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Brain Temperature and Ethanol Sensitivity in C57 Mice: A Radiotelemetric Study

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BEJANIAN, M., B. L. JONES, P. J. SYAPIN, D. A. FINN AND R. L. ALKANA. *Brain temperature and ethanol sensitivity in C57 mice: A radiotelemetric study.* PHARMACOL BIOCHEM BEHAV **39**(2) 457–463, 1991.—This study investigated the relationship between ethanol sensitivity and brain temperature using radiotelemetric techniques. Radiotelemetric brain probes were implanted in the lateral cerebral ventricle of C57BL/6 mice. Rectal and brain temperatures, duration of loss of righting reflex (LORR), and blood and brain ethanol concentrations at the return of righting reflex (RORR) were measured following intraperitoneal (IP) injection with 3.6 g/kg ethanol and exposure to 12, 15, 22 or 34°C. Rectal and brain temperatures were significantly correlated in untreated and intoxicated mice. Brain temperatures were lower than rectal temperatures in untreated mice, but were not different than rectal temperatures in intoxicated mice. Ethanol sensitivity, measured by the duration of LORR and ethanol concentrations at RORR, was significantly correlated with brain as well as rectal temperatures at RORR. Brain probe implantations did not significantly affect ethanol sensitivity. The direct positive relationship between brain temperature and ethanol sensitivity in C57 mice fits predictions based on membrane actions of ethanol and supports the hypothesis that temperature-induced changes in behavioral sensitivity to ethanol are mediated through changes in brain membrane temperature.

Alcohol-ethyl Temperature Brain temperature Ethanol sensitivity Temperature challenge Radiotelemetry

ETHANOL impairs thermoregulation in mice and other mammals (18, 27, 33). Rectal temperature during intoxication is dependent on the dose of ethanol and the environmental conditions to which the subject is exposed (18, 30, 33). In addition, rectal temperature during intoxication has been shown to affect sensitivity to ethanol-induced depression of brain function and performance in mice and rats (19, 30, 32, 35). Temperature affects ethanol sensitivity at subhypnotic (35), hypnotic (1,30) and lethal (19,32) doses of ethanol. Increasing rectal temperature during intoxication has reportedly increased behavioral and lethal effects of ethanol in C57 mice (30,32). Ethanol sensitivity, at a hypnotic dose measured by the duration of LORR and blood and brain ethanol concentrations at the RORR, is positively correlated and linearly related to rectal temperature in C57 and BALB mice, and Long-Evans rats (1, 2, 16, 40). The effects of temperature on the behavioral response to ethanol appear to be mediated via changing brain sensitivity to ethanol per se and not by changing ethanol pharmacokinetics (1, 8, 16, 30, 35).

The mechanism by which temperature affects brain sensitivity to acute ethanol administration is uncertain. Evidence from biophysical (25,29) and in vitro (9, 13, 23) studies suggests that an increase in the temperature of the brain membranes should enhance the ethanol-induced disordering of brain membranes which is thought to underlie intoxication, and therefore should increase the resultant behavioral effects of ethanol. The characteristics (linearity and direction) of the temperature-related changes in brain sensitivity to ethanol measured behaviorally in C57 mice are consistent with, and could result from, the interaction between temperature and ethanol's perturbing effects on brain membranes that have been found in vitro. Therefore, changes in brain temperature during intoxication could alter ethanol sensitivity by changing the membrane actions of ethanol.

Previous studies of the interaction between ambient temperature and brain sensitivity to ethanol have measured rectal temperature during intoxication (1, 19, 30, 32, 35). Consequently, any conclusions reached on the relationship between brain temperature and brain sensitivity to ethanol were based on the assumption that rectal temperatures are indicative of brain temperatures in intoxicated animals.

