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Declarations under Rule 4.17:

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(54) Title: USE OF AICAR AND RELATED COMPOUNDS

(57) Abstract: A method for prophylaxis or treatment of obesity that includes providing a patient, particularly a human patient, suffering from or believed to be at risk of suffering from obesity and administering intermittently to the patient a therapeutic composition including an amount of AICAR, AICAR analog or AICAR precursor that is therapeutically effective at preventing or treating obesity by reducing abdominal fat in the patient is disclosed. Intermittent administration of AICAR according to the method of the invention, e.g., three days per week, at low doses for an extended period of time, appears to cause the specific loss of abdominal fat with little if any decrease in food intake and few if any negative side effects.

TITLE OF THE INVENTION

USE OF AICAR AND RELATED COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the priority of U.S. Provisional Application No. 60/209,819 filed June 6, 2000 entitled, USE OF AICAR (5-AMINO-4-IMIDAZOLE CARBOXIMIDE RIBOSIDE) AND RELATED COMPOUNDS TO TREAT AND PREVENT OBESITY, the whole of which is hereby incorporated by reference herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made in part with United States Government Support under Contract Number NK 19514 awarded by the National Institutes of Health. Therefore, the U.S. Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

Even in the face of burgeoning discoveries as to the effects of hormones, such as leptin, and neural pathways in regulating energy balance and body weight, attention to more traditional studies of the intracellular metabolic machinery that controls the synthesis and oxidation of lipid fuels can produce valuable results. One component of this metabolic machinery, malonyl coenzyme A (CoA), is a critical participant in the regulation of lipid fuel metabolism as it has effects on both fatty acid oxidation in the mitochondria and the

synthesis of various lipids. Disturbances in malonyl CoA regulation leading to alterations in signal transduction may contribute to insulin resistance and obesity. Abu-Elheiga et al. (Science 291:2613-2616, 2001) have recently shown that malonyl CoA in certain key tissues (such as heart and skeletal muscle) is a crucial regulator of fat metabolism and energy balance.

Malonyl CoA, synthesized by the enzyme acetyl CoA carboxylase (ACC), has two principal tasks in the cell. It provides acetyl groups that are incorporated into fatty acids during their synthesis, and it inhibits the enzyme carnitine palmitoyltransferase, which controls transfer of long-chain fatty acyl CoA molecules to the mitochondria, where they are oxidized to provide energy. Increasing the fuel supply of muscles by treating them with glucose and insulin increases the concentration of malonyl CoA and diminishes fatty acid oxidation by increasing the activity of ACC2 (also called ACCβ), the predominant ACC isoform in cardiac and skeletal muscle. Conversely, exercise lowers the concentration of malonyl CoA by activating an AMP-activated protein kinase (AMPK), which phosphorylates and inhibits ACC2. 5-Aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) is a naturally occurring analogue of adenosine that is taken up by muscle and liver and phosphorylated to form 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranosyl-5'-monophosphate (ZMP), which also activates AMPK. Thus, various efforts at using AICAR treatment to understand the metabolic effects of increasing AMPK activity have been attempted. In muscle, AICAR administration has been shown to reproduce many of the effects of exercise,

including phosphorylation and inhibition of ACC, and to increase fatty acid oxidation and glucose transport. In rat thymocytes, it has been shown to inhibit apoptosis, and in cardiac endothelium, it can activate or inhibit nitric oxide synthase.

BRIEF SUMMARY OF THE INVENTION

The method of the invention is directed to the use of intermittent, low dose, sustained administration of AICAR (5-amino-4-imidazole carboxamide riboside) and related compounds in the prevention or treatment of obesity and closely related disorders, e.g., those associated with insulin resistance. Other compounds useful in the method of the invention include analogs of AICAR (such as those disclosed in U.S. Patent No. 5,777,100, hereby incorporated by reference herein) and prodrugs or precursors of AICAR (such as those disclosed in U.S. Patent No. 5,082,829, hereby incorporated by reference herein), which increase the bioavailability of AICAR, all of which are well-known to those of ordinary skill in the art.

