Motor Performance in Rats Exposed to Severe Forebrain Ischemia: Effect of Fasting and 1,3-Butanediol

David J. Combs and Louis G. D’Alecy

ATTEMPTS to quantify neurologic recovery have been made by numerous investigators in a wide variety of species. Subjectivity is a particular problem in neurologic assessment often due to the passive nature of the testing. We have attempted to increase the objectivity of motor function evaluation by adapting quantifiable behavioral tests and actively testing the motor capabilities of rats exposed to a cerebral ischemic insult. We hypothesized that active testing would reveal motor deficits which were not readily apparent to casual observation, and that such testing would provide a more sensitive means of experimental neurologic assessment.

The four-vessel occlusion (4-VO) model was developed by Pulsinelli and Brierley and has been heavily scrutinized with regard to its histologic, metabolic, and blood flow characteristics. With the exception of the work on learning and memory by Volpe et al, little has been published on the functional deficits produced in this model.

To test the sensitivity of the motor tests in differentiating between animals of varying levels of impairment, it was necessary to attempt modification of the neurologic outcome from cerebral ischemia. To accomplish this, animals were manipulated as to their nutritional status prior to the ischemic insult. Fed or fasted rats were pretreated just prior to ischemia with saline or the ketogenic alcohol 1,3-butanediol (BD). These treatments were chosen because fasting has been shown to favorably influence the outcome of cerebral ischemia and BD treatment has been shown to have significant protective effects in hypoxia and ischemic-hypoxic insults.

Materials and Methods
We adapted the 4-VO model using male Wistar rats (Charles River Breeding Farms) that weighed 230–290 g and were maintained in a 12-hour light-dark cycle in quarters on standard rat chow and water. The rats were anesthetized with sodium pentobarbital (65 mg/kg i.p.) and supplemented (i.p. or i.v.) as needed.

The right and left common carotid arteries were isolated and cardiovascular silk (5-0) was passed through underlying musculature and around each carotid artery, carefully excluding the vagus nerve from the snare. Each snare exited the wound site through a 2.5 cm long guide tube (PE-50); the free ends of each snare were knotted to prevent the guide tube or the snare from being displaced. The left jugular vein was catheterized, and the cannula exited at the nape of the neck. The tail artery was cannulated with a 5 cm long cannula (PE-50 tubing) filled with heparinized saline (100 U/ml). Elastic surgical tape coated with quinine was used to close the tail wound and to cover the catheter.
The vertebral arteries were electrocauterized (Bantam Bovie Unit) through the alar foramen. EEG leads, consisting of self-tapping 3/16-in. stainless steel screws silver-soldered to 30-gauge multistranded stainless steel wire (5–7 cm long), were inserted into 3 holes in the skull and insulated from surrounding tissue with dental acrylic. Immediately after surgery, each rat was given physiologic saline (0.5 ml/100 g i.v.) to provide postsurgical hydration and placed in individual cages with free access to water throughout the remainder of the experiment. Fasted rats received no food until after the ischemic insult, whereupon food was provided for the remainder of the experiment. Fed groups had access to food at all times. After surgery, all rats were housed in a 12-hour light-dark cycle facility. The ischemic insult occurred 22–26.5 hours after the last anesthetic supplement.

Approximately 30 minutes before 4-VO, rats received an i.p. injection of either 47 mmol/kg BD (50% v/v BD in water, 8.43 ml/kg) or an equivalent volume of physiologic saline. Five to 10 minutes before the induction of cerebral ischemia the tail artery cannula was connected to a pressure transducer (Statham P23Dc). The cannula was kept patent by flushing with heparinized saline (100 U/ml); the total amount of heparin given to any rat never exceeded 75 units. The EEG leads were connected to an amplifier (Grass Model 7P511G) and displayed on an oscillograph (Grass Model 7 polygraph).

**Induction of 4-VO**

For the induction of 4-VO the rat was restrained by hand, and the carotid arteries were occluded by placing traction on the snares and securing the snares with bulldog clamps. Once the animal became unconscious, a thermistor probe (Yellow Springs Instruments Model 402) was inserted 8 cm into the rectum to allow an initial measurement of body temperature approximately 2 minutes into the insult. A heat lamp was used to maintain body temperature at this value. Then the rat’s tail was tapped to test the righting response. The righting response was also tested just before the end of the ischemic insult.

