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Quinpirole-Induced Alterations of Tail Temperature Appear as Hyperalgesia in the Radiant Heat Tail-Flick Test

DAVID S. ROANE, JEFFREY K. BOUNDS, CHOO-YAW ANG AND AHMAD A. ADLOO

Division of Molecular Pharmacology, School of Pharmacy, Northeast Louisiana University, Monroe, LA 71209-0470

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ROANE, D. S., J. K. BOUNDS, C.-Y. ANG AND A. A. ADLOO. *Quinpirole-induced alterations of tail temperature appear as hyperalgesia in the radiant heat tail-flick test.* PHARMACOL BIOCHEM BEHAV **59**(1) 77–82, 1998.—Several reports in the recent literature argue both for and against the importance of alterations of tail-temperature in the outcome of the tail-flick test. The data we present here support the assertion that drug-induced changes of tail-temperature may have a highly significant effect on tail-flick latency independent of drug-induced changes in nociception. We previously reported that peripherally administered injections of the dopamine agonist, quinpirole, produce significant reductions in the latency of response in the tail-flick test. This present work confirms our earlier findings; however, it indicates that the apparent hyperalgesia is an artifactual function of quinpirole-induced increases in tail temperature. Quinpirole (0.1–1.0 mg/kg IP) produced significant ($p < 0.001$), dose-dependent, and highly correlated increases in tail temperature and decreases in tail-flick latency 15 min following injection. When controls for the change in tail temperature were applied, there was no distinguishable effect of the drug on tail-flick latencies. Sixty minutes following the administration of quinpirole there was no observable effect of the drug on either tail-temperature or tail-flick latency. The results of this study indicate that a) peripherally administered quinpirole has no effect on nociception as measured in the tail-flick test apart from its ability to alter tail temperature; and b) alterations in tail temperature may significantly alter the outcome of the tail-flick test. © 1998 Elsevier Science Inc.

Antinociception Temperature Tail-flick Hyperthermia Hyperalgesia Quinpirole

WE have previously reported that the dopamine agonist, quinpirole, produces significant reductions in nociceptive thresholds (27) when nociception was measured using the tail-flick assay (3). The rationale for this previous study came from reports noting that alterations in plasma glucose affect tail-flick latencies (16,22,25,29,30) and quinpirole elevates plasma glucose (28). Our findings were statistically significant, consistent with a developing hypothesis and made what we felt was an important contribution to the growing body of knowledge regarding glucose metabolism and the potency of opioid analgesics. We now believe that our previous interpretations about quinpirole's hyperalgesia were incorrect. We have evidence that quinpirole, in addition to producing hyperglycemia, also causes a transient hyperthermia of the rat tail that is capable of mimicking hyperalgesia in the tail-flick assay.

Numerous recent studies indicate that skin temperature may (1,5–8,11,12,19–21,26,32–34), or may not (13,17) have a profound effect on the results of the radiant heat nociceptive testing in rats, mice, and cats. The importance of this issue is obvious to all investigators employing the tail-flick test as a means of assessing nociceptive thresholds, i.e., it indicates the possible presence of an artifact in the assay that may undermine the assertions of a large number of previous studies that have used the radiant-heat tail-flick test.

To explore the possible involvement of quinpirole-induced alterations in tail-skin temperature on the outcome of the tail-flick test we performed three separate experiments. The first experiment was designed to examine the relationship between deliberately altered tail-skin temperature and the tail-flick latencies. The second experiment was designed to examine any relationship between tail-skin temperature and tail-flick latency in animals receiving various doses of quinpirole. The third experiment was designed to reexamine the effects of quinpirole on tail-flick latency while controlling for any drug-induced changes in tail-skin temperature.

Requests for reprints should be addressed to David S. Roane, School of Pharmacy, Northeast Louisiana University, Monroe, LA 71209-0470.

METHOD

In all cases we used male albino Sprague–Dawley rats (220–350 g) from the School of Pharmacy vivarium. All animals were housed in individual wire cages in the vivarium under standard 12 L:12 D lighting conditions and were given ad lib access to Harlen TekLad rat chow and tap water. All animals were gently handled on at least three occassions prior to testing. The ambient room temperature was maintained at 22–24°C throughout the study.