Unexpectedly, it has been found that intermittent administration of AICAR, e.g., three days per week, at low doses for an extended period of time appears to cause the specific loss of abdominal fat with little if any decrease in food intake and few if any negative side effects. Furthermore, while the mass of retroperitoneal, mesenteric and epididymal fat can be diminished by 30-40% following AICAR treatment according to the invention, the weights of heart, liver and various muscles remain the same.

Thus, the invention is directed to a method for prophylaxis or treatment of obesity that includes providing a patient, particularly a human patient, suffering from or believed to be at risk of suffering from obesity and administering intermittently to the patient a therapeutic composition including an amount of AICAR, AICAR analog or AICAR precursor that is therapeutically effective at preventing or treating obesity by reducing abdominal fat in the patient. Preferably, the frequency of administration of the therapeutic composition according to the method of the invention ranges from once per week to every other day. Furthermore, the preferred route of administration is by subcutaneous injection or oral ingestion. AICAR administration according to the method of the invention is effective at reducing abdominal fat, particularly intra-abdominal fat, without acute side effects, e.g., hypoglycemia (low glucose levels), hyperlacticacidemia (high lactic acid levels) or hyperuricemia (high uric acid levels).

BRIEF DESCRIPTION OF THE DRAWINGS

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof and from the claims, taken in conjunction with the accompanying drawings, in which:

Fig. 1 shows the effect of AICAR administration (3 times/week) on food intake in rats on chow diet;

Fig. 2 shows blood glucose levels following AICAR injection (250 mg/kg);

Fig. 3 shows body weight changes in rats injected with AICAR (250 mg/kg) 3 times /week;

Fig. 4 shows the acute effects of AICAR administration on gastroc. muscle malonyl CoA and ACC activity;

Fig. 5 shows the acute effects of AICAR administration on liver malonyl CoA and ACC activity;

Fig. 6 shows plasma glucose levels as a function of time as determined in an oral glucose tolerance test on rats treated with AICAR;

Fig. 7 shows plasma insulin levels as a function of time as determined in an oral glucose tolerance test on rats treated with AICAR;

Table 1 shows the effect of 25 days of treatment with AICAR (250 mg/kg) on fat depot weight and muscle triglyceride;

Table 2 shows the effect of 25 days of treatment with AICAR (250 mg/kg) on body and organ weight;

Table 3 shows the acute effects of AICAR on plasma metabolites and hormones;

Table 4 shows the effect of 25 days of treatment with AICAR (250 mg/kg) on plasma metabolites and hormones;

Table 5A shows the effect of 16 weeks of treatment with AICAR (250 mg/kg) on adipose depot weight;

Table 5B shows the effect of 16 weeks of treatment with AICAR on body and organ weight;

Table 6 shows the effect of 16 weeks of treatment with AICAR (250 mg/kg) on weight, blood and plasma; and

Table 7 shows food consumption and body weight over 12 weeks in control and AICAR treated rats.

DETAILED DESCRIPTION OF THE INVENTION

The methods reported here, methods of using AICAR (or a related compound, as described above) for the prevention and/or treatment of obesity, are based on experiments showing that intermittent administration, e.g., three times per week or even one to two times per week, of low doses of the chosen therapeutic compound for an extended period of time appears to be most effective in mimicking the positive effects of exercise in preventing or treating obesity while minimizing any negative side effects.

In experiments with juvenile rats, each weighing about 400 gms, AICAR was administered subcutaneously at a dose of 250 mg/kg on M, W, F of each week for 25 days. At post-mortem evaluation, e.g., as shown in Table 1, the mass of specific intra-abdominal (retroperitoneal, mesenteric, epididymal) fat depots was diminished by 20-40% and muscle triglycerides by approximately 20%. As shown in Table 2, no differences were observed in the weights of the heart, liver or other organs in AICAR treated rats at 25 days; however, an increase in muscle mass is suggested at 106 days (Table 5).