Little information is currently available regarding the effects of ethanol on brain temperature or on the relationship between brain and rectal temperature in intoxicated animals. Recent work using immediate postmortem brain temperature measurements indicates that rectal and brain temperatures are highly correlated and linearly related with each other in intoxicated temperature-challenged C57 mice (7). Although correlated, brain and rectal temperatures in these mice did not change in parallel with each other. Brain temperature increased less rapidly than rectal temperature in response to increasing ambient temperature. This finding agrees with evidence from other species (3, 4, 6, 10,

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12, 28) indicating that thermoregulatory mechanisms can control brain temperature independently from rectal and other measures of core temperature. Therefore, the evidence in C57 mice and other species suggests that brain temperature in intoxicated mice may become dissociated from rectal temperature under some conditions and that indirect means of brain temperature measurements may lead to erroneous conclusions regarding the relationship between brain temperature and ethanol sensitivity.

The present study investigated the relationship between brain sensitivity to ethanol measured behaviorally, and brain temperature at the time of behavioral testing. This study used radiotelemetric brain probes that were chronically implanted in the cerebral ventricle for directly measuring brain temperature in unrestrained mice. The effect of the chronically implanted temperature probes on behavioral sensitivity to ethanol was also evaluated.

METHOD

Drug naive adult male C57BL/6J mice were housed four per cage and were acclimated to a 12-hour light:dark cycle (0700 on) in a room maintained at $23 \pm 1°C$ for at least one week before experimentation. Standard laboratory chow (Purina Laboratory Blox) and water were provided ad lib. The mice were 10- to 12-weeks old and weighed 25.1 ± 0.3 grams at testing.

The mice were implanted with X-PM (Mini-mitter Co., Sunriver, OR) brain temperature probes and housed singly four days prior to ethanol challenge. On the day of testing, baseline brain and rectal temperatures were recorded before the mice were injected with 3.6 g/kg ethanol. The mice were injected IP with ethanol as a 20% (w/v) solution in freshly prepared normal saline. Ethanol injections on the test day were carried out between 1000 and 1130 hours. Following the LORR, the mice were placed on their backs in a v-shaped trough and were exposed to ambient temperatures of 12, 15, 22 or 34°C in a temperature-controlled chamber (Model CEC 50 LPT, Rheem, Weaverville, NC). One ambient temperature was tested each day. The duration of LORR was measured using previously described techniques (1,30). Briefly, the duration of LORR consisted of the total amount of time from the initial LORR (mouse could no longer support itself from a vertical wire mesh screen) until the animal regained its righting reflex (mouse could touch all four paws to the surface of the v-shaped trough twice within 30 seconds). The brain temperatures were recorded continuously during intoxication. Upon regaining their righting reflexes, the mice were removed from the chamber, rectal temperatures were recorded and blood samples were taken in 20 μl volumes from the orbital sinus (36). The mice were euthanized by cervical dislocation, decapitated, and the brains were removed. The blood and brain samples taken at RORR were prepared and frozen for subsequent determination of ethanol concentrations using headspace gas chromatography (31). In this study, brain sensitivity to ethanol is defined as the duration of LORR and the blood and brain ethanol concentrations at RORR. The blood and brain ethanol concentrations at the return of function (RORR) represent a direct measure of ethanol sensitivity which, unlike LORR duration, is independent of direct influence by alterations in ethanol pharmacokinetics.

Along with the implanted mice, a nonimplanted control group of mice was singly housed four days before ethanol challenge. On the day of testing, baseline rectal temperatures were recorded and the mice were treated as described above. The implanted and control groups were tested simultaneously using a counterbalanced design.

Rectal Temperature Measurements

Rectal temperatures were measured in hand-held-unrestrained mice, with a digital thermometer (Bailey Instruments Co., Saddle Brook, NJ, Model BAT-12) using a glycerol-lubricated probe (Bailey Instruments Co., Model RET-3) inserted 1.9 cm into the rectum (1). A five-second equilibration time was allowed before each reading.

