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Capsaicin Treatment and Stress-Induced Analgesia

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BODNAR, R. J., D. A. SIMONE, J. H. KORDOWER, A. L. KIRCHGESSNER AND G. NILAVER. *Capsaicin treatment and stress-induced analgesia.* PHARMACOL BIOCHEM BEHAV **18**(1) 65–71, 1983.—Capsaicin modulates animal pain perception, increasing chemosensitive and pressure thresholds following systemic administration, increasing thermal thresholds following intrathecal administration, and decreasing electric shock thresholds following intracerebroventicular (ICV) administration. Since morphine analgesia is decreased in a dose-dependent manner following ICV capsaicin, the present study examined whether ICV injections of capsaicin (0, 25, 50, 100 μg) would alter other analgesic responses as well. Experiment 1 demonstrated that the analgesic response to a 450 mg/kg dose of 2-deoxy-D-glucose was significantly reduced by the 25 and 50, but not the 100 μg capsaicin dose. Further, while analgesia induced by cold-water swims (CWS) in a 2°C bath was significantly attenuated by the 25 μg capsaicin dose, the entire dose range eliminated analgesia induced by CWS in a 15°C bath. Experiment 2 indicated that the capsaicin-induced alterations in CWS analgesia were not attributable to parallel changes in CWS hypothermia. Experiment 3 demonstrated that capsaicin failed to alter both the non-opioid analgesic response induced by 20 inescapable foot shocks (FS) and the opioid analgesic response induced by 80 FS. These data are discussed in terms of the similarities to and/or dissimilarities from capsaicin-induced effects upon morphine analgesia.

Capsaicin Cold-Water swim analgesia Foot shock analgesia 2-deoxy-D-glucose analgesia Rats

CAPSAICIN (CAP), the active ingredient of Mexican red peppers and Hungarian hot peppers, has been employed recently as an agent to modulate nociceptive thresholds. Systemic CAP injections produce an insensitivity to chemical [25] and pressure [20] stimuli in rats, effects which may be attributed to irritation around the injected area (see review: [42]). Thermal analgesia has been observed following CAP in normal rats following intrathecal [42], but not systemic [12] routes of administration. Furthermore, CAP increases hot-plate and tail-flick latencies in spontaneously hypertensive rats [41], produces thermal analgesia in guinea pigs [11] and impairs heat discrimination learning [33]. Neonatal administration of CAP also induces analgesic responses when these animals are tested as adults [12, 22, 32].

Initial observations indicated that CAP altered pain thresholds by producing a calcium-dependent release and subsequent depletion of substance P from spinal primary sensory neurons located in the superficial layers of the dorsal horn following systemic [11, 12, 18, 26, 28, 40], intrathecal [30,44] and intracisternal [24] administration in adults. A similar pattern is observed in neonatally-treated animals receiving systemic CAP [21, 31, 32]. Like substance P, CAP produced excitatory potentials when applied microiontophoretically into the trigeminal nucleus caudalis [36]. However, despite the depletion of substance P by CAP pretreatment, nociceptive units in the trigeminal nucleus caudalis were found to be unaffected [35]. Yet, C-fiber conduction in the sciatic nerve is blocked by CAP [43]. Moreover, further studies have indicated that CAP possessed multiple modes of action. These include depletion of somatostatin [30] from the dorsal horn, a decrease of opiate [17,32] and GABA [38] receptors on primary sensory neurons, and an increase in the tissue concentrations of histamine and serotonin [23]. In addition, cholecystokinin is depleted from the dorsal horn when CAP is administered systemically to adults [1,45], but not when it is administered to neonates [29,37].

The route of administration is another integral factor in assessing CAP's effects. Our laboratory [7] found that intracerebroventricular (ICV) injections of CAP produced a short-lived hyperalgesic effect on the flinch-jump test and decreased the analgesic response to morphine in a dose-dependent manner. Using immunocytochemical procedures, we found that ICV injections of CAP failed to alter substance P in either the periaqueductal gray, nucleus raphe magnus, medullary reticular formation, the dorsolateral funiculus or the superficial layers of the spinal cord and fifth cranial nerve. The present study examined whether ICV injections of CAP would alter other analgesic responses as well. These analgesic responses were chosen specifically because of their respective similarities to and differences from morphine analgesia, factors that will be discussed in further detail. Experiment 1 was designed to examine CAP's dose-dependent (0, 25, 50, 100 μg) effects following ICV injection upon the analgesic responses following 2°C and 15°C cold-water swims (CWS) as well as a 450 mg/kg dose of 2-deoxy-D-glucose (2DG). Since CAP decreases core body temperature [15, 27, 34] and neural responses to thermal

stimuli in the hypothalamus [15,34], Experiment 2 assessed whether any of CAP's effects upon CWS analgesia were attributable to changes in CWS hypothermia. Finally, Experiment 3 investigated whether the same icv CAP dose range altered differentially the analgesic responses following 20, 40, 60 or 80 trials of inescapable foot shock (FS) [19].