Referring to Fig. 1, it can be seen that food intake was diminished by approximately 25% over the first 24 hrs following each injection. The rats appear to compensate by eating more on the following day. This pattern was evident after 1-2 weeks of AICAR administration and continued indefinitely thereafter. Thus, the anorexigenic action of AICAR does not appear to be due to an acute aversion to food. Cumulative net food intake was

diminished only modestly (about 3%) during all long-term studies.

AICAR moderately diminished blood glucose levels 2-6 hours following its administration (Fig. 2). At high doses, the acute effect of AICAR was to increase blood lactate and decrease plasma free fatty acid (FFA) levels (Table 3). AICAR at all doses studied did not significantly alter plasma triglycerides or leptin at 2 hrs (Table 3).

Referring to Table 4, in rats chronically treated with AICAR (e.g., for 25 days), plasma leptin was significantly diminished at 24 hrs following the last injection. This is in keeping with the diminished adiposity of the treated subjects. Muscle triglyceride was reduced by 25% (Table 1) and plasma triglycerides by 40% (Table 4).

Table 7 shows that food intake was diminished by 3-4% during a 12-week study period and that weight gain was less by 32 g in the AICAR group. Due to interanimal variability and the small number studied, neither difference was statistically significant.

Measurement of the activity of ACC and malonyl CoA concentration in liver and muscle two hours after AICAR injection revealed the site of AICAR action. Dose response curves are shown in Fig. 4 and 5. Fig. 5 shows that AICAR significantly diminished both ACC activity and malonyl CoA concentration in liver when administered at a dose of 250 mg/kg, although a maximal effect was not observed until a higher dose (500 mg/kg) was administered. In contrast, at the 250 mg/kg dose, AICAR had no effect on malonyl CoA levels in muscle and it did

not depress ACC significantly, although a trend for ACC to be diminished was evident.

Winder et al. (J. Appl. Physiol. 88:2219-2226, 2000) have shown that AICAR administration at a daily dose of 1000 mg/kg/day for 28 days induces the expression of a number of molecules in skeletal muscle. These include the GLUT 4 glucose transporter, hexokinase and various mitochondrial enzymes including cytochrome C oxidase and citrate synthase. These investigators also found that AICAR therapy at the dosage used increased muscle glycogen. In contrast, it was observed here, in experiments supporting the method of the invention, that when RT-PCR (GLUT 4, UCP3 and cytochrome C oxidase) and direct enzyme activity measurement (citrate synthase) were used as indicators, no changes were found in these parameters using a 250 mg/kg AICAR dose administered intermittently, e.g., 3 days/wk over 106 days.

Winder (*ibid.*) noted hepatic enlargement in rats treated with AICAR at a dose rate of 1000 mg/kg body weight daily for 28 days. Although Winder also noted some decrease in food intake in these rats, it was not possible to determine whether this was due to hepatotoxicity. In addition, Winder pair-fed the control rats so that their food intake matched that of the AICAR-treated rats. In contrast, no hepatic enlargement with the AICAR dosage regimen used here was found. Also, no evidence of hepatocellular damage was observed morphologically (light microscope).

Increases in abdominal fat, particularly intra-abdominal fat, are associated with insulin resistance and increases in muscle triglyceride. Therefore, the effect

of chronic AICAR treatment, at the dosage used, on plasma insulin levels or glucose tolerance was assessed. As shown in Table 4, plasma insulin levels were significantly diminished in rats treated with AICAR. In addition, lower glucose and insulin levels were observed during an oral glucose tolerance test (Figs. 6 & 7).

USE

The experiments reported here show that AICAR administration substantially diminishes intra-abdominal fat without diminishing the mass of other organs. In addition, chronic treatment with AICAR diminished plasma leptin and insulin levels in keeping with decreases in adiposity, and it decreased plasma triglycerides and cholesterol. Thus, treatment of human patients according to the method of the invention not only will treat obesity, but also will improve insulin sensitivity and decrease the risk of other diseases associated with the insulin resistance syndrome in humans (e.g., diabetes, hypertension, gallstones).