Approximately 3 minutes before the end of 4-VO, 2% lidocaine was injected into the wound site around the guide tubes. After 20 minutes of carotid artery occlusion the bulldog clamps were removed as were the guide tubes and snares. The wound was quickly reopened and reestablishment of flow confirmed by looking at and manipulating each carotid artery. The wound was then closed with wound clips, and the rat’s temperature, EEG, and blood pressure were monitored for the 2-hour posts ischemic period (the carotid arteries of responsive rats [see “Results”] were not checked due to excessive movement). The rat was then returned to its individual cage and allowed free access to food and water.

Any rats with unabolished or returning EEG activity during 4-VO were eliminated from the study as were rats that died of respiratory failure during the ischemic insult. Any rats that died from seizures were not included in the study. After the 48-hour neurologic assessment, the rats were placed under halothane anesthesia, and their carotid arteries were visually checked for patency; a clogged carotid artery resulted in removal from the study.

**Experimental Protocol**

The experiment took place over 4 days. The events of each day are listed in Table 1 to indicate the timing of the neurologic tests relative to all other aspects of the experiment. To limit the influence of chance or observer bias each of the motor tests was given twice on each occasion, and the best performance was chosen as the rat’s score. A 2–3 minute rest period between each type of motor test was given to minimize any fatigue factor. All tests were carried out in a quiet area under subdued lighting. The scoring of the motor performance tests is described in Table 2.

**Screen test**

This test is a variation of the inclined screen test used for mice and rats and serves as an indicator of general muscle strength. We used a 29 x 30 cm screen that could be rotated from 0° (horizontal) to 90° (vertical). Grid size of the screen was 0.6 x 0.7 cm. The screen was situated such that when in the vertical position, it was 70 cm above a foam rubber pad (7.5 cm thick). Each rat was placed on the horizontally positioned screen. The screen was then rotated to the vertical position, and time on the screen was recorded to a maximum of 15 seconds.

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**Table 1.** Experimental Protocol

<table>
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<th>Day 1 — Surgery</th>
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<tr>
<td>Pentobarbital anesthesia</td>
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<td>EEG leads</td>
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<td>Blood vessel cannulas</td>
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<td>Preischemic motor tests</td>
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<td>Screen test</td>
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<td>Balance beam test</td>
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<tr>
<td>Prehensile-traction test</td>
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<tr>
<td>Drug treatment (approx. 30 minutes before 4-VO)</td>
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<td>Induction of 4-VO (22-26.5 hours after anesthesia)</td>
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<th>Day 3 — 24 Hours after 4-VO</th>
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<td>Motor tests</td>
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<td>Screen test</td>
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<tr>
<td>Balance beam test</td>
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<tr>
<td>Prehensile-traction test</td>
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<th>Day 4 — 48 Hours after 4-VO</th>
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<td>Motor tests</td>
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<td>Screen test</td>
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<td>Balance beam test</td>
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<tr>
<td>Prehensile-traction test</td>
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<tr>
<td>Carotid check (halothane anesthesia)</td>
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B3ALANCE BEAM TEST. This test serves as an indicator of equilibrium, although body strength becomes the major factor tested once the rat loses its balance. An unfinished wooden rod (2.5 cm diameter) was positioned horizontally 40 cm above a foam pad (7.5 cm thick). The rod was supported by clamps 70 cm apart. The rod was placed at the center of the wooden rod, and the time to falling off was recorded to a maximum of 30 seconds.

PREHENSILE-TRACTION TEST. This test is adapted from similar tests in mice. The prehensile portion of the test involves the rat’s ability to hang onto a horizontal rope by its forepaws and is a measure of muscle strength. The traction portion involves the animal’s ability to bring one of its rear limbs up to the rope and depends on equilibrium and muscle strength. A 0.5 cm diameter nylon cord was placed horizontally 70 cm above a foam rubber pad (7.5 cm thick). A rat’s forepaws were placed on the rope, and the animal was released. The rat was allowed to hang onto the rope for up to 5 seconds. Time to falling was noted as well as whether or not the rat brought a rear limb up to the rope.