EXPERIMENT 1: CAPSAICIN AND CWS AND 2DG ANALGESIA

Method

Twenty-four male albino Sprague-Dawley rats were anesthetized with Pentothal (50 mg/ml sterile water/kg body weight, IP). One stainless steel 22 ga guide cannula (Plastic Products) was stereotaxically (Kopf) implanted into each rat's brain and aimed so that its tip was positioned 0.3 mm above the left lateral ventricle. With the incisor bar set at +5 mm, lateral ventricle coordinates were 0.5 mm anterior to the bregma suture, 1.3 mm lateral to the sagittal suture and 3.6 mm from the top of the skull. The cannula was secured to three stainless steel screws with dental acrylic. Ten days were allowed for recovery from surgery.

In a modification of Evans' [16] procedure, electric shocks were delivered by a 60-Hz constant shock generator (BRS/LVE) and grid scrambler through a 30 cm by 24 cm floor composed of 16 grids. Using an ascending method of limits, the flinch threshold was defined in mA as the lowest intensity that elicited a withdrawal of a single paw from the grids. The jump threshold was defined as the lowest of two consecutive intensities that elicited simultaneous withdrawal of both hindpaws from the grids. Each trial began with the animal receiving a 300-msec foot shock at a current intensity of 0.1 mA. Subsequent shocks occurred at 10-sec intervals and were increased in equal 0.05 mA steps until each nociceptive threshold was determined. After each trial, the current intensity was reset to 0.1 mA for the next trial until 6 trials were completed. Daily flinch and jump thresholds were each computed as the mean of these six trials. Stable baseline flinch-jump thresholds were determined over four days.

After baseline determinations, animals were assigned to one of four matched groups which received an ICV injection of CAP at doses of 0, 25, 50 and 100 μg respectively. CAP (Sigma Co.) was dissolved in 50% dimethylsulfoxide and 50% normal saline at a concentration of 2.5 mg/ml [44]. The ICV injections were infused at a rate of 1 μg every 15 sec through a stainless steel 28 ga internal cannula which extended 0.5 mm ventral to the guide cannula. Beginning one week after injection, each group was exposed to three pairs of control and experimental conditions 30 min before flinch-jump testing according to an incomplete counterbalanced design. The three experimental conditions consisted respectively of an injection of a 450 mg/kg dose of 2DG (300 mg 2DG/ml sterile water/kg body weight, IP), a 3.5 min swim in a 2°C bath, and a 3.5 swim in a 15°C bath. The 2DG control condition consisted of an injection of equal volume of water (1.5 ml/kg body weight, IP). The CWS controls consisted of flinch-jump determinations without swims. A minimum of 72 hr elapsed between experimental conditions. The experimenter conducting the tests was unaware of assignments of animals to groups. Following completion of the experiment, rats were anesthetized and perfused with normal saline and 10% buffered formalin. Their brains were removed, blocked, mounted and stained with cresyl violet to allow determination of cannula placements.

Results

The cannula placements of the 24 rats impinged upon the rostro-caudal extent of the lateral ventricles with all groups displaying similar variability in exact placement. Significant differences in jump thresholds were observed among injection groups, $F(3,12)=3.60$, $p<0.05$, across CWS and 2DG conditions, $F(2,24)=24.64$, $p<0.001$, and between control and experimental manipulations, $F(1,12)=190.28$, $p<0.001$. Moreover, significant differences were observed for the interactions between groups and manipulations, $F(3,12)=7.37$, $p<0.005$, between conditions and manipulations, $F(2,24)=31.15$, $p<0.001$, and among groups, conditions and manipulations, $F(6,24)=2.59$, $p<0.05$. The order in which the experimental conditions were presented failed to produce significant effects, $F(2,12)=0.26$, indicating that acute exposure to a given stressor failed to alter subsequent analgesic responses following acute exposure to other stressors. Like jump thresholds, flinch thresholds varied significantly between control and experimental manipulations, $F(1,12)=115.12$, $p<0.001$, as well as for the interactions be-between groups and manipulations, $F(3,12)=8.68$, $p<0.003$, and between conditions and manipulations, $F(2,24)=3.64$, $p<0.42$.