The therapeutic compositions may be administered orally, topically (e.g., by skin patch), or parenterally (e.g., intranasally, subcutaneously, intramuscularly, intravenously, or intra-arterially) by routine methods in pharmaceutically acceptable inert carrier substances. For example, the therapeutic compositions of the invention may be administered according to the method of the invention in a sustained release formulation using a biodegradable biocompatible polymer, or by on-site delivery using micelles, gels or liposomes. The therapeutic compound can be administered in a dosage of,

e.g., 5 mg/kg/day to 100 mg/kg/day. The dosage levels used in rats in the experiments reported herein correspond to approximately 50 mg/kg human body weight/day or about 3-4 grams dosage per human/day. Optimal dosage and modes of administration can readily be determined by conventional protocols.

For prophylactic or therapeutic use with human patients, subcutaneous injection of AICAR is the preferred route of administration for long-term treatment, since it should produce a more sustained increase in AICAR concentration in plasma than intraperitoneal administration. Other forms of administration can be developed to take advantage of forms of AICAR with increased bioavailability. In a human patient, reduction in abdominal fat can be determined easily by serial measurment of waist circumference.

It is understood that those with skill in this and related fields (e.g., synthetic organic chemistry) will develop and identify other agents, e.g., analogs of AICAR, that will function equally well in the method of the invention. Because of the low absorption rate of the AICAR when administered orally (approximately 5%), compounds that release AICAR after ingestion, prodrugs that activate the upstream AMPK kinase, methods that will result in the release of AICAR (e.g., encapsulation), and other methods of administration (e.g., usage of pumps that deliver small amounts continuously) will also prove useful. In addition, those with skill in the field will identify variations of the invention which are consistent with the disclosure herein.

While the present invention has been described in conjunction with a preferred embodiment, one of ordinary skill, after reading the foregoing specification, will be able to effect various changes, substitutions of equivalents, and other alterations to the compositions and methods set forth herein. It is therefore intended that the protection granted by Letters Patent hereon be limited only by the definitions contained in the appended claims and equivalents thereof.

CLAIMS

What is claimed is:

1. A method for prophylaxis or treatment of obesity, said method comprising the steps of:

providing a patient suffering from or believed to be at risk of suffering from obesity; and

administering intermittently to said patient a therapeutic composition comprising an amount of 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside(AICAR), AICAR analog or AICAR precursor that is therapeutically effective at preventing or treating obesity by reducing abdominal fat in said patient.