TOTAL MOTOR SCORE. This score is the sum of the scores for the screen, balance beam, and prehensile-traction tests, and therefore ranges from 0 to 9.

Treatment Groups

Manipulation of the animals’ nutritional state and the drug treatment produced 4 groups. Rats that were either fed or fasted before cerebral ischemia received either BD (47 mmol/kg i.p.) or an equivalent volume of physiologic saline about 30 minutes prior to 4-VO. The resulting experimental groups, therefore, were fasted-saline, fasted-BD, fed-saline, and fed-BD. Since some of the fasted-saline and fed-saline rats responded differently (details given in “Results”) to 4-VO, responsive and unresponsive categories were designated within both of these groups and are compared in “Results.”

To control for the effect of surgery, nutritional state, and drug treatment on motor performance, 4 control groups were tested: fasted-saline, fasted-BD, fed-saline, and fed-BD (n = 3 for each group). These animals received the full surgical procedure. The next day, they were given a preischemic neurologic examination, treated with an appropriate i.p. injection, and about 30 minutes later had the guide tubes removed from the neck wound without occluding the arteries. These rats were then returned to their cages and treated in the usual manner.

Statistical Analysis

Both parametric and nonparametric statistical tests were used and are described in “Results.”

Responsive and unresponsive rats within both the fasted-saline and fed-saline groups were compared using Student’s t test for all variables except the motor performance scores (Kruskal-Wallis test for rank data). Statistical significance was accepted for p < 0.05.

Physiologic data such as blood pressure, body temperature, and EEG return time were compared among the 4 experimental groups using one-way analysis of variance (ANOVA). When ANOVA indicated a significant difference (p < 0.05), further analysis was done with Student’s t test using a Bonferroni correction factor for error protection. In this case, only 4 specific comparisons were made to examine the effects of drug and nutritional status: fasted-saline vs. fasted-BD, fed-saline vs. fed-BD to examine the effect of nutritional status. Since no group was involved in more than 2 comparisons, a difference was considered significant at the 5% level if p < 0.05/2 or p < 0.025.

Motor performance data for all 4 control groups were compared using the Kruskal-Wallis test for ranked data. Since the testing indicated no significant differences among these control groups (carotid not occluded) for any motor performance variable, they were combined. To test for changes in performance over 3 days of motor testing, the 24- and 48-hour postischemic total motor scores of the combined control group were compared to the preischemic performance using the Wilcoxon paired rank test, and α error protection was provided by accepting p < 0.025 for the 5% significance level.

Individual groups were compared using the Kruskal-Wallis test to examine motor performance data from experimental groups. Three comparisons were made for each group: one to test the effect of BD, one to test the effect of preischemic nutritional status, and one to compare with appropriate operated controls. To account for multiple comparisons, α error protection was provided. Since any experimental group was in-

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**Table 2. Scoring Codes for Individual Motor Tests**

<table>
<thead>
<tr>
<th>Score</th>
<th>Screen</th>
<th>Balance beam</th>
<th>Prehensile-traction</th>
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<tbody>
<tr>
<td>0 Falls off in 0–5 seconds</td>
<td>Unable to maintain grip or balance on wooden beam</td>
<td>Hangs on 0–2 seconds</td>
<td></td>
</tr>
<tr>
<td>1 Falls off in 6–10 seconds</td>
<td>Remains on beam up to 10 seconds</td>
<td>Hangs on 3–4 seconds</td>
<td></td>
</tr>
<tr>
<td>2 Falls off in 11–14 seconds</td>
<td>Remains on beam 11–20 seconds</td>
<td>Hangs 5 seconds; no third limb up to rope</td>
<td></td>
</tr>
<tr>
<td>3 Stays on screen full 15 seconds</td>
<td>Remains on beam 21–30 seconds</td>
<td>Hangs on 5 seconds; brings rear limb up to rope</td>
<td></td>
</tr>
</tbody>
</table>

All measured times were rounded to the nearest whole second. The best time of 2 trials determined the coded score for all tests during each testing session. Scores of 3 were assigned to animals that climbed to the top of the screen, walked to the balance beam supports, or climbed to the prehensile-traction rope supports.
involved in 3 comparisons, a comparison was considered significant at the 10% level only when $p < 0.033$.