As illustrated in Fig. 1, the dose employed was critical in CAP's ability to attenuate the analgesic response following a 450 mg/kg dose of 2DG. While 2DG significantly increased jump thresholds above placebo values in rats treated with 0 μg, $F(1,12)=61.57$, $p<0.01$, 25 μg, $F=9.00$, $p<0.01$, and 100 μg, $F=80.97$, $p<0.01$, CAP doses, it failed to do so in rats receiving the 50 μg CAP dose ($F=0.08$). Indeed, jump thresholds following 2DG were significantly lower in rats treated with the 25 μg ($F=38.33$, $p<0.01$) and 50 μg ($F=57.85$, $p<0.01$) CAP doses than in rats treated with the 0 μg injection condition. In contrast, the 0 and 100 μg CAP doses elicited comparable 2DG analgesia as measured by jump thresholds ($F=0.39$). The flinch threshold data yielded an identical pattern of effects.

CAP's effects upon CWS analgesia varied as functions of the dose employed and the swim temperature. The 2°C swim significantly increased jump thresholds above control values in all four CAP groups. However, the magnitude of analgesia was significantly decreased in rats treated with the 25 μg CAP dose ($F=12.61$, $p<0.01$) as compared to the 0 μg injection condition. In contrast, the 50 μg ($F=1.22$) and 100 μg ($F=4.16$) CAP doses elicited comparable analgesia following the 2°C swim as the 0 μg injection condition. Again, flinch threshold data yielded an identical pattern of effects.

While the 15°C swim significantly increased jump thresholds above control values in rats treated with the 0 μg injection condition ($F=26.86$, $p<0.01$), it failed to do so in rats treated with the 25 μg ($F=0.88$), 50 μg ($F=0.59$) and 100 μg ($F=1.44$) CAP doses. Indeed, jump thresholds following the 15°C swim were significantly lower in rats treated with the 25 μg ($F=18.03$, $p<0.01$), 50 μg ($F=19.07$, $p<0.01$) and 100 μg ($F=15.68$, $p<0.01$) CAP doses than in rats treated with the 0 μg injection condition. Flinch thresholds differed in pattern from jump thresholds in that only the 25 μg CAP dose was capable of returning swim-induced thresholds to within control levels ($F=0.02$) that were significantly lower ($F=14.93$, $p<0.01$) than swim-induced thresholds of rats receiving the 0 μg injection.

It should be noted that the analgesic responses to CWS and 2DG are accompanied by hypoactivity [9]. It is conceivable that the selective dose-dependent changes induced by CAP upon CWS and 2DG analgesia could occur through