Radiotelemetric Brain Temperature Measurements

Brain temperatures were measured in freely moving mice via radiotelemetric probes (Model X-PM, Mini-mitter Co., Sunriver, OR) implanted in the lateral ventricles. The X-PM brain probes consist of a cylinder containing a miniature radio transmitter with a battery, and a thermistor probe encased in a 25 gauge stainless steel needle tubing that extends down (3.0 mm) from the cylinder. The cylindrical portion of the probe was encased in a plastic guard to protect the probe and to facilitate its attachment to the skull. The brain probe, along with the plastic guard attached, weighed approximately 1.4 grams.

The transmitter sends a pulse-modulated signal at a rate that is proportional to the local temperature. The AM signal from each probe was received by an individual receiver board (RA 1010, Mini-mitter Co.) and sent to a computer through a consolidation matrix (BCM-100, Mini-mitter Co.). Brain temperature during intoxication was recorded at one-minute intervals using an automated data acquisition system (Dataquest III, Mini-mitter Co.). Probes were calibrated manually using a frequency counter (Model 8060A Multimeter, John Fluke Mfg. Co., Everett, WA). The frequency counter was also used for the baseline brain temperature recordings.

Brain Probe Implantation

The technique for implanting the X-PM probes into the lateral ventricles was adapted from a nonstereotaxic method previously established for chronic cannula implantation (11,14). Mice were anesthetized with an IP injection of 0.4 g/kg tribromoethanol. The anesthetic was prepared as a 50% (w/v) solution in 1,2-propanediol and diluted in normal saline to an 8% (v/v) injection solution on the day of use. Each mouse also received a prophylactic dose (100,000 units) of penicillin G prepared in normal saline and injected subcutaneously. Following the onset of anesthesia, the portion of the scalp and fascia midway between the eyes to behind the ears was removed using aseptic techniques. A hole was drilled by hand with a 2/0 round dental bit 1.0 mm lateral to the midsagittal suture with its posterior end on the coronal suture. Care was taken not to penetrate the dura at this time. A 25 gauge sterile brain thermistor probe was inserted through the dura and brain matter until the cylindrical portion of the miniature transmitter housing contacted the skull surface. The probe was fixed in place on the skull by bonding (cyanoacrylate) the plastic guard that surrounds the exposed transmitter section. Probes were implanted alternatively into the right or left lateral ventricle. Each experimental group had approximately the same number of right and left implants. Visual inspection of brain slices in pilot studies verified the position of the probe in the lateral ventricle in all cases.

Data Analysis

The data were analyzed using the BMDP statistical package (BMDP Statistical Software, Inc., Los Angeles, CA). One-way analysis of variance (ANOVA) was used to compare baseline rectal and brain temperatures of animals subsequently exposed to different ambient temperatures and to assess the effect of ambient temperature on rectal and brain temperatures measured at

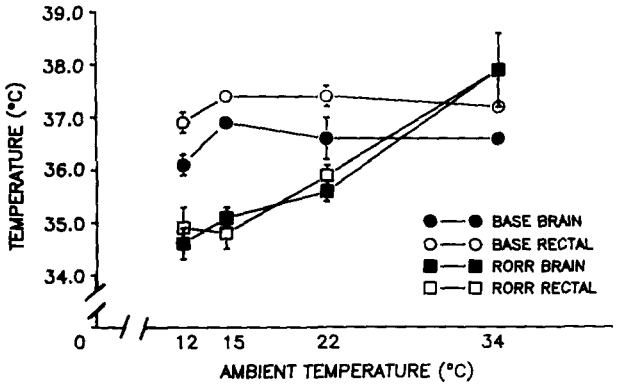

FIG. 1. Rectal and brain temperatures at baseline and RORR at each ambient temperature in the brain probe-implanted mice. There was a significant effect of ambient temperature on brain and rectal temperatures at RORR. Baseline rectal and brain temperatures were consistent across the ambient temperatures tested. The values shown represent the mean ± SE for 4 to 7 animals per group.