2. The method of claim 1, wherein said patient is a human patient.

3. The method of claim 1, wherein said intermittent administration is every other day.

4. The method of claim 1, wherein said intermittent administration is twice a week.

5. The method of claim 1, wherein said intermittent administration is once a week.

6. The method of claim 1, wherein said administration is subcutaneous.

7. The method of claim 1, wherein said administration is oral.

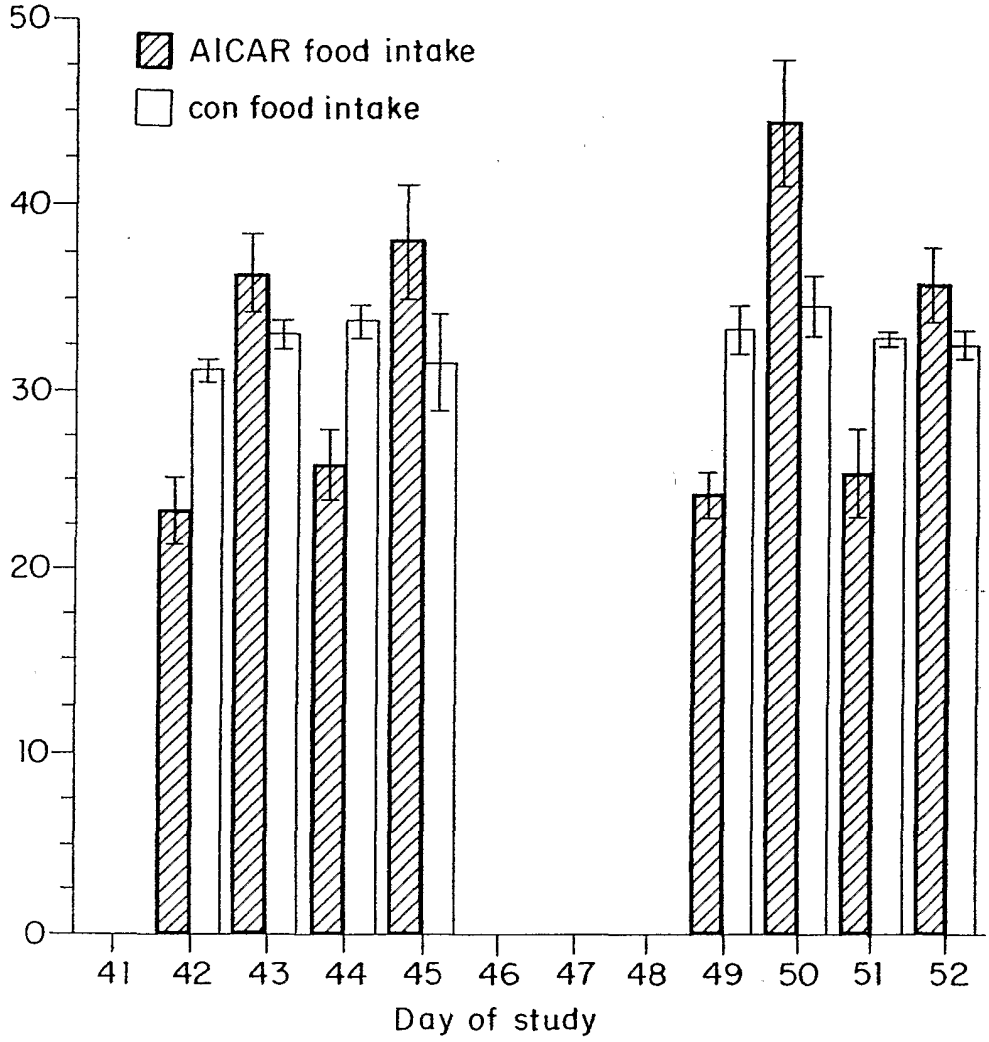
8. The method of claim 1, wherein said therapeutic composition comprises AICAR.

9. The method of claim 1, wherein said therapeutic composition comprises an AICAR analog.

10. The method of claim 1, wherein said therapeutic composition comprises an AICAR precursor.

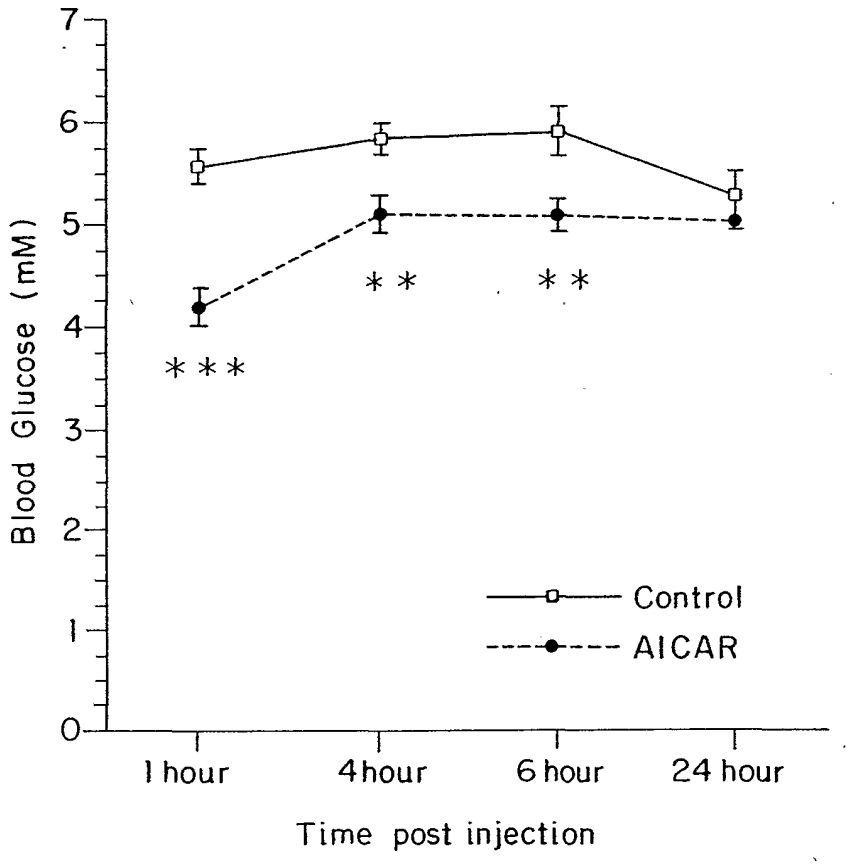
11. The method of claim 1, wherein said therapeutic composition is administered to said patient for at least three weeks.

