The Antidepressant Properties of the Ketogenic Diet

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Background: *The ketogenic diet is used to treat epilepsy refractory to anticonvulsant medication. Individuals with epilepsy often have behavioral problems and deficits in attention and cognitive functioning. The ketogenic diet has been found to effect improvements in these domains. It has also been suggested that the ketogenic diet may act as a mood stabilizer.*

Methods: *The present research used the Porsolt test, an animal model of depression, to determine whether the ketogenic diet has antidepressant properties. Porsolt test scores of rats on the ketogenic diet were compared with those of rats on a control diet.*

Results: *The rats on the ketogenic diet spent less time immobile, suggesting that rats on the ketogenic diet, like rats treated with antidepressants, are less likely to exhibit "behavioral despair."*

Conclusions: *It is concluded that the ketogenic diet may have antidepressant properties.*

Key Words: Depression, ketogenic diet, behavior, animal model, Porsolt test

The ketogenic diet is a high-fat, low-carbohydrate, low-protein diet which has been in use since the 1920s for the treatment of drug-resistant epilepsy (Peterman 1924). Although it is not known how the ketogenic diet works to prevent seizures, it is thought to force the brain to use ketone bodies as a fuel instead of glucose (Prasad et al 1996; Swink et al 1997). Individuals with epilepsy often have behavioral problems, cognitive deficits, and psychiatric disorders (MacCracken and Scalisi 1999; Ounstead 1955; Pulliainen et al 2000; Semrud-Clikeman and Wical 1999). Anecdotal reports (Kinsman et al 1992; MacCracken and Scalisi 1999) and formal studies (Pulsifer et al 2001) involving human subjects suggest that the ketogenic diet can alleviate some of these problems. The diet has been found to improve symptoms of autism in children (Evangeliou et al 2003). It has also been suggested that the ketogenic diet may have mood-stabilizing properties (El-Mallakh and Paskitti 2001).

The Porsolt test is an established animal model of depression (Porsolt et al 1978), which has been used as a screen in the development of new antidepressants (Ali et al 1998; Einat et al 1999; Kroczka et al 2001). The test consists of two parts. In the first part, the subject is placed in a container of water from which it cannot escape. Eventually, the animal "gives up" and becomes immobile. This part of the test establishes "behavioral despair." The second part of the test is used to measure the effects of antidepressants on this behavior. The animal is again placed in the container of water, and the time spent immobile is measured. Pretreatment with antidepressants has been found to lessen the time spent immobile (Porsolt et al 1977, 1978). The present research used the Porsolt test to determine whether treatment with the ketogenic diet could duplicate the behavioral effects of antidepressants.

Methods and Materials

The present research was approved by the Animal Care Committee of the University of Toronto and conducted in accordance with the guidelines of the Canadian Council on Animal Care.

Subjects

Forty adult male Wistar rats, weighing between 250 and 350 g, served as subjects (Charles River Canada, St. Constant, Quebec, Canada). The animals were individually housed in a vivarium which was maintained at a temperature of 21°C. A 12-hour light/dark cycle (lights on 7:00 AM–7:00 PM) was in effect.

Diets and Groups

After 3 weeks in the vivarium, subjects were randomly divided into two groups of 20. Subjects were weighed. Group 1 received a 4:1 (fat to protein and carbohydrate) ketogenic diet, and Group 2 received a control diet (.082:1), different from the usual diet (DYETS Inc., Bethlehem, Pennsylvania). Diets were matched for protein, vitamins, and minerals and differed only in the ratio of fat to carbohydrates (Likhodii 2001). Subjects fasted for 24 hours before the initiation of the diets. Animals in both groups were allowed access to food for 2.5 hours a day, between the hours of 11:00 AM and 1:30 PM, following the "limited access" procedure of Bough and Eagles (2001).

Handling Test

Immediately preceding the Porsolt test, a 12-point scale (Table 1) was used to rate how difficult the subjects were to handle. This was done to determine the general level of reactivity. Rats were held and handled for 1 minute while being rated. A single researcher handled and rated all animals.

Procedure for the Porsolt Test

In each trial, the subject was placed for 10 minutes in a plastic bucket measuring 39.5 cm in height and 30 cm in width, which was filled with water to a height of 25 cm. Water was changed between subjects and maintained at 25°C. The first trial was conducted before fasting. The second trial was conducted after 7 days on the diets. The time spent immobile during the second trial was measured in seconds. Immobility was defined as moving the limbs only enough to stay above water. All testing took place between 9:00 AM and 11:00 AM. The animals were weighed before the second trial of the Porsolt test.

Ketosis

After all testing was completed, blood samples were taken from 12 animals in each group. Animals to be tested were chosen at random. Subjects were not fed on the day samples were taken. Samples were obtained by cardiac puncture from rats anesthetized with sodium pentobarbitol (Somnitol; MTC Pharmaceuticals, Cambridge, Ontario, Canada). Levels of β-hydroxybutyrate,

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Table 1. Handling Rating Scale

0	Did not struggle at all, or vocalize
1	Did not struggle at all, but vocalized softly
2	Did not struggle at all, but vocalized loudly
3	Struggled, but calmed within 15 seconds
4	Struggled, and vocalized softly, but calmed within 15 seconds
5	Struggled, and vocalized loudly, but calmed within 15 seconds
6	Struggled for longer than 15 seconds
7	Struggled for longer than 15 seconds, and vocalized softly
8	Struggled for longer than 15 seconds, and vocalized loudly
9	Struggled for longer than 15 seconds, and attempted to bite
10	Struggled for longer than 15 seconds, vocalized softly, and attempted to bite
11	Struggled for longer than 15 seconds, vocalized loudly, and attempted to bite

one of the ketones produced by the ketogenic diet, were measured (KetoSite, GDS Diagnostics, Elkhart, Indiana). A high level of this ketone has been used as an indication of ketosis (Likhodii et al 2000; Bough and Eagles 2001).