The tail-flick assay was performed as the method of D'Amour and Smith (3). Rats were loosely restrained in a cotton cloth and positioned so that the light beam focused on the tail approximately 3 cm from the tip. Tail temperatures were recorded from a proximally adjacent region of the tail using a 6-mm skin probe thermistor linked to a YSI telethermometer. Throughout all experiments tail temperatures were recorded immediately prior to the tail-flick test.

In all cases drugs were administered intraperitoneally (IP). Saline was administered IP in the control animals. Quinpirole HCl (RBI, Natick, MA) was dissolved in saline prior to injection.

Experiment 1: Examination of the Relationship Between Tail-Temperature and Tail-Flick Latency

The tail-flick latencies of 12 rats were measured six times over a period of 10 days, one measure per day. The order in which animals were tested was pseudorandomized. The animals' tail-skin temperature was manipulated by immersing the tails in water of temperature ranging from 20 to 45°C in 5°C increments. Following a 60-s immersion the tails were rapidly dried and the tail-skin temperature was recorded immediately before the nociceptive test. The data (tail-flick latency as a function of tail-skin temperature) were analyzed by linear regression.

Experiment 2: Characterization of Quinpirole's Dose-Related Effect on Tail-Flick Latency and Tail-Skin Temperature

Thirty-six rats were divided into four groups of nine each. Animals within each group received one dose of either 0.0, 0.1, 0.3, or 1.0 mg/kg quinpirole HCl. Tail-skin temperatures and tail-flick latencies were recorded at 15 and 60 min following injection. The data (tail-flick latency as a function of tail-skin temperature) were analyzed by linear regression. Additionally, ED_{50}s were calculated for quinpirole's effects on tail-flick latency and tail-skin temperature using the ALLFIT program (4). Individual dose effects were analyzed by ANOVA and Tukey's post hoc test.

Experiment 3: The Effect of Normalizing Tail-Skin Temperature on Quinpirole Hyperalgesia

Part a. Eighteen animals were divided into two groups of nine. One group was injected with 0.25 mg/kg quinpirole HCl; the other group received saline. Tail-skin temperatures and tail-flick latencies were measured 15 min following the injections.

Part b. Sixteen animals were divided into two groups of eight and received injections of 0.25 mg/kg quinpirole HCl or saline. Fifteen minutes after injection tail-skin temperatures were recorded. The tails of the saline-injected animals were immersed in 41°C water for 2 to 12 s. The tails of the quinpirole-treated animals were immersed in water at room temperature (22°C). Immediately following the immersion the tails were dried, and tail-skin temperature and tail-flick latencies were recorded.

The data in both parts a and b were analyzed by the two-tailed, unpaired Student's *t*-test.

RESULTS

Experiment 1

The results show a highly significant correlation between tail-skin temperature and tail-flick latency (slope ± 95% confidence interval (C.I.) = -0.258 ± 0.032, $r^2 = 0.77$, $p < 0.001$ $n = 72$). The data are shown in Fig. 1 (closed symbols).

Experiment 2

Over all doses of quinpirole tested there was a highly significant correlation between tail-skin temperature and tail-flick latency (slope, ± 95% C.I. = -0.516 ± 0.069, $r^2 = 0.62$, $p < 0.0001$, $n = 36$). The slope of the regression line is significantly different from the slope of the regression line from the data in Experiment 1, $F(1, 107) = 18.48$, $p < 0.0001$. These data are also shown in Fig. 1 (open symbols).

The data for both tail-skin temperature and tail-flick latencies show classic dose–response relationships. ED_{50}s (±95% C.I.) for quinpirole effects on temperature and latency at 15 min postinjection were 0.056 ± 0.0059 and 0.036 ± 0.086 mg/kg, respectively, and were not significantly different (Fig. 2).

Analysis of variance on the tail-skin temperatures at 15 min postinjection showed a highly significant effect due to the drug, $F(3, 32) = 26.17$, $p < 0.0001$. Tukey's Multiple Comparison Test indicates that the tail-skin temperatures at each dose of quinpirole were significantly different from the saline control ($p < 0.001$). A comparable analysis on the tail-flick latency data showed a highly significant effect of the drug, $F(3, 32) = 8.86$, $p < 0.0002$, with the two highest doses producing effects significantly different from the saline controls.