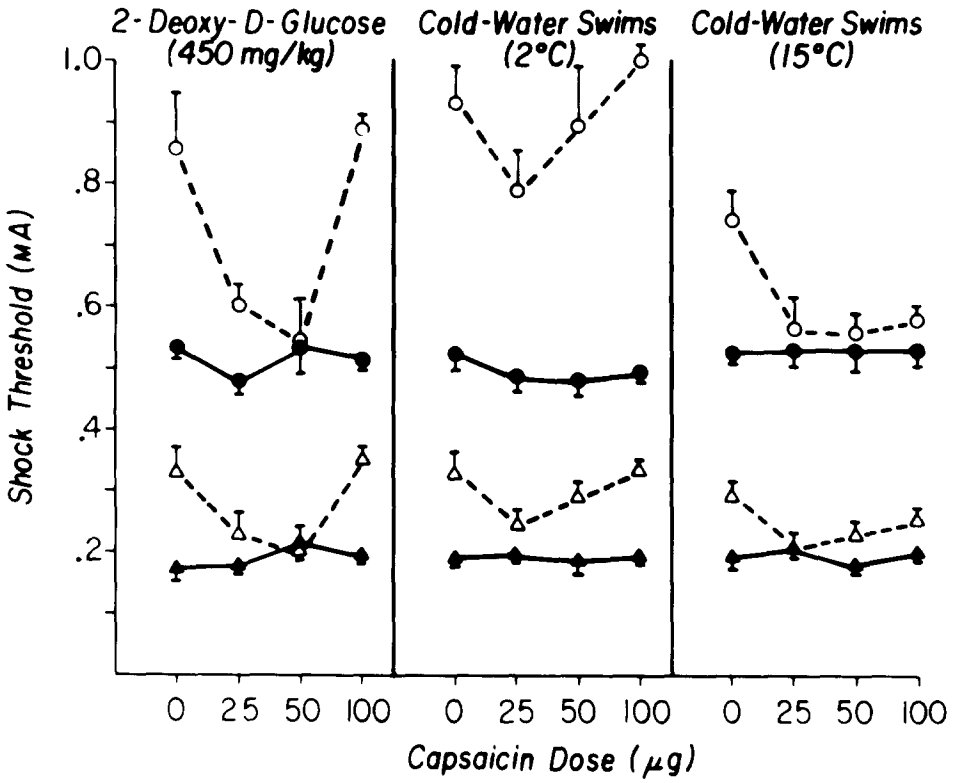

FIG. 1. Mean values (+SEM) for jump (circles) and flinch (triangles) thresholds following control (closed) and experimental (open) conditions in rats treated with 0, 25, 50 and 100 μg doses of capsaicin. Six animals comprise each group.

alterations in activity levels. Further research should be done to investigate this possibility.

EXPERIMENT 2: CAPSAICIN AND CWS HYPOTHERMIA

Method

Twenty-four naive male albino Sprague-Dawley rats were prepared sugically with a lateral ventricle cannula as in Experiment 1. After recovery from surgery, animals were assigned randomly to one of four groups which received an ICV injection of CAP at doses of 0, 25, 50 and 100 μg respectively according to the injection procedure described previously. Seven days after injection, half of the animals were subjected to a 3.5 min swim in a 2°C bath. Core body temperatures for each animal were determined 0, 15, 30, 60 and 90 min following CWS by inserting a rectal probe until a stable reading was obtained on a Bailey digital thermometer (BAT-8). This procedure was repeated three days later for this group, except the temperature of the bath was set at 15°C. The remaining half of the animals were exposed to the swim conditions in reverse order. The experimenter conducting the tests was unaware of assignments of animals to groups and histological verification of cannula placement was performed as described previously.

Results

The cannula placements of 22 rats impinged upon the rostro-caudal extent of the lateral ventricles with all groups displaying similar variability in exact placement. As summarized in Table 1, the 2°C swims elicited a hypothermic response that varied significantly over time, $F(4,72)=54.64$, $p<0.001$, but failed to differ either among injection groups ($F(3,18)=0.45$) or for the interaction between groups and time ($F(12,72)=1.23$). In like fashion, the 15°C swims elicited a hypothermic response that varied significantly over time, $F(4,68)=50.04$, $p<0.001$, but failed to differ either among injection groups ($F(3,17)=1.29$) or for the interaction between groups and time ($F(12,68)=1.51$). In short, it appears that the CAP-induced alterations in CWS analgesia observed in Experiment 1 are not explained in terms of parallel changes in CWS hypothermia.

EXPERIMENT 3: CAPSAICIN AND FS ANALGESIA

Method

Twenty-four naive male albino Sprague-Dawley rats were prepared surgically with a lateral ventricle cannula as in Experiment 1. After recovery from surgery, animals were assessed for their responsiveness to noxious radiant heat according to the procedure of D'Amour and Smith [14]. A radiant heat source (IITC Aanalgesia Meter) was mounted 8 cm above the dorsum of the tail of a restrained animal, 4 cm proximal to the tip. During a typical test session, tail-flick latencies were determined over three trials set at 30 sec intervals. The intensity of the thermal stimulus was set so as to produce stable tail-flick latencies between 2.5 and 3.5 sec. To avoid tissue damage, a trial was automatically terminated if a response did not occur within 6 sec.

After baseline determinations, animals were assigned to

TABLE 1

TIME COURSE OF COLD-WATER SWIM-INDUCED HYPOTHERMIA (°C, ±SEM) IN CAPSAICIN-TREATED RATS

Capsaicin Dose (μg)	Post-Swim (min) 0	15	30	60	90
(A) 2°C Swim					
0	28.55(4.38)	25.60(4.50)	27.68(4.94)	30.58(5.36)	32.43(5.84)
25	25.55(5.05)	24.97(2.04)	26.35(3.17)	32.22(0.77)	34.63(1.18)
50	27.63(4.68)	26.25(2.40)	28.38(1.85)	31.33(0.90)	34.53(0.79)
100	28.08(4.55)	26.78(3.02)	29.77(2.92)	33.63(2.31)	34.90(2.58)
(B) 15°C Swim					
0	28.68(4.71)	30.58(1.87)	32.06(2.08)	33.98(2.96	34.70(2.48)
25	31.43(3.07)	30.00(2.38)	32.57(2.92)	35.05(1.54)	35.28(1.54)
50	32.03(2.90)	32.95(2.61)	34.25(1.42)	36.80(0.47)	37.28(0.29)
100	31.50(2.90)	29.28(2.57)	31.40(3.26)	33.70(2.49)	35.57(1.89)