12. The method of claim 1, wherein said therapeutic composition is administered to said patient for at least three months.



AICAR (250 mg/kg) was injected at 10 AM on days 42, 44, 49 and 51. Food intake was measured over each 24 hour period (10 AM to 10 AM). As evident from the figure, AICAR treated rats ate less on the day of its administration and more the following day. In contrast food intake by control rats was remarkably constant. Results are means ± SE (n=5).

FIG. 1



Tail vein blood glucose was measured using a Precision QID glucose meter. Values are means ± SE. (n=6-7).

Significantly different from Control : * $p < 0.05$; *** $p < 0.0001$.

FIG. 2

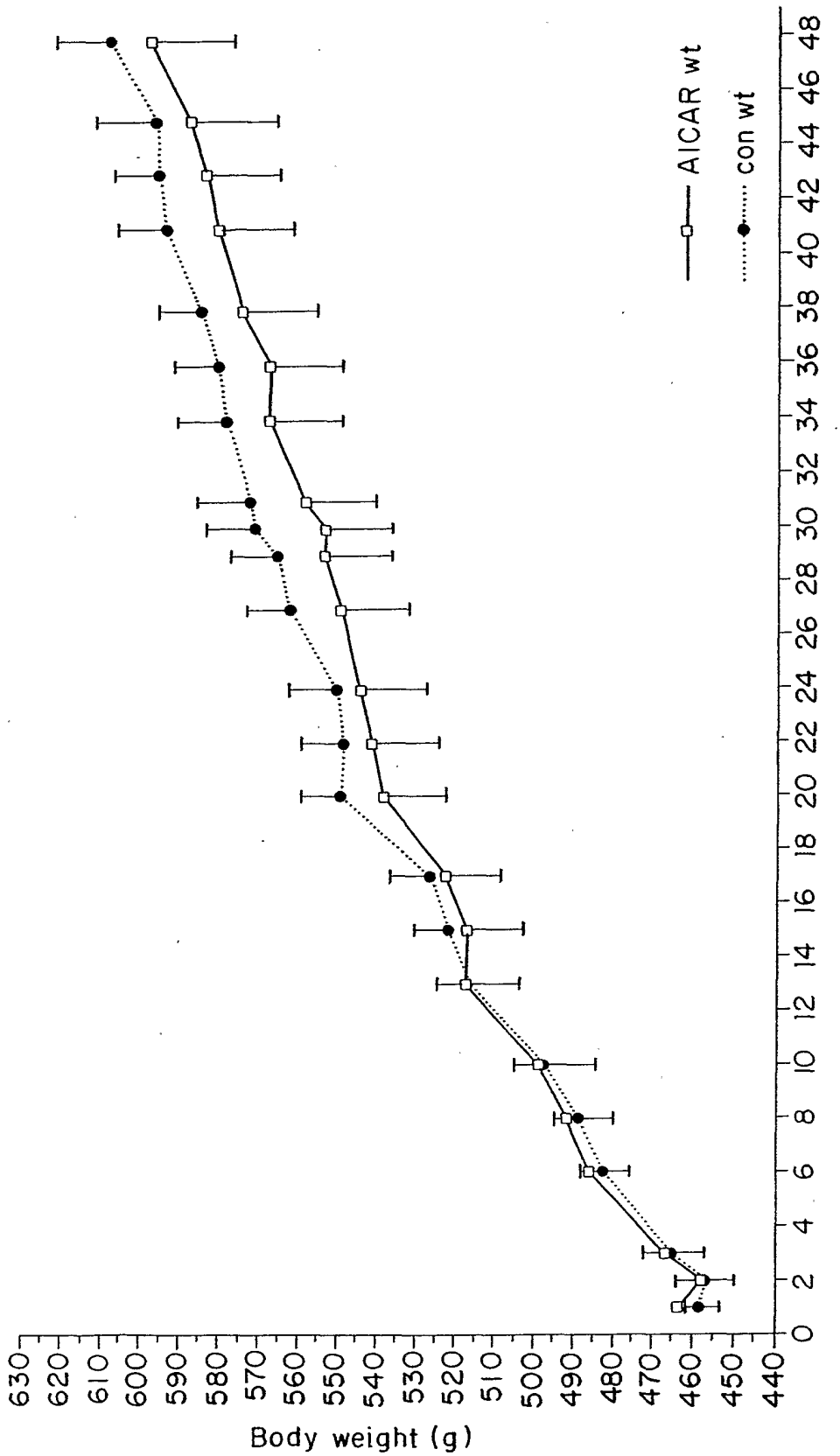

AICAR wt
con wt
Body weight (g)
Study Day
630
620
610
600
590
580
570
560
550
540
530
520
510
500
490
480
470
460
450
440
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
46
48

FIG. 3

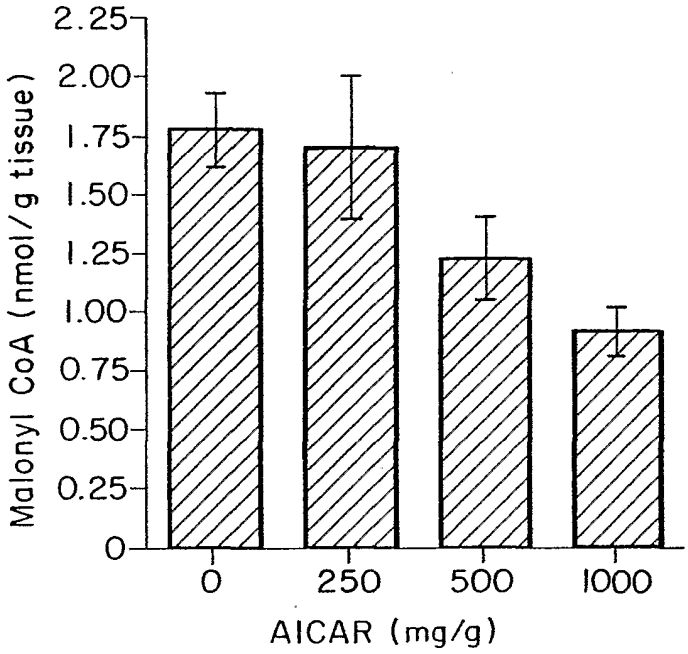

Malonyl CoA (nmol/g tissue)
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0
0
250
500
1000
AICAR (mg/g)