Analysis of variance on both the tail-skin temperature and tail-flick latencies at the 60-min time point showed no evidence of a drug effect across any of doses, $F(3, 32) = 0.42$, and $F(3, 32) = 0.71$, respectively (Fig. 3).

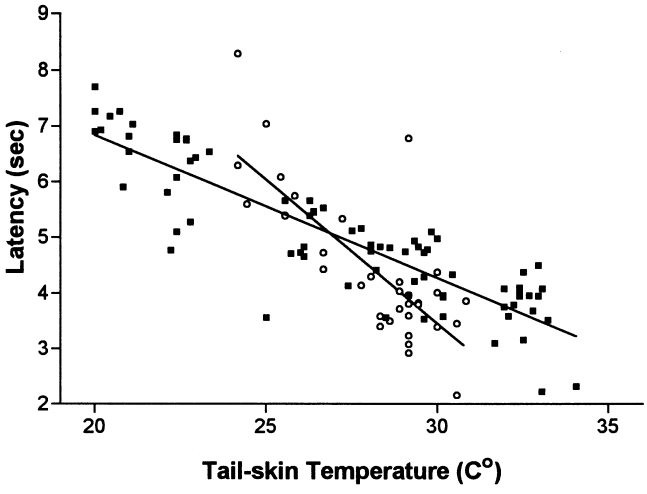

FIG. 1. In this graph, the closed symbols (■) and the associated regression line the show the highly significant correlation between tail-skin temperature and tail-flick latency in rats whose tail-skin temperature was artificially manipulated by immersing the tails in heated water (slope = -0.258 ± 0.032, $p < 0.001$, $r^2 = 0.77$, $n = 72$). The open circles (○) show the data and the regression line for the animals injected with saline and all doses of quinpirole (slope = -0.516 ± 0.069, $r^2 = 0.62$, $p < 0.0001$, $n = 36$). The slopes of the two lines are different ($F(1, 107) = 18.48$, $p < 0.0001$).

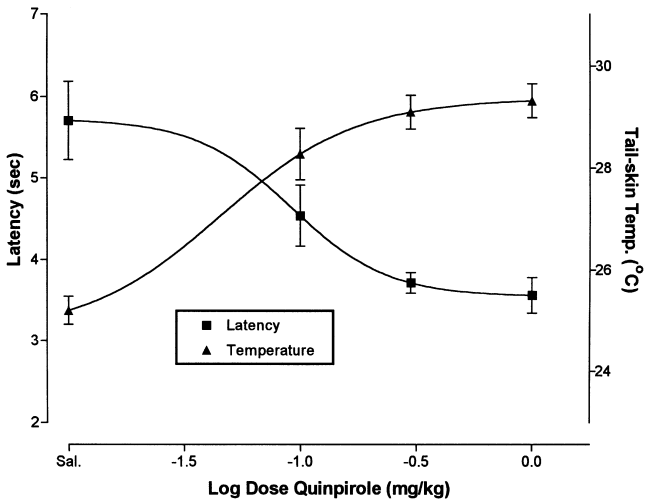

FIG. 2. This figure shows the dose–response relationship between quinpirole and both tail-flick latency (squares, ■, referenced to the left-side y axis) and tail-skin temperature (triangles, ▲, referenced to the right-side y axis). The measurements were recorded at 15 min postinjection. The ED_{50}s are 0.036 and 0.056 mg/kg (NS).

Experiment 3

Part a. The tail-skin temperatures of the saline and quinpirole HCl-injected animals were 25.31 ± 0.47 and 28.99 ± 0.35°C, respectively ($t = 6.253$, $p < 0.0001$), and the tail-flick latencies were 5.1 ± 0.16 and 4.3 ± 0.2, respectively ($t = 2.845$, $p = 0.012$). These data are shown in Fig. 4A and B.

Part b. Fifteen minutes after the injection of 0.25 mg/kg quinpirole the treated animals show a highly significant increase in tail-skin temperature compared to the controls (27.43 ± 0.4°C vs. 23.61 ± 0.2°C, $t = 8.839$, $p < 0.0001$). After immersion in water the tail-skin temperatures were similar between the two groups (26.9 ± 0.35 vs. 27.2 ± 0.13°C, $t = 0.734$, NS) and the tail-flick latencies were also similar (5.24 ± 0.37 vs. 5.48 ± 0.38, $t = 0.45$, NS). These data are shown in Fig. 4C and D.