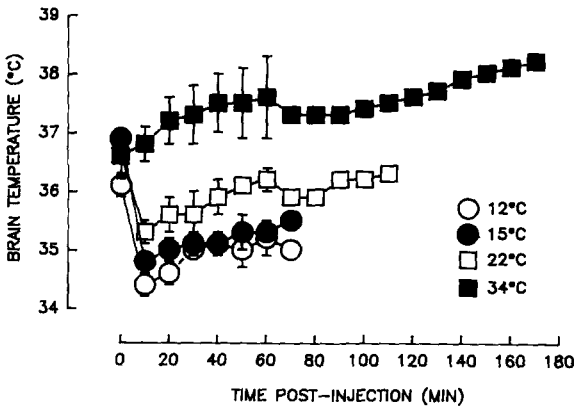

FIG. 2. Brain temperatures before and during intoxication. Temperatures were taken immediately before and at 10-minute intervals after ethanol injection, until the animals regained their righting reflexes. The values shown represent the mean ± SE of brain temperatures. There were 7 animals per ambient temperature group at 12, 15 and 22°C, and 4 animals at 34°C.

RORR. Bonferroni and Tukey Studentized Range Methods were used for post hoc analysis. Two-way ANOVA was used to determine the overall effect of probe implantation and ambient temperature on duration of LORR and parameters measured at RORR. If there was a significant interaction of the two main factors, Bonferroni and Tukey Studentized Range Methods were used for post hoc analysis.

Linear regression and correlational analyses were used to investigate the relationship between brain and rectal temperatures and each measure of ethanol sensitivity. Correlational analysis was also used to investigate the relationship between rectal and brain temperatures.

Rectal temperatures at baseline and at RORR were compared with their respective brain temperatures at each ambient temperature using Student's *t*-test (2 tailed). The level of statistical significance was set at $p<0.05$ for all analyses.

RESULTS

Figure 1 shows the rectal and brain temperatures of brain probe implanted mice measured at baseline and at RORR. There were no significant differences in the respective baseline temperatures (brain and rectal) between groups of mice subsequently injected with ethanol and exposed to different ambient temperatures. Exposure to increasing ambient temperatures from 12–34°C during intoxication resulted in an increase in brain, $F(3,21)=16.82$, $p<0.001$, and rectal, $F(3,21)=12.26$, $p<0.001$, temperatures at RORR. The ethanol-induced hypothermia, which was evident at 12, 15 and 22°C, was offset by exposure to 34°C during intoxication. Brain and rectal temperatures at RORR in animals exposed to 34°C were significantly higher than their corresponding temperatures at 12, 15 and 22°C. Similar effects of ambient temperature were present on the rectal temperatures of the control mice at RORR (data not shown).

Baseline brain temperatures were significantly lower than their corresponding baseline rectal temperatures in groups of mice subsequently injected with ethanol and exposed to 12, 15 and 34°C (Fig. 1). There was also a trend ($0.05<p<0.10$) towards lower baseline brain versus rectal temperature in animals which were subsequently tested at 22°C. In contrast, there were no statistically significant differences between rectal and brain temperatures at RORR in intoxicated mice at all ambient temperatures tested.

Brain temperatures taken immediately before and at 10-minute intervals after ethanol injection until animals regained their righting reflexes are shown in Fig. 2. Ethanol in animals exposed to 12, 15 and 22°C produced hypothermia, with maximum hypothermia occurring at 10 minutes postinjection. The ethanol-induced hypothermia in the brain was offset by exposure to 34°C during intoxication.

Figure 3 shows the scatter plots of brain temperatures versus rectal temperatures recorded at baseline (Fig. 3A) and at RORR (Fig. 3B). Brain temperature was significantly positively correlated with rectal temperature both at baseline ($r=.859$, $n=25$, $p<0.001$) and at RORR ($r=.924$, $n=25$, $p<0.001$).