**Results**

Six of the 48 rats exposed to 4-VO (12.5%) failed to show a fully abolished EEG tracing during cerebral ischemia. Four rats (8.3%) died of respiratory failure during the ischemic insult, while 1 rat (2.1%) died of seizures between 24 and 48 hours after ischemic injury. Two animals were eliminated because they failed to meet the criterion of 2 observably patent carotid arteries at the 48-hour carotid check.

Among the saline-treated rats (fasted or fed) exposed to ischemia, 2 subgroups were observed: responsive and unresponsive. Unresponsive rats showed abolished EEG activity for the full duration of the ischemic period, no response to tail tap at either the beginning or end of 4-VO, and no significant movement throughout the ischemic period. Responsive rats, in contrast, maintained isoelectric EEG but either showed a remnant of the righting response to one of the tail taps or moved significantly during the insult; significant movement was considered spontaneous righting with or without transient running motion, or reverse rolling (i.e., the rat rolled over in a direction opposite to that expected for righting). BD-treated rats were all unresponsive. Unresponsive fasted saline-treated rats showed no significant differences in physiologic or neurologic parameters when compared with responsive fasted saline-treated rats, and they were combined to form the fasted-saline group. A comparison between unresponsive fed saline-treated (UFS) rats and responsive fed saline-treated (RFS) rats was also made. Only one significant difference was found, for blood pressure 10 minutes into the ischemic period. UFS rats had a higher blood pressure (156 mm Hg) than RFS rats (142 mm Hg; $p = 0.03$, Student's $t$).

Given the similarity of the 2 groups, the UFS and RFS rats were combined to form the fed-saline group.

**Physiologic Data**

The physiologic data were analyzed by ANOVA followed, when appropriate, by multiple Student's $t$ tests using the Bonferroni correction factor for $\alpha$ error protection. Four experimental group comparisons were made for the physiologic data: fasted-saline vs. fasted-BD, fed-saline vs. fed-BD, fasted-saline vs. fed-saline, and fasted-BD vs. fed-BD.

In Figure 1, blood pressure increased markedly during ischemia and returned to control levels after ischemia. ANOVA detected no differences among the 4 groups at either control or postischemic time points. Ten minutes into ischemia, blood pressure in the fed-saline group was significantly greater than in either the fasted-saline or fed-BD group. ANOVA indicated that at 20 minutes of ischemia there was a significant difference among the means; however, none of the 4 comparisons of interest were significant by Student's $t$ test.

ANOVA with accompanying Student's $t$ tests revealed that fasted-saline rats had a significantly higher body temperature (38.7 ± 0.1°C) than did fasted-BD rats (37.6 ± 0.2°C; $p < 0.05$, Student's $t$ test). The same difference was observed among the fed animals, with fed-saline rats showing a greater body temperature (38.8 ± 0.1°C) than fed-BD rats (38.1 ± 0.1°C; $p < 0.05$, Student's $t$ test). No significant differences existed between fed and fasted rats within each drug treatment. No significant differences were found in the EEG return data, with the overall average being 961 seconds.

**Motor Performance**

No significant differences were found among the 4 operated control groups when analyzed by the Krus-
TOTAL MOTOR SCORE - CONTROL RATS (N=12)

Figura 2. Distribution of total motor scores for the combined control groups over the course of the experiment.

The fasted-BD rats showed no significant differences in total motor score compared with their operated controls at any time after ischemia. The fasted-saline rats were different at the 10% level from their operated controls 24 hours after ischemia (p = 0.01, Kruskal-Wallis) but not at 48 hours. While no difference was detected between groups before 4-VO, there was a difference significant at the 10% level 24 hours after ischemia (Figure 3). The fasted-saline rat distribution was considerably further down the coded score axis than the fasted-BD group distribution, indicating better performance by the fasted-BD group. This difference, however, was gone by 48 hours.