TABLE 2

TIME COURSE OF BASAL TAIL-FLICK LATENCIES (SEC ±SEM) IN CAPSAICIIN-TREATED RATS

Capsaicin Dose (μg)	Post-Injection (days) PRE	1	3	5	7
0	2.81(0.96)	2.75(1.10)	2.87(1.57)	2.96(0.94)	2.71(0.88)
25	2.68(0.36)	2.93(0.38)	2.41(0.34)	2.51(0.73)	2.64(0.28)
50	2.74(0.41)	2.52(0.36)	2.88(0.98)	2.26(0.41)	2.72(0.32)
100	2.75(0.23)	2.26(0.25)	2.19(0.29)	2.24(0.27)	2.87(0.27)

one of four matched groups which received an ICV injection of CAP at doses of 0, 25, 50 and 100 μg respectively according to the injection procedure described previously. Tail-flick latency sessions occurred immediately prior to the injections (PRE) and 1, 3, 5 and 7 days after the injection. Following the post-injection tail-flick determination on the seventh day, all animals were exposed to 80 FS trials which were subdivided into four equal 20 trial blocks. Each 1.0 mA FS was delivered for 5 sec by a 60-Hz constant current shock generator (BRS/LVE) and grid scrambler through a 30 cm by 24 cm floor composed of 16 grids. Shocks were delivered within and between blocks on a 1 min variable interval schedule. After each 20 trial FS block, each animal was removed from the chamber and tail-flick latencies were determined after 20, 40, 60 and 80 FS trials. The experimenter conducting the tests was unaware of assignments of animals to groups and histological verification of cannula placement was performed as described previously.

Results

The cannula placements of 23 rats impinged upon the rostro-caudal extent of the lateral ventricles with all groups displaying similar variability in exact placement. As summarized in Table 2, the post-injection tail-flick latencies failed to differ significantly either among the injection groups ($F(3,19)=0.46$), across the post-injection time course ($F(4,76)=0.89$), or for the interaction between groups and time ($F(12,76)=1.08$). In short, basal tail-flick latencies were unaffected by the CAP dose range 1, 3, 5 and 7 days after microinjection.

As summarized in Table 3, tail-flick latencies were significantly increased over baseline levels following the four blocks of FS trials, $F(4,76)=14.02$, $p<0.001$, but were not altered as functions of injection groups ($F(3,19)=0.20$) or the interaction between groups and blocks ($F(12,76)=1.29$). Thus, the analgesic responses over baseline levels following 20, $F(1.44)=44.87$, $p<0.01$, 40 ($F=23.23$, $p<0.01$, 60 ($F=27.98$, $p<0.01$ or 80 ($F=35.29$, $p<0.01$) FS trials did not vary as a function of CAP dose.

DISCUSSION

CAP exerts selective effects upon analgesic responses to stressors that vary as functions of the CAP dose employed and the stressor employed. However, before considering how CAP-induced changes in stress-induced analgesia are similar to or dissimilar from its effects upon morphine analgesia, the effects of CAP upon basal pain thresholds should be reviewed. As stated previously, systemic CAP produces insensitivity to chemical and pressure stimuli in rats [20,25], but fails to alter responsiveness to thermal stimuli [12]. In contrast, if CAP is injected intrathecally [44],