Individually performed two-way ANOVA showed a significant main effect of ambient temperature on duration of LORR, $F(3,46)=4.28$, $p<0.01$, brain, $F(3,21)=16.82$, $p<0.001$, and rectal, $F(3,46)=27.02$, $p<0.001$, temperatures at RORR and blood, $F(3,46)=6.22$, $p<0.005$, and brain, $F(3,45)=10.68$, $p<0.001$, ethanol concentrations at RORR, but no main effect of probe implantation on these parameters. There were no significant interactions of probe implantation and ambient temperature on all the dependent variables measured at RORR except for the brain ethanol concentrations, $F(3,45)=5.77$, $p<0.005$. Post hoc analysis indicated that brain ethanol concentrations at RORR were significantly different in implanted and control mice only at 12°C. Since there were no systematic differences between the control and probe-implanted mice, the data for the two groups at each ambient temperature were collapsed for the following correlational analyses of the relationship between temperature (rectal and brain) and ethanol sensitivity.

There was a statistically significant positive correlation between the duration of LORR and brain temperatures at RORR ($r=.551$, $n=25$, $p<0.005$; Fig. 4A). Duration of LORR was also significantly positively correlated with rectal temperature at RORR ($r=.475$, $n=54$, $p<0.001$; Fig. 4B). Blood ethanol concentrations at RORR were significantly negatively correlated with brain ($r=-.443$, $n=25$, $p<0.05$) and rectal ($r=-.409$, $n=54$, $p<0.01$) temperatures at RORR (Fig. 5). Brain ethanol concentrations at RORR were also significantly negatively cor-

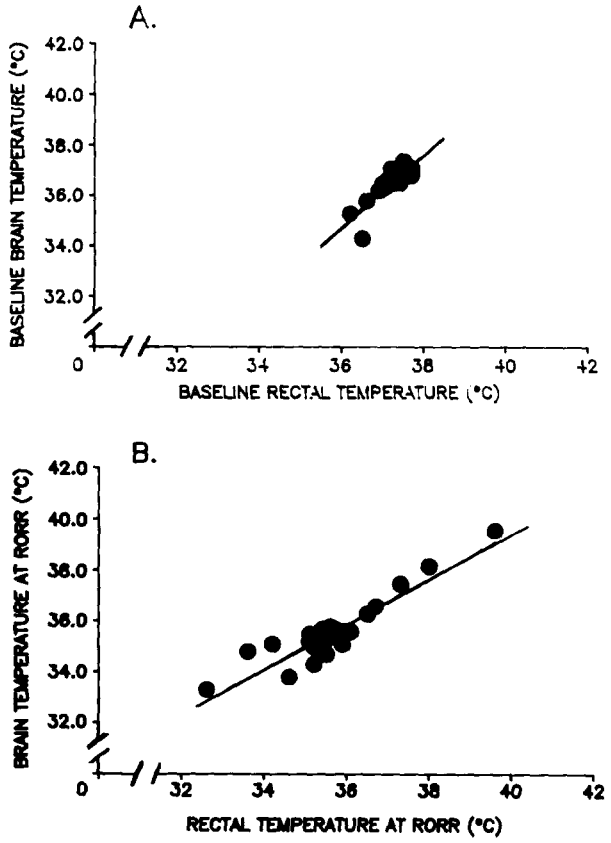

FIG. 3. Scatter plots of brain temperatures versus rectal temperatures recorded at baseline (A) and RORR (B). Brain temperature was significantly correlated with rectal temperature both at baseline ($r=.859$, $n=25$, $p<0.001$) and at RORR ($r=.924$, $n=25$, $p<0.001$).