Statistical Analysis

Handling data were not normally distributed, and results were analyzed by means of the Mann–Whitney Rank Sum test. Results from the Porsolt test were analyzed by means of the Student *t* test. Group weights were compared using the Mann–Whitney Rank Sum test, as the variances at second weighing were not equal. The β-hydroxbutyrate levels were analyzed using the Student *t* test. All results were considered significant at the .05 level.

Results

No group difference in ratings for difficulty in handling was found (Table 2). The subjects in the ketogenic diet group spent less time immobile than did the subjects in the control group (Table 3). There was no significant group difference in weight before the initiation of the diets. At time of behavioral testing, the rats on the ketogenic diet were significantly heavier than the rats on the control diet (Table 4). No significant correlation between weight and time spent immobile during the Porsolt test was found, however ($r = -.270$, $df = 38$, $p > .050$). The subjects in the ketogenic group had significantly higher levels of β-hydroxybutyrate at the end of the experiment than did the subjects in the control group (Table 5).

Discussion

The subjects in the ketogenic diet group spent less time immobile than did the subjects in the control diet group. This suggests that the ketogenic diet has effects that are similar to antidepressant drugs in the Porsolt test. This result suggests, in turn, that the ketogenic diet may be useful in the treatment of depression.

The handling test was included only to determine if reactivity was related to performance in the Porsolt test. The rats on the ketogenic diet were not more difficult to handle than the rats on the control diet, so the decrease in immobility seen in the Porsolt test does not seem to be the result of irritability or reactivity. Previous research has shown that rats on the ketogenic diet are less active than rats on a control diet (Murphy et al, in press). These findings suggest that the decrease in immobility seen in the rats on the ketogenic diet in the Porsolt test was not simply the result of an increase in energy. Porsolt et al (1978) also found that antidepressants reduce immobility in the test but also reduce or do not affect activity level in the open field.

The difference in immobility was not connected to a difference in weights. Although the groups did differ on this measurement (the rats in the ketogenic diet gained slightly more weight during the experiment than did the control rats), the correlation between these two variables was very low and not significant. Subjects were checked daily by various researchers and the staff of the Department of Comparative Medicine. No signs of ill health or odd behaviors were noted.

The ketogenic diet and the control diet were matched for mineral, vitamin, and protein content. The diets only differed in the ratios of fat to carbohydrate. This suggests that the behavioral change is related either to an increase in fat or to a decrease in carbohydrates.

The present experiment involved feeding the ketogenic diet on a "limited access" schedule. It is not likely that this schedule is necessary to achieve a decrease in immobility. Past experiments have shown that feeding the ketogenic diet ad lib will result in behavioral changes (i.e., a decrease in activity level) (Murphy et al, in press). These results taken with those obtained in the present experiment suggest that the diet can affect behavior whatever the feeding schedule.

The present experiment did not demonstrate whether or not ketosis is necessary to effect a behavioral change. As ketosis was not manipulated, this variable cannot be used to explain a difference in behavior. Although the ketogenic diet group achieved a higher level of ketosis than the control group, this level was quite low. A low level of ketosis was also found in the control group.

There is no evidence to suggest that ketosis is necessary to achieve behavioral change. In addition, human studies investigating the behavioral effects of the ketogenic diet have shown that seizure control and behavioral change are separable. Improved behavior and improved mental alertness have been noted, even though seizure control has not been attained (MacCracken and Scalisi 1999; Pulsifer 2001). The present research suggests that the ketogenic diet deserves further study as a possible treatment for depression.

Table 2. Handling (Ratings)

Group	*n*	Median	25%	75%	*t*	*p*
Ketogenic Diet	20	.000	.000	1.000	35.000	.107
Control Diet	20	1.000	.000	2.000		

Table 3. Time Spent Immobile During the Porsolt Test (second)

Group	*n*	Mean	SD	SE	*t*	*p*	*df*
Ketogenic Diet	20	194.550	64.612	14.448	−4.536	<.001	38
Control Diet	20	304.650	87.238	19.507			

Table 4. Weights of Rats (grams)

Group	*n*	Median	25%	75%	*t*	*p*
Before Diet						
Control diet	20	276.500	269.500	284.000	352.500	.123
Ketogenic diet	20	280.500	269.500	284.000		
After Diet						
Control diet	20	300.000	293.000	303.000	524.000	.002
Ketogenic diet	20	313.500	300.000	326.000		

Table 5. Levels of Beta-Hydroxybutyrate (mmol/L)

Group	*n*	Mean	SD	SE	*t*	*p*	*df*
Ketogenic Diet	12	.579	.177	.0511	4.642	<.001	22
Control Diet	12	.304	.104	.0299			

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