Pretreatment (prior to acetaminophen injection)
Naltrexone (NTX)	10	s.c.	10 min[a]
Naltrindole (NTI)	10	s.c.	10 min
Nor-binaltorphimine (nor-BNI)	1	i.p.	24 h
SR 141716A	3	i.m.	30 min
JTC-801	1	i.p.	30 min

[a] Naltrexone was also administered a second time, 90 min following APAP administration, because of its relatively short half-life.

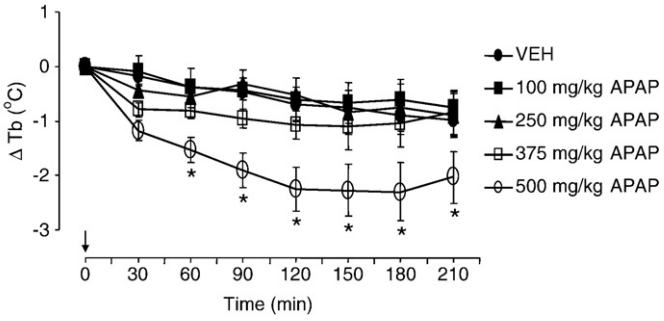

Fig. 1. Effect of APAP (APAP) on body temperature. APAP (100, 250, 375 or 500 mg/kg) or vehicle (VEH) was injected following a 90-min baseline interval. Data were expressed as change in body temperature [ΔTb (°C)] compared to baseline. $N = 7–8$ rats per group. *$P<0.05$ compared to VEH.

3. Results

3.1. Effect of APAP on body temperature

Effects of progressively increasing doses of APAP (100, 250, 375 and 500 mg/kg) on body temperature are presented in Fig. 1. There was a significant drug effect [F (4, 31) = 26.38; $P<0.001$] and time effect [F (7, 217) = 9.005; $P<0.001$] but not a significant drug × time interaction [F (28, 217) = 0.8304; $P = 0.7143$]. The highest dose (500 mg/kg) of APAP produced significant hypothermia, compared to vehicle, 60, 90, 120, 150, 180 and 210 min following administration ($P<0.05$). A maximal hypothermia of 2.7 ± 0.5 °C was observed 120 min post-administration. A submaximal dose of APAP (400 mg/kg) was used in all subsequent experiments.

3.2. Effect of opioid receptor antagonists on APAP-induced hypothermia

The effect of naltrexone (10 mg/kg) on APAP-induced hypothermia is presented in Fig. 2. There was a significant drug effect [F (3, 33) = 122.1; $P<0.001$]; time effect [F (7, 231) = 17.321; $P<0.001$]; and drug × time interaction [F (21, 231) = 4.869; $P<0.001$] (Fig. 2A). Compared to drug-naïve rats (i.e., vehicle/vehicle), rats co-treated with a combination of vehicle and APAP (400 mg/kg) displayed significant hypothermia 60, 90, 120, 150, 180 and 210 min post-injection ($P<0.05$) (Fig. 2A). Rats co-exposed to a combination of naltrexone (10 mg/kg) and vehicle also displayed significant hypothermia, compared to drug-naïve rats, 60, 90, 120, 150 and 180 min post-injection ($P<0.05$). However, body temperatures of rats exposed to vehicle/APAP (400 mg/kg) were not different significantly from rats treated with naltrexone (10 mg/kg)/APAP (400 mg/kg) ($P>0.05$).