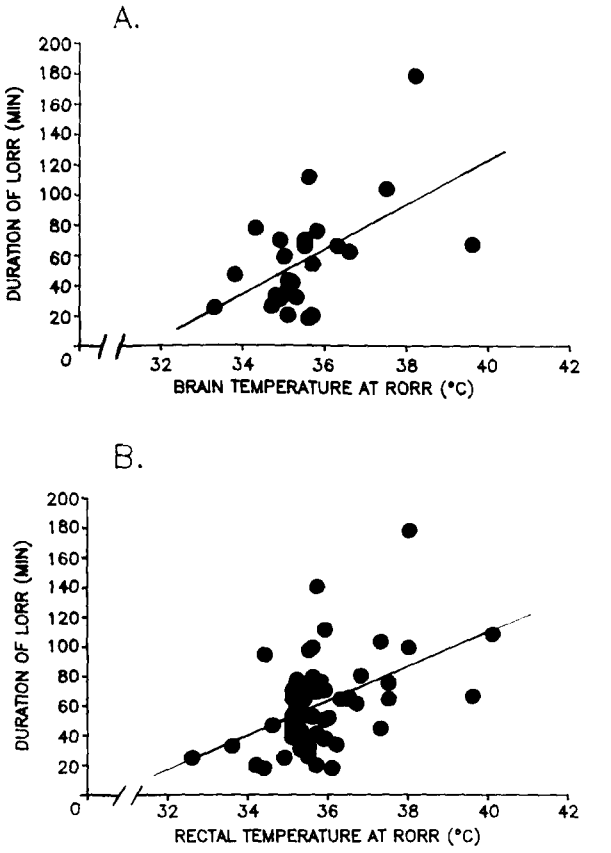

FIG. 4. Scatter plots of duration of LORR versus brain (A) and rectal (B) temperatures at RORR. There was a statistically significant correlation between duration of LORR and brain temperature at RORR ($r=.551$, $n=25$, $p<0.005$). Duration of LORR was also significantly correlated with rectal temperature at RORR ($r=.475$, $n=54$, $p<0.001$).

related with brain ($r=-.501$, $n=25$, $p=0.01$) and rectal ($r=-.414$, $n=53$, $p<0.005$) temperatures at RORR (Fig. 6).

DISCUSSION

Exposing intoxicated C57 mice to temperatures of 12 to 34°C, altered their rectal and brain temperatures during intoxication and affected their sensitivity to ethanol-induced depression. Brain sensitivity to ethanol, measured by the duration of LORR and the blood and brain ethanol concentrations at RORR, was significantly correlated and linearly related to brain as well as rectal temperatures at RORR. As brain temperature increased during intoxication, there was an increase in duration of LORR and a decrease in the ethanol concentrations at the RORR. These findings confirm the results of previous investigations (1) which found a significant correlation between rectal temperature during intoxication and brain sensitivity to ethanol and extend this finding to show a direct relationship between ethanol sensitivity and brain temperature during intoxication. The latter finding, along with in vitro studies (9, 13, 23), supports the hypothesis that temperature-induced changes in behavioral sensitivity to ethanol in C57 mice are mediated through changes in the brain membrane actions of ethanol.

Brain probe implantations did not adversely affect the measures of ethanol sensitivity used in this study. With one exception, there were no significant differences between the measures of ethanol sensitivity taken in control versus probe-implanted mice. Therefore, radiotelemetric measurement of brain temperature appears to represent a useful means of monitoring brain temperature in untreated and intoxicated unrestrained mice.

There was a significant correlation between brain and rectal temperatures recorded at baseline. The brain temperatures recorded at baseline were consistently lower than their respective rectal temperatures. These findings are consistent with our previous results (7) where immediate postmortem nonradiotelemetric measurements of brain temperature were recorded in saline-injected, temperature-challenged mice. The presence of this differential between rectal and brain temperatures may result from independent cooling mechanisms in the base of the brain which protect the brain against environmental- and exercise-induced heat stress in mammals (4, 5, 21, 39).