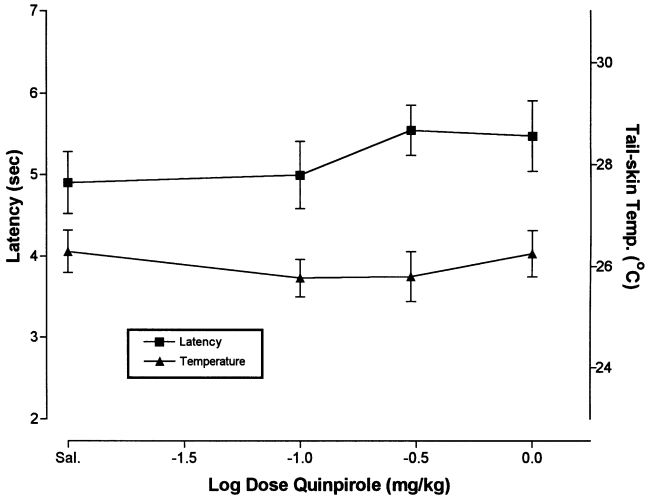

FIG. 3. This figure shows the dose–response relationship between quinpirole and both tail-flick latency (squares, ■, referenced to the left-side y-axis) and tail-skin temperature (triangles, ▲, referenced to the right-side y-axis). The measurements were recorded at 60 min postinjection. ANOVA failed to reveal any significant effect of the drug on either variable.

DISCUSSION

The data from Experiment 1 demonstrate that it is possible to construct simple experimental conditions in which tail-flick latencies vary significantly as a function of tail-skin temperature. The slope of the regression on these data is consistent with numerous other reports on the relationship between tail-skin temperature and tail-flick latency (15,20,26,32,33).

The data from the second experiment demonstrate several phenomena. First, 15 min following the injection of quinpirole there is a dose–response relationship between the drug and reductions in tail-flick latencies. This effect of quinpirole [which is a dopamine agonist at D_2 and D_3 receptors (10)] is similar to the hyperalgesic tail-flick effects of other D_2/D_3 agonists (35).

Secondly, at the 15-min time point there is a dose–response relationship between quinpirole and increased tail-skin temperature. This finding is consistent with previous reports of a dopamine-receptor mediated hot flush in tail-skin temperature (14).

Both phenomena, decreased tail-flick latency and increased tail-skin temperature, occur simultaneously and with increasing magnitude as a function of the administered dose of quinpirole; the ED_{50} of quinpirole is apparently similar for both effects. At the 60-min time point neither effect is evident—the tail-skin temperature and hyperalgesic effects of quinpirole are transient. This transience is in contrast to some of the other pharmacological effects of quinpirole such as effects on feeding (31) or locomotion (9) that last for many hours. These data, together with the data from the first experiment, are supportive of the hypothesis that the apparent transient hyperalgesia seen with quinpirole is due to the fact that quinpirole causes a transient increase in tail-skin temperature.

The third noteworthy finding from the second experiment deals with the slopes of the regression lines relating tail-flick latency to tail-skin temperature. The data from the animals injected with quinpirole showed a slope of −0.516 ± 0.069. The data taken from the animals whose tails had been dipped in water, in Experiment 1 showed a regression slope of −0.258 ± 0.032. These slopes are highly significantly different, $F(1, 107) = 18.48$, $p < 0.0001$. The inference we make from this finding is that the mechanism by which alterations in tail temperature occur can dictate the magnitude of the effect on tail-flick latency due to the fact that the temperature gradients through the skin may differ according to the methods. The quinpirole-induced temperature changes are internal in origin, probably arising from vasodilatation while the changes in skin temperature due to water immersion are primarily external in origin. If the differing methods do produce different temperature gradients through the skin it is plausible to assume that the resulting effects on tail-flick latency would occur to varying magnitudes.

These findings may have important implications for future investigations if the slope of a regression line is used to derive a "temperature-correction" factor as it appears that pharmacologically mediated changes in skin temperature produce the greater alterations in tail-flick latencies than do those arising from external sources.