Effects of naltrindole (1 mg/kg) and nor-BNI (10 mg/kg) on the hypothermic effect of APAP (400 mg/kg) are presented in Fig. 2B and C, respectively. Rats exposed to a combination of naltrindole (1 mg/kg) and APAP (400 mg/kg) displayed body temperatures that were not different significantly from rats treated with APAP (400 mg/kg) by itself (i.e., vehicle/APAP) ($P>0.05$) (Fig. 2B). A kappa opioid receptor antagonist, nor-BNI (10 mg/kg) was also ineffective as body temperatures in rats co-treated with nor-BNI (10 mg/kg) and APAP

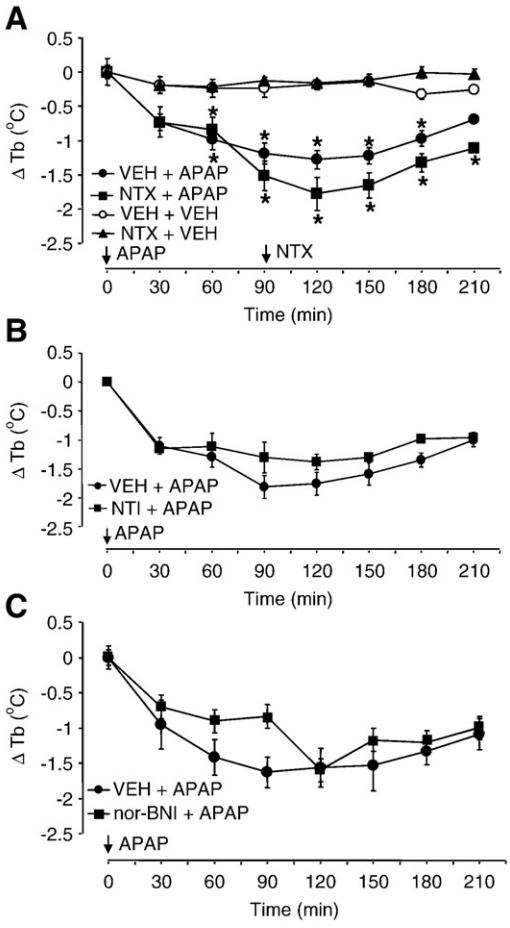

Fig. 2. Effect of opioid receptor antagonists on the hypothermic effect of APAP (APAP). A: Rats were injected with APAP (400 mg/kg) or vehicle (VEH) 10 min following the administration of naltrexone (NTX) (10 mg/kg) or VEH. NTX (10 mg/kg) was administered again 90 min following APAP administration. B–C: Rats were injected with APAP (400 mg/kg) 10 min following naltridole (NTI) (1 mg/kg) or 24 h following nor-BNI (10 mg/kg) administration. Data were expressed as change in body temperature [ΔTb (°C)] compared to baseline. $N = 6$–11 rats per group. *$P < 0.05$ compared to VEH + VEH.

(400 mg/kg) were not significantly different than the body temperatures of rats exposed to APAP (400 mg/kg) by itself ($P > 0.05$) (Fig. 2C). Prior work conducted in this laboratory has demonstrated that naltrindole or nor-BNI does not alter body temperature when given by itself (Wang et al., 2008).

3.3. Effect of a cannabinoid CB_1 or NOP receptor antagonist on APAP-induced hypothermia

The effects of SR 141716A (3 mg/kg) and JTC-801 (1 mg/kg) on the hypothermic effect of APAP (400 mg/kg) are presented in Fig. 3. APAP (500 mg/kg), when given by itself, produced hypothermia that was not significantly different from the hypothermia produced by co-treatment with APAP (400 mg/kg) and SR 141716A (3 mg/kg) or APAP (400 mg/kg) and JTC-801 (1 mg/kg) ($P > 0.05$) (Fig. 3A–B). This laboratory has demonstrated that SR 141716A or JTC-801 does not alter body temperature when given by itself (Rawls et al., 2002, 2007).

4. Discussion

The present study tested the hypothesis that APAP produces hypothermia in non-febrile rats that depends on opioid and cannabinoid CB_1 receptor activation. We found that APAP produces hypothermia in rats, an effect which is consistent with the hypothermic response to APAP in humans (Denes et al., 2004; Dippel et al., 2003; Van Tittelboom and Govaerts-Lepicard, 1989) and mice (Walker et al., 1981; Ayoub et al., 2004; Li et al., 2008). Maximal hypothermia observed in rats (2.7 ± 0.5 °C) was similar to the peak hypothermia reported in mice (2–4 °C) (Ayoub et al., 2004; Li et al., 2008). Although the dose of APAP used in our experiments was high compared to its therapeutic dose in humans (Björkman, 1995), its concentration remained below toxic levels in rats and mice (Ganados-Soto et al., 1992; Hunskaar et al., 1986). Furthermore, similarly high doses are required to induce hypothermia in mice (Ayoub et al., 2004).