Brain and rectal temperatures recorded at RORR were also highly correlated with each other. The range of temperatures in the intoxicated animals (Fig. 3B) was greater than in the untreated animals at baseline (Fig. 3A) reflecting the combined effect of ethanol-induced impairment of thermoregulation and the manipulation of body temperature with ambient temperature. Further, rectal and brain temperatures during intoxication changed in a similar fashion as the ambient temperature increased from

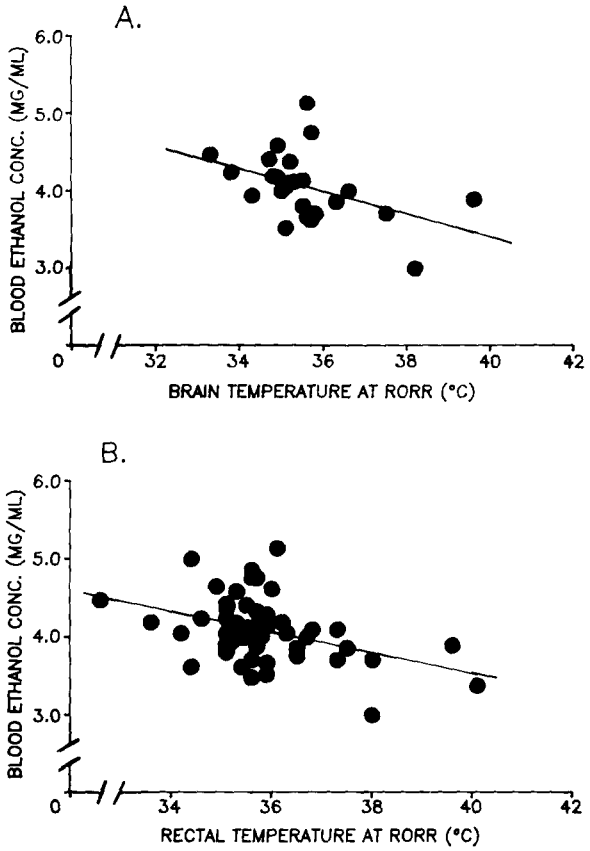

FIG. 5. Scatter plots of blood ethanol concentrations versus brain (A) and rectal (B) temperatures at RORR. Blood ethanol concentrations were significantly correlated with brain ($r = -.443$, $n = 25$, $p < 0.05$) and rectal ($r = -.409$, $n = 54$, $p < 0.01$) temperatures at RORR.