TABLE 3

ALTERATIONS IN TAIL-FLICK LATENCIES (SEC, ±SEM) FOLLOWING INESCAPABLE FOOT SHOCK (FS) IN CAPSAICIN-TREATED RATS

Capsaicin Dose (μg)	Number of FS Trials				
	PRE	20	40	60	80
0	2.72(0.88)	4.46(1.54)	4.31(1.43)	3.88(1.67)	4.32(1.58)
25	2.64(0.28)	4.78(0.96)	3.47(1.23)	3.78(1.58)	3.71(1.80)
50	2.72(0.32)	4.02(1.30)	4.25(0.93)	5.08(0.70)	4.72(0.99)
100	2.87(1.01)	4.22(1.44)	3.72(1.80)	3.60(1.93)	4.14(2.05)

it will produce analgesia on the tail-flick test. In the latter study, Yaksh and co-workers reported that this intrathecal effect upon tail-flick latencies was quite selective since ICV administration of a 40 μg CAP dose failed to alter latencies. The third experiment of the present study confirms and extends this observation by indicating that the 25, 50 and 100 μg CAP doses failed to alter tail-flick latencies at 1, 3, 5 and 7 days after ICV injection. This contrasts with the transient hyperalgesia noted on the flinch-jump test following ICV CAP [7]. Therefore, in assessing CAP effects upon basal nociception, it is important to note that the pain test employed and the route of administration are crucial variables. This may provide insight into determining subpopulations of peptides and transmittters that act differentially upon nociception at different spinal and suprasegmental levels.

Five analgesic responses to stress were examined in the present study with each displaying certain similarities to and/or differences from morphine analgesia. 2DG analgesia develops both cross-tolerance [39] and synergy [3] with morphine analgesia and both procedures are potentiated in hypophysectomized [4] and haloperidol-treated [9] rats. Unlike morphine analgesia, 2DG analgesia fails to be attenuated by either naloxone [3] or parachlorophenylalanine [8]. CWS analgesia induced by 2°C swims fails to develop cross-tolerance with morphine [6] and is not eliminated following naloxone [5] or parachlorophenylalanine [8]. Also unlike morphine analesia, CWS analgesia induced by 2°C swims is attenuated in hypophysectomized [2] and Brattleboro [10] rats. In contrast, CWS analgesia induced by 15°C swims is eliminated by naloxone (Reference Note 1). The analgesic responses to FS vary with respect to morphine analgesia as a function of the number of shocks delivered [19]. While exposure to 20 inescapable shocks produced an analgesic effect that was not altered by opiate antagonists, exposure to 80 shocks elicited a naltrexone-reversible analgesia.

Previously, we have reported that morphine analgesia is attenuated following ICV CAP in a dose-dependent manner with the 100 μg dose producing significant effects [7]. Based upon the previously cited evidence, one would expect that the analgesic responses following 2DG, CWS in a 15°C bath, and the 80 FS condition would mimic the CAP-induced decrements in morphine analgesia. Like morphine analgesia, 2DG analgesia was significantly attenuated by ICV CAP. However, the effectiveness of the CAP doses differed for the two responses. While morphine analgesia was significantly reduced by the 100 μg, but not the 25 or 50 μg, CAP doses, 2DG analgesia was significantly reduced by the 25 and 50 μg, but not the 100 μg, CAP doses. This general similarity persisted in CAP's effects upon CWS analgesia induced by the 15°C swim. Again, while morphine analgesia was significantly reduced by the 100 μg, but not the 25 or 50 μg CAP doses, CWS analgesia induced by a 15°C swim was significantly reduced by all CAP doses. Further, the reduction of CWS analgesia by CAP could not be attributed to parallel alterations in CWS hypothermia. These data suggest that CAP may alter these analgesic processes by direct or indirect manipulation of endogenous opioid systems, albeit in a differential manner that is dose-sensitive. However, if this supposition were correct, one would then expect that the analgesic response following 80 FS would be attenuated by CAP. Yet, neither the 25, 50 nor 100 μg CAP doses were capable of altering this response.

Based upon the previously cited evidence, one would expect that the analgesic responses following CWS in a 2°C bath and the 20 FS condition should dissociate from the CAP-induced decrements in morphine analgesia. Yet, like its effects on morphine analgesia, CAP decreased CWS analgesia in a 2°C bath. However, the former response was attenuated by a 100 μg CAP dose while the latter response was attenuated by a 25 μg CAP dose. Again, changes in this form of CWS analgesia by CAP could not be attributed to parallel changes in CWS hypothermia. Like the 80 FS condition, the analgesic response following 20 FS was unaffected by CAP, dissociating this response further from morphine analgesia.

Considerable research has been conducted indicating that CAP can alter nociceptive responding. However, as the present and other studies have shown, interpretation of CAP effects upon nociceptive and analgesic processes must take into account the route of administration, the CAP dose, the pain test employed and the analgesic manipulation. Given the apparent diversity of CAP effects upon nociceptive reactivity, this supports the notion of heterogeneous influences upon pain perception and pain inhibition.

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