Experimental results disproved the second portion of our hypothesis — that opioid and cannabinoid CB_1 receptor activation mediates APAP-induced hypothermia. We had speculated that kappa opioid, delta opioid and cannabinoid CB_1 receptors would play a permissive role in the hypothermic response to APAP because opioid agonists produce hypothermia in rats and mice by activating kappa and delta opioid receptors and cannabinoid agonists produce hypothermia by activating cannabinoid CB_1 receptors (Compton et al., 1992; Rawls et al., 2002, 2005; Baker and Meert, 2002; Handler et al., 1992; Geller et al., 1982). Yet, none of the receptor antagonists (naltrexone, naltrindole, nor-BNI or SR 141716A) tested in our experiments altered APAP-induced hypothermia. The ineffectiveness of opioid and cannabinoid CB_1 receptor antagonists is different from their effects on APAP-evoked analgesia in rats (Pini et al., 1997; Bujalska, 2004; Ottani et al., 2006). Even though APAP lacks affinity for opioid receptors *in vitro* (Pelissier et al., 1996), acute antagonism of kappa, delta or mu opioid receptors reduces the antinociceptive efficacy of APAP in the Randall and Selitto paw withdrawal test (Bujalska, 2004). Moreover, cannabinoid CB_1 receptor antagonism prevents the antinociceptive effect of APAP in the hot-plate assay of thermal nociception (Ottani et al., 2006). These combined results suggest that APAP-induced hypothermia and antinociception are mediated by dissimilar mechanisms, with the antinociceptive effect depending on downstream activation of opioidergic and cannabinergic systems and the hypothermic response occurring independently of opioid and cannabinoid receptors (Pini et al., 1997; Bujalska, 2004; Ottani et al., 2006).

NOP receptor activation also produces hypothermia in rats and mice and modulates APAP-induced antinociception (Sandrini et al., 2005). NOP receptors, and their endogenous ligand, N/OFQ, are distributed

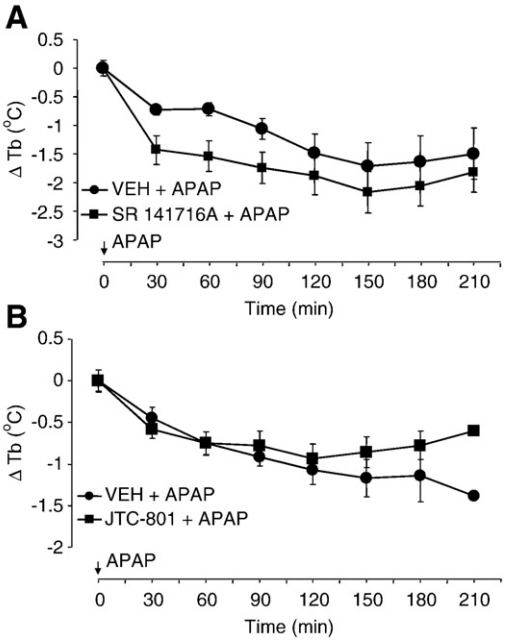

Fig. 3. Effect of a cannabinoid CB_1 or NOP receptor antagonist on the hypothermic effect of APAP (APAP). Rats were injected with APAP (400 mg/kg) 30 min following the administration of either SR 141716A (5 mg/kg) or JTC-801 (1 mg/kg). Data were expressed as change in body temperature [ΔTb (°C)] compared to baseline. $N = 6$–8 rats per group.