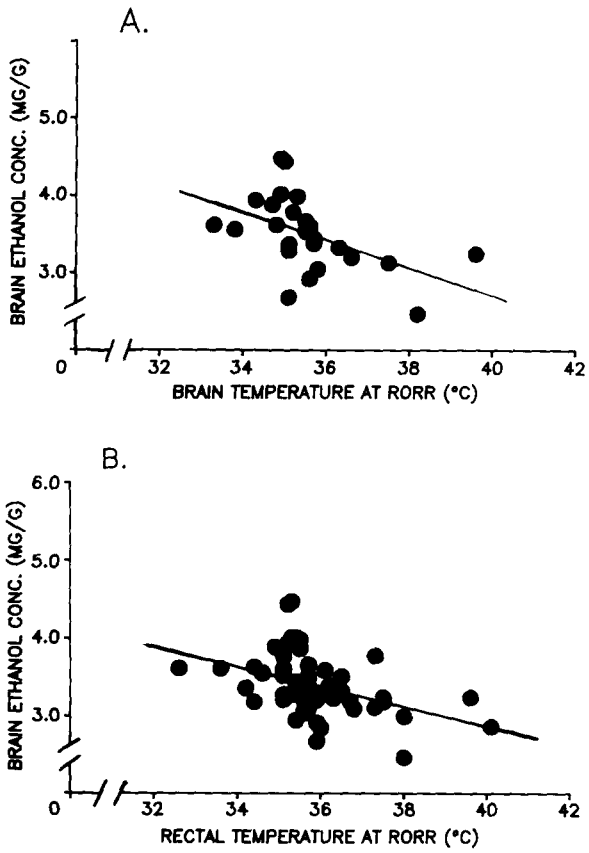

FIG. 6. Scatter plots of brain ethanol concentrations versus brain (A) and rectal (B) temperatures at RORR. Brain ethanol concentrations were significantly correlated with brain ($r = -.501$, $n = 25$, $p = 0.01$) and rectal ($r = -.414$, $n = 53$, $p < 0.005$) temperatures at RORR.

12 to 34°C (Fig. 1). In contrast to the significant differences between baseline brain and rectal temperatures, there were no significant differences between rectal and brain temperatures in the intoxicated mice tested at each ambient temperature. These results indicate that rectal temperature during intoxication can be used to reliably estimate brain temperature in temperature-challenged C57 mice. The reason for the disappearance of the differential between rectal and brain temperatures during intoxication is unknown, but could reflect impairment of the brain's thermoregulatory processes in general, or specifically, impairment of the brain's cooling system (3,4).

The significant correlation between rectal and brain temperatures during intoxication in the current study is consistent with our previous findings based on the use of immediate postmortem measurements (7). However, there were differences between the present results, which are based on measurements in vivo, and the previous postmortem study. In the current study, the rectal and brain temperatures during intoxication were not significantly different from each other and changed in a similar manner with changes of ambient temperature. The previous study found no significant differences between the rectal and brain temperatures during intoxication in animals exposed to lower ambient temperatures (15 and 22°C). However, in contrast to the present study, brain temperature was significantly lower than rectal temperature in animals which were exposed to higher ambient temperatures (32 and 34°C), suggesting that the brain's cooling system (3,4) was functioning at higher brain temperatures.

The discrepancies found between the results of the current study and the previous study in C57 mice (7) could be due to both differences in experimental design, as well as the differences in the technique of brain temperature measurements. The previous study recorded the brain and rectal temperatures at set intervals following injection with ethanol or saline. The temperature recordings of the current study were before injection with ethanol and following injection, at the times the animals regained their righting reflexes. Therefore, the time postinjection was based on the duration of LORR, and was different in each animal. With respect to technical differences, the postmortem study used a relatively large probe which was inserted into the third ventricle and the surrounding brain matter. In contrast, the radiotelemetric technique provided a continuous temperature measurement from the lateral ventricle, during the behavioral testing. Since the implantation of radiotelemetric brain probe does not appear to alter brain sensitivity to ethanol, and it is used in unrestrained, untreated and intoxicated animals, we conclude that radiotelemetry is a more accurate and useful means of brain temperature measurements when compared to the previous postmortem technique.

In summary, rectal and brain temperatures in ethanol-intoxi-

cated C57 mice are highly correlated and linearly related with each other. Brain sensitivity to ethanol, measured by the duration of LORR and blood and brain ethanol concentrations at RORR, is significantly correlated with brain as well as rectal temperatures at RORR. These results along with interaction of temperature and ethanol on membrane properties found in vitro (9) support the hypothesis that temperature-induced changes in ethanol sensitivity in C57 mice result from changes in brain temperature and the subsequent changes in the membrane actions of ethanol. Therefore, brain temperature during intoxication like other factors including genetic background (15, 24, 26, 37), ethanol metabolizing enzymes (37), neuroadaptive responses (20, 22, 38) and age (34,41) appears to have an important influence on brain sensitivity to ethanol. More recent studies (17) indicate that the relationship between body temperature and ethanol sensitivity may vary in other genotypes and suggest that the effects of temperature on ethanol sensitivity cannot be explained by simple unidirectional changes in membrane properties. Further studies are necessary to determine whether the results of the current study in C57 mice extend to other genotypes.

ACKNOWLEDGEMENTS

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