The third experiment was conducted to control for quinpirole's effect on tail-skin temperature while reexamining the

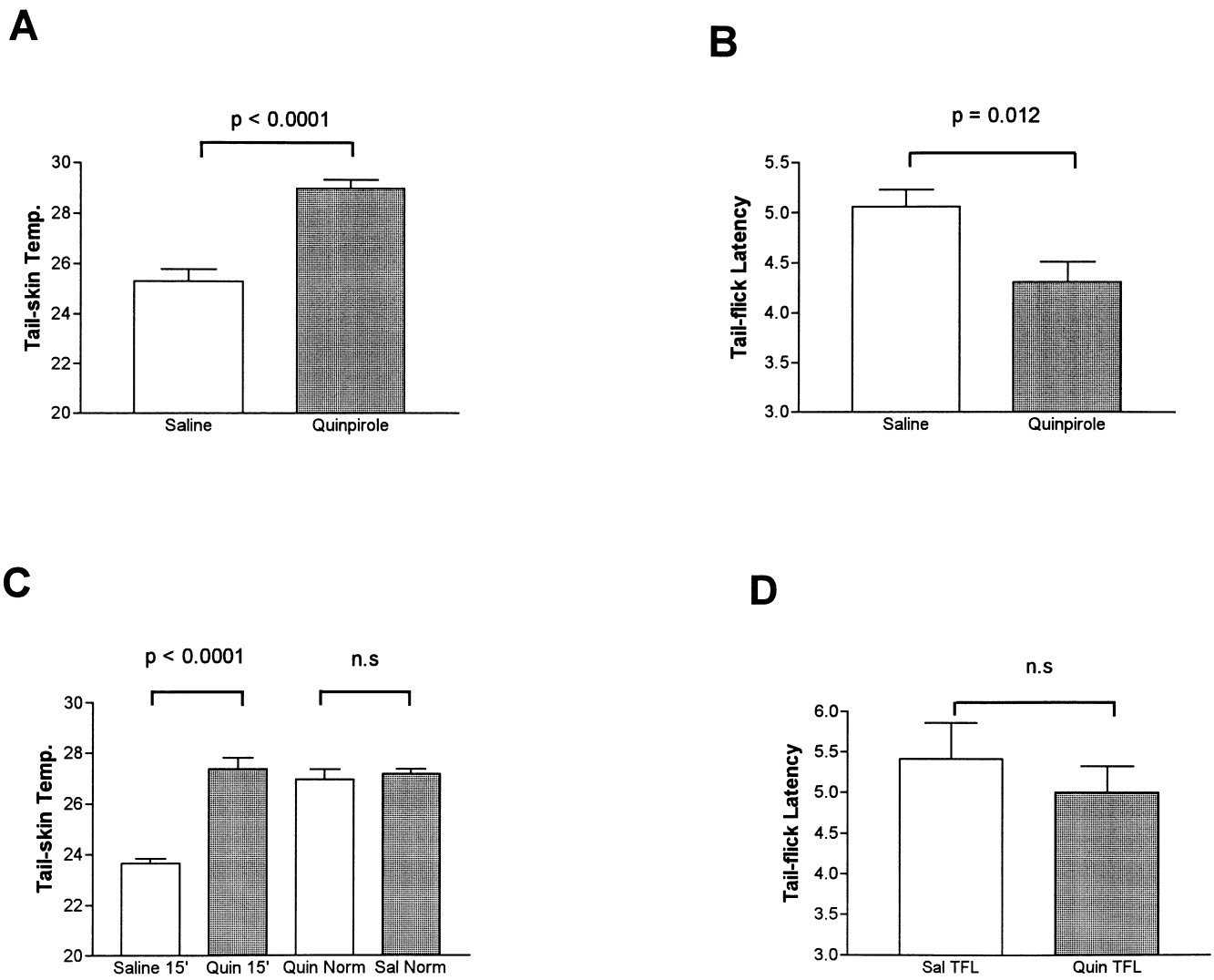

FIG. 4. A and B show the effects of 0.25 mg/kg quinpirole HCl on tail-skin temperature (A) and tail-flick latency (B). Both tail-skin temperature ($t = 6.253$, $p < 0.0001$, $n = 9$) and tail-flick latency ($t = 2.845$, $p = 0.012$, $n = 9$) were significantly affected by the drug 15 min following injection. C shows the effect of 0.25 mg/kg quinpirole 15 min following injection ($t = 8.839$, $p < 0.0001$), and the absence of an observable effect following normalization of the skin temperature by water immersion. D shows the similarity of the tail-flick latencies between the two groups immediately following the skin temperature normalization.