Fed-Saline vs. Fed-BD

Overall motor performance in fed-BD rats was reduced below that of their operated controls at 24 hours after 4-VO (p = 0.02, Kruskal-Wallis) but became statistically equivalent by 48 hours. However, total motor performance among fed-saline rats remained significantly below that of their operated controls throughout the postischemia phase of the experiment (p = 0.01 at both 24 and 48 hours postischemia, Kruskal-Wallis). There was no significant difference between the 2 groups (Figure 4). It does appear that the fed-BD rats showed greater improvement by 48 hours postischemia; however, the p value of 0.09 does not allow the improvement to be considered significant at the 10% level.

Figura 3. Distribution of total motor score for fasted-saline vs. fasted-butanediol (BD) rats over the course of the experiment (p value shown for between-group comparison, * significant at the 10% level).
Fasted-Saline vs. Fed-Saline

Overall motor performance of the fed-saline group was significantly depressed below that of their controls throughout the 48-hour recovery phase. The difference between fasted-saline and their controls was significant at 24 hours but not at 48 hours after 4-VO. Performance fell similarly in the 2 groups 24 hours after 4-VO (Figure 5). By 48 hours after the insult, however, the fasted-saline rats performed significantly better than the fed-saline animals.

Fasted-BD vs. Fed-BD

Only the fed-BD rats were significantly worse in total motor score than their respective controls \((p = 0.02, \text{Kruskal-Wallis})\) 24 hours after 4-VO. Neither group was statistically distinguishable from their controls at 48 hours postischemia. The overall motor performance of these 2 groups is illustrated in Figure 6. Although the motor performance of fasted-BD rats appears to be better than that of fed-BD rats 24 hours after 4-VO, this difference was not significant.

Discussion

Interpretation of Changes in Total Motor Score

We have attempted to increase the objectivity of motor function evaluation by adapting quantifiable behavioral tests and actively testing the abilities of the rat before and after cerebral ischemia. One advantage of active testing over passive observation may be that deficits which are not necessarily obvious on simple observation are uncovered. With the exception of the work on learning and memory by Volpe et al, little has been done on the neurologic deficits produced by this model, perhaps because the deficits seemed relatively mild or nonexistent. Indeed, Pulsinelli et al described fasted saline-treated rats 24 hours after 20 minutes of 4-VO as “No animal pretreated with saline convulsed, and all walked well with no signs of neurologic dysfunction at 24 hours.” While fasted saline-treated rats in our study also looked normal on casual observation, active testing indicated that motor performance was seriously impaired 24 hours after 4-VO, and that by 48 hours postischemia there was still a trend indicating that performance was below control.
levels. The fasted-BD group was the only one that did not fall significantly below its respective control in total motor score 24 hours after ischemia. Experimental groups manifested varying degrees of improvement by 48 hours posts ischemia. The fact that total motor score could discern both deteriorations and improvements in motor performance suggests that this parameter is more sensitive than casual observation. Although the scores probably reflect decreased motor capability, motivational considerations cannot be eliminated as a factor contributing to rat performance.

Total motor score followed a distinct pattern after cerebral ischemia with a sharp drop after 4-VO, followed by improvement by 48 hours after the ischemic insult. Whether the drop in performance represents actual cerebral ischemic damage or a diaschisis-like functional depression is not known. Recovery may represent a dual-phase process involving reemergence of function from depressed areas or recovery through neural reorganization. The rapidity of recovery makes reorganization unlikely, and this tends to favor the hypothesis that improved motor performance represents reemergence of functionally depressed neurons.

The rapid onset of improvement is particularly surprising in view of a study which indicated that histologically evaluated neuronal damage progresses between 24 and 72 hours in rats exposed to 30 minutes of 4-VO. Clearly correlative studies of neuronal changes with motor recovery over more extended periods would address many of these questions. It is possible that a shorter time course of motor recovery will be found to indicate a smaller lesion.