widely in the central and peripheral nervous systems (Mollereau and Mouledous, 2000; Meunier, 1997). Prior work indicates that N/OFQ administration causes hypothermia (Yakimova and Pierau, 1999; Chen et al., 2001; Higgins et al., 2001; Rawls et al., 2007) whereas NOP receptor knockout, or knockdown, causes hyperthermia (Uezu et al., 2004; Blakley et al., 2004). Unlike opioid and cannabinoid CB_1 receptor activation, which enhance the antinociceptive effect of APAP (Pini et al., 1997; Bujalska, 2004; Ottani et al., 2006), NOP receptor activation inhibits APAP-induced antinociception (Sandrini et al., 2005). In our experiments, we examined the effect of a NOP receptor antagonist, JTC-801, on APAP-induced hypothermia and found that it was ineffective. Because the dose of JTC-801 used here abolishes the hypothermic effect of N/OFQ (Rawls et al., 2007), it is unlikely that NOP receptor activation is a major factor in the hypothermic effect of APAP.

The present findings indicate that the hypothermic effect of APAP is mediated by opioid and cannabinoid receptor-independent substrates. One possibility is the APAP-sensitive PGHS isoform PGHS-1b (COX-3), a splicing variant of PGHS-1 retaining intron-1 (Simmons et al., 2000; Chandrasekharan et al., 2002; Ayoub et al., 2004). It has been suggested that selective inhibition of hypothalamic COX-3 by APAP causes a reduction in brain levels of prostaglandin (PGE2), believed to be the final fever mediator in the brain, and that this action of APAP is responsible for its hypothermic effect (Ayoub et al., 2004). At least three lines of evidence support a COX-3-related mechanism: (1) APAP penetrates the brain following peripheral administration (Courade et al., 2001; Anderson et al., 1998), rapidly decreases COX-3 mRNA (Botting and Ayoub, 2005), and reduces brain PGE_2 levels (Ayoub et al., 2006); (2) COX-3 inhibitors aminopyrine and antipyrine also cause dose-dependent hypothermia in rats and mice (Polk and Lipton, 1975); and (3) intracerebroventricular APAP administration produces hypothermia that is rapid in onset (Massey et al., 1982). The proposed COX-3 mechanism of action for APAP is controversial because of inconclusive evidence that PGE_2 participates in the control of normal body temperature and recent evidence that hypothermia induced by APAP in non-febrile mice is not paralleled by a significant, similarly transient decrease in brain or plasma PGE_2 levels (Ayoub et al., 2004; Aronoff and Romanovsky, 2007; Satinoff, 1972; Li et al., 2008). Another mechanism of the hypothermic effect of APAP may be related to its antioxidant and anti-glutamatergic properties (Maharaj et al., 2004, 2006). Blockade of free radical production inhibits PGE_2 production and prevents fever (Gourine, 1995; Feleder et al., 2007), and antioxidants antagonize the elevation of hypothalamic hydroxyl radicals generated by glutamate release (Huang et al., 2004). Hence, the ability of APAP to inhibit glutamate-induced neuronal excitability by reducing thiol groups attached to NMDA receptor might contribute to its hypothermic, as well as antipyretic, effects (Huang et al., 2004; Canini et al., 2003). The ability of APAP to increase forebrain levels of norepinephrine might also contribute to its hypothermic action (Courade et al., 2001). Indeed, prior work shows that norepinephrine administered into the hypothalamus causes hypothermia similar to that produced by APAP (Feleder et al., 2004).

In summary, we report that APAP produces hypothermia in non-febrile rats, and that hypothermia is not altered by pharmacological antagonism of opioid, cannabiniod CB_1 or NOP receptors. These data provide pharmacological evidence that opioid, cannabinoid CB_1 and NOP receptors do not play a permissive role in the hypothermic effect of APAP in rats. This is different from APAP-induced antinociception, which is positively modulated by opioid and cannabinoid CB_1 receptors and negatively modulated by NOP receptors (Pini et al., 1997; Bujalska, 2004; Ottani et al., 2006; Sandrini et al., 2005).

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