drug's effects on tail-flick latency. In part a of the third experiment we noted that 0.25 mg/kg quinpirole significantly increased tail-skin temperature and decreased tail-flick latency. In part b, after the tail-skin temperatures were "normalized" by brief immersion in water, there were no detectable differences in the tail-flick latencies between the drug and saline-injected animals. Our interpretation of this finding is that it is strongly supportive of the hypothesis that the apparent hyperalgesia of quinpirole is an artifact of quinpirole's hyperthermic effect on tail-skin temperature.

Lichtman et al. (17) have reported, based on their results from the testing of several pharmacological and nonpharmacological treatments, no evidence of a significant correlation between tail-skin temperature and tail-flick latency. The authors "conclude that monitoring tail-skin . . . temperatures when employing the tail-flick test is unnecessary . . . ." The authors further conclude that "the tail-flick response is relatively impervious to tail-skin temperatures," (p. 293). In view of our present findings it is our position that Lichtman et al.'s conclusions, in the general sense, are not correct, or are at least overstated. The preponderance of the data (1,5–8,11,12,19–21,26,32–34) indicates that in numerous instances, and under a variety of circumstances, tail-skin temperature is profoundly important in determining the outcome of the tail-flick test.

Certainly there are many cases where the importance of tail-skin temperature is trivial in determining the outcome of the tail-flick test. This would especially be true with powerful analgesic agents. However, there are likely a large number of situations in which drug-induced changes in tail-skin temperature are the predominant factor in producing alterations in tail-flick latency. Ness and Gebhart (24) reported that tail-flick latencies vary as a function of stimulus intensity, and that the mean tail-skin temperature at which rats respond is a constant and is independent of the stimulus strength. Under nor-

mal, nondrug conditions the tail-flick response will be seen when the radiant energy applied to the tail raises the temperature of the portion of the tail containing the appropriate response-initiating elements to a given temperature. The tail-flick test essentially measures the amount of time required for this event to occur. If a pharmacological or nonpharmacologic treatment to the animal elevates the temperature of the tissue surrounding the response-initiating elements, and if the treatment has no other relevant effects, then the amount of time required for the elements to reach their threshold will necessarily be reduced. Exceptions to this scenario will be seen in the case of treatments that alter neuronal transmission, synaptic communication, and/or muscle function. Powerful analgesic agents are capable of radically altering tail-flick latencies, regardless of what effect they have on tail-temperatures. On the other hand, treatments that mildly or moderately affect tail-flick latencies are susceptible to the effects of altered tail-skin temperature. We would speculate that there is a reciprocal relationship between efficacy of an analgesic agent and the influence of tail-skin temperature on the outcome of the tail-flick test.

In a recent dialog in Pain, Lichtman and Martin (18) continue to question "the assertion that changes in tail skin temperature have a relevant impact on the TF response," while Berge and Tjolsen (2) maintain that Lichtman et al. (17) have only shown "that it is possible to conduct a series of experiments without recording significant changes in tail temperature." Our interpretation of the findings we present here strongly lead us to side with Berge and Tjolsen. Tail-temperatures may be a decidedly important factor in interpreting the results of the tail-flick test.

In the dialog, Berge and Tjolsen (2) express the concern that "it would be unfortunate if the paper [Lichtman et al., 1993] is used by other researchers as an excuse to ignore changes in tail skin temperature as a confounding factor in the TF test." Unfortunately, Berge and Tjolsen's concern has been realized; a recent review of the literature reveals four manuscripts citing Lichtman et al.'s (17) contentions as a valid reason for discounting treatment-induced temperature effects. One of the papers goes so far as to state ". . . Lichtman et al. recently, again, demonstrated that the tail flick latency appears independent of changes in tail-skin temperature . . ." (23).

In conclusion, the results we present here strongly indicate that drug-induced alterations in tail-skin temperature may significantly affect the outcome of the tail-flick test and may actifactually produce evidence of changes in nociception. These findings and interpretations are in agreement with numerous previous findings cited above. Our results and conclusions generally disagree with the conclusions of Lichtman et al. (17).

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