

were randomly selected for blood sampling and fat measurements (retroperitoneal and epididymal). As described in Example 1, 2-3 animals from each group were sacrificed every 8 hours beginning at the onset of light. All animals were fasted 6 hours prior to blood sampling and sacrifice. Plasma triglyceride, total cholesterol, glucose, and insulin concentrations were measured as described in Example 1.

TABLE 2

Effect of Timed Fusaric Acid Administration on Fat Stores and Various Metabolic Indices in the Male Sprague-Dawley Rat			
	Control	Fusaric Acid (0700)	Fusaric Acid (1900)
Retroper. fat (g)	4.63 ± 0.27 ^{1,2}	3.19 ± 0.50 ^a	3.18 ± 0.50 ^a
Epididymal fat (g)	7.47 ± 0.44	5.16 ± 0.57 ^a	5.67 ± 0.50 ^a
PI. Triglyceride (mg/dL)	149 ± 22	104 ± 23	113 ± 9 ^a
PI. Cholesterol (mg/dL)	172 ± 10	175 ± 12	132 ± 23 ^{a,b}
PI. Glucose (mg/dL)	159 ± 6	160 ± 12	108 ± 14 ^{a,b}
PI. Insulin (μU/mL)	178 ± 11	157 ± 9	113 ± 5 ^{a,b}

¹Mean ± standard error of the mean (n = 7-8/group).

²Food consumption did not differ significantly between groups.

^aDiffers significantly from control (P < 0.05).

^bDiffers significantly from 0700 administration time.

The experiment reported in this Example was designed to test for differences in the effectiveness of fusaric acid based on time of administration. Times were selected to target fusaric acid treatment either toward (1900) or away (0700) from the peak interval of lipogenic and glycogenic activity in the healthy Sprague-Dawley rat.

Both times of fusaric acid treatment were equally effective in producing significant reductions in retroperitoneal and epididymal fat stores (both were decreased approximately 30%) (TABLE 2). However, only the 1900 h administration time significantly reduced plasma cholesterol, glucose and insulin concentrations compared to both the control and the 0700 h administration.

These results underscore the additional benefit of appropriate timing in the administration of fusaric acid. Only the 1900 time simultaneously reduced body fat stores in conjunction with reductions in indices associated with non-insulin dependent diabetes mellitus.

EXAMPLE 3

Indirect (Long-Term) Effect of Timed Fusaric Acid Administration on Metabolic Indices 3 Months After Cessation of Treatment

Three months after cessation of fusaric acid treatment, blood samples were taken from the remaining 4 animals in control and treatment groups described in Example 2. Blood samples were taken over a twenty-four hour period in order to obtain overall mean daily concentrations of plasma triglyceride, cholesterol, glucose and insulin. All measurements were made according to the methodologies described in Example 1.

TABLE 3

Effects of Fusaric Acid Administration on Metabolic Indices 3 Months After Cessation of Treatment			
	Control	Fusaric Acid (0700)	Fusaric Acid (1900)
PI. Triglyceride (mg/dL)	164 ± 4 ¹	180 ± 7	117 ± 10 ^{a,b}
PI. Cholesterol (mg/dL)	162 ± 4	186 ± 5 ^a	139 ± 6 ^{a,b}
PI. Insulin (μU/mL)	165 ± 10	143 ± 6	107 ± 6 ^{a,b}

¹Mean ± standard error of the mean (n = 4/group).

^aDiffers significantly from control (P < 0.05).

^bDiffers significantly from 0700 group (P < 0.05).

Three months after cessation of treatment, plasma triglyceride, cholesterol, and insulin concentrations were still significantly reduced in the 1900 fusaric acid treatment group compared with either the control or the 0700 group (p<0.05). In fact, plasma values for these parameters (1900 group) were not significantly different from those obtained only 2.5 weeks after treatment. The 0700 h fusaric acid treatment, however did not lower triglyceride, cholesterol, or insulin levels compared with the controls.

3.5 months after cessation of treatment, blood samples were again taken from individuals rats in control (n=3) and fusaric acid treated (0700, n=4; 1900, n=4) rats for the determination of plasma prolactin concentrations. Samples were taken by orbital sinus puncture beginning at the onset of light (0700) and continuing every 4 hours thereafter over a 24 hour period. Plasma prolactin was measured utilizing an antibody and a rat prolactin standard supplied by the National Pituitary Program.

3.5 months after treatment overall mean prolactin levels in the 1900 treated group (8.3 ng/mL; FIG. 2b) were significantly lowered compared to the controls (22 ng/mL; FIG. 2d) and similar to the prolactin levels of young, healthy, 8-week old rats that are lean and insulin sensitive (9.2 ng/mL; FIG. 2c). The prolactin levels in the 0700 treated group (19.8 ng/mL; FIG. 2a) were similar to those of 50-week old insulin-resistant controls (22 ng/mL).

Furthermore, the prolactin profile of the 1900 treated group approached the profile of young, lean, insulin-sensitive rats even though at the time of the prolactin test the members of the treated 1900 group were 50 weeks old. This experiment provides evidence that fusaric acid administered at the appropriate time adjusts prolactin profile to a profile approaching that of a young healthy individual and resets prolactin rhythm, in that the favorably modified profile persists for a considerable period of time after cessation of the timed treatment with fusaric acid.

These effects of properly timed fusaric acid treatment demonstrate long-term improvements in metabolic conditions associated with non-insulin dependent diabetes mellitus that persist long after the cessation of treatment.

The invention was described above with reference to preferred embodiments. In light of this description, however, it will be apparent to those skilled in the art that many omissions, additions and modifications are possible, all within the scope of the following claims.

What is claimed is:

1. A method for modifying lipid metabolism in a vertebrate animal or human subject in need of such treatment which comprises administering to said animal or said human