The 4-VO Model
An observation, which to our knowledge is unique, deals with the criteria used to define an acceptable 4-VO preparation. According to Pulsinelli et al, the only animals included for analysis are those that "become unresponsive and completely lose their righting reflex for the duration of carotid artery occlusion;" they tested the righting reflex just after carotid occlusion and just before the release of the occlusion. The reflex was tested using the tail or hind paw flick while the animals were on their right and left sides. These criteria seem rigid, except that the meaning of complete loss of righting reflex is not clear. In another study from the same laboratory, loss of the righting reflex referred to the loss of the "ability to arise from a recumbent position," thus allowing some range of movement as long as the rat does not arise from recumbency. In the data reported here, tail tap and EEG helped define classification and rejection criteria. Although all rats in the study maintained isoelectric EEG during the insult, saline-treated rats fell into responsive and unresponsive categories (see "Results"). The fact that responsive rats maintained isoelectric EEG implies that cortical blood flow must have been below the threshold for failure of electrical neuronal function (functional threshold). Since the righting reflex does survive low decerebration, we deduce that subcortical structures regained enough blood flow for righting function to be maintained in the responsive animals. How great the disparity between forebrain blood flow in responsive vs. unresponsive groups cannot be directly addressed. However, the difference was relatively minor in terms of the neurologic endpoints measured.

The BD-treated rats showed no such dispersion into responsive and unresponsive groups. A possible explanation for this is that cerebral function may have been depressed by the intoxicating effect of BD and could have resulted in rats that had relatively higher cerebral blood flow but remained unresponsive nonetheless. It could be argued that BD may have helped rats "pass" the inclusion criterion of isoelectric EEG by these very same depressive effects, thereby allowing rats with exceptionally high forebrain blood flows to remain in the study. This is unlikely since there is evidence that BD decreases the functional threshold for isoelectric EEG.

Effects of Fasting and BD on Motor Performance
Fasting has been shown to be protective in cerebral ischemia in terms of neurologic, metabolic, and
cerebral blood flow indices. In this experiment, fasting was beneficial to neurologic recovery as well (Figure 5). Physiologic considerations do not account for the improved motor recovery, for neither cerebral perfusion pressure nor body temperature favored the fasted-saline vs. fed-saline rats. Whether or not the 2 groups would maintain their difference over more extended periods was not addressed in this study.

As can be seen from Figure 3, fasted rats given BD had better motor performance when compared with fasted rats given saline. This improvement was relatively mild in that by 48 hours posts ischemia, there was no longer a significant difference between the fasted-BD and the fasted-saline group. While these results are not as dramatic as the >500% increases in hypoxic tolerance we observed earlier in hypoxic mouse studies, it suggests that BD does, at least transiently, favorably alter the effects of cerebral injury. The fasted-BD rats did not benefit from higher cerebral perfusion pressure, but body temperature changes may have benefitted them in that their body temperature was significantly lower than that of their saline-treated counterparts. Hypothermia protects the central nervous system from hypoxia, hypoxia-ischemia, and ischemia. Although no studies have demonstrated that a temperature difference of only 1.1° C is protective to the brain during ischemia, a recent study on spinal cord ischemia suggests that such changes in body temperature can be beneficial to recovery of function in the central nervous system. As a result, we cannot rule out the possibility that lower body temperature accounted for the improvement in motor performance provided by BD. It is also possible that the sedative effects produced by BD contributed to its effectiveness; however, the protection conferred by BD in the hypoxic survival model in mice could not be fully explained by its sedative effects since similar doses of BD and ethanol, an alcohol with similar central nervous system effects, did not produce the same increases in hypoxic survival time. The ability of BD to induce ketosis may have also contributed to its ability to alter cerebral ischemic outcome.

In summary: The motor tests designed for these experiments appear to be more sensitive than passive observation in detecting changes in the level of motor deficits in rats after 20 minutes of 4-VO. This more sensitive testing was able to detect both increases and decreases in motor function that were not apparent on inspection. Fasting significantly improved performance among saline-treated rats, supporting the observations of other investigators. Fasted rats given BD also had an improved time course of recovery in that the return of function occurred earlier than in the saline-treated animals.

Acknowledgments

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