FIG. 4A

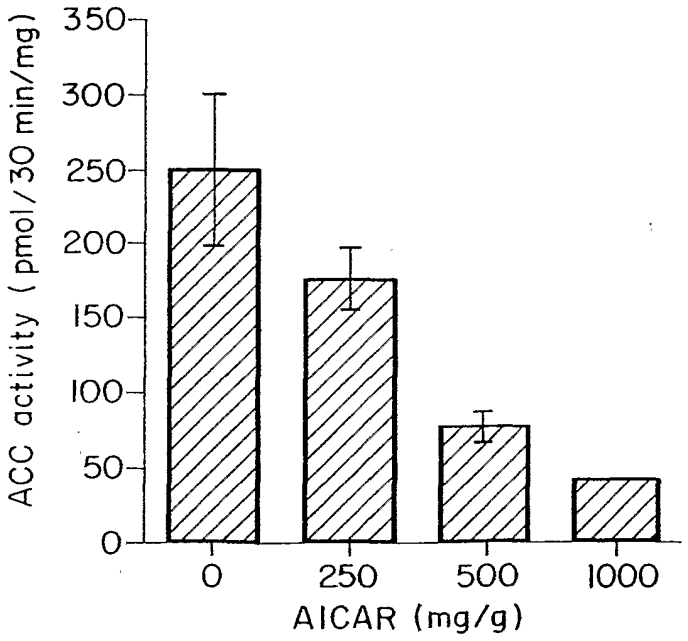

ACC activity (pmol/30 min/mg)
350
300
250
200
150
100
50
0
0
250
500
1000
AICAR (mg/g)

FIG. 4B

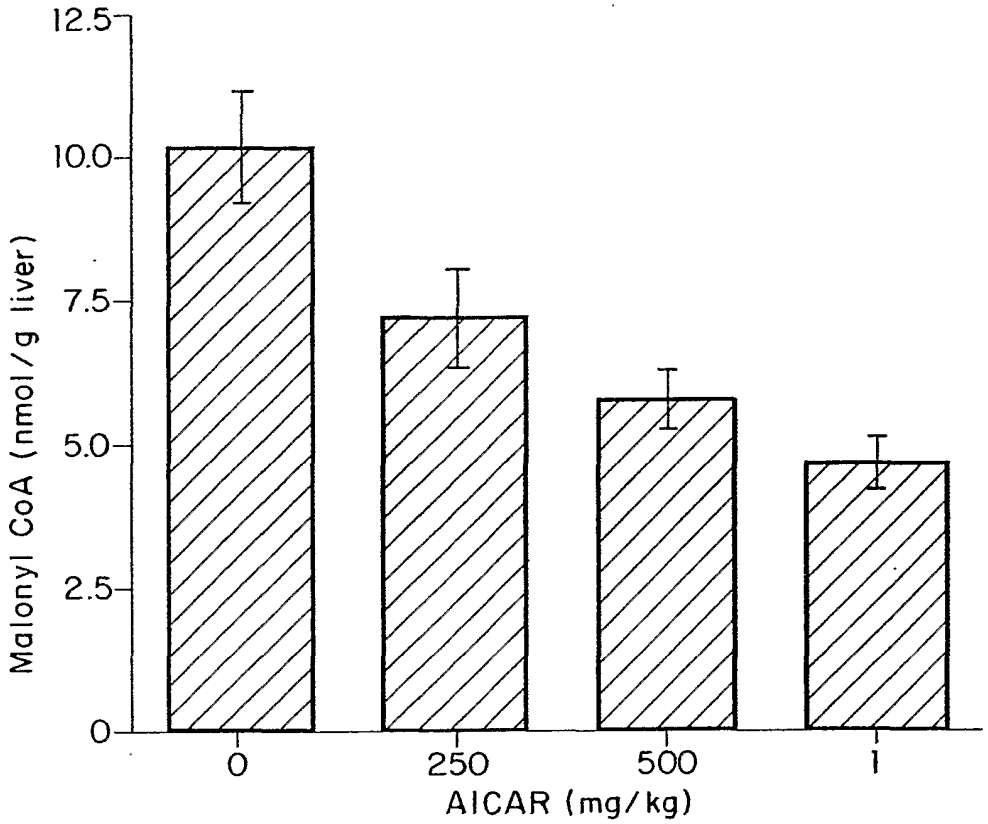

12.5
10.0
7.5
5.0
2.5
0
Malonyl CoA (nmol/g liver)
0
250
500
1
AICAR (mg/kg)

FIG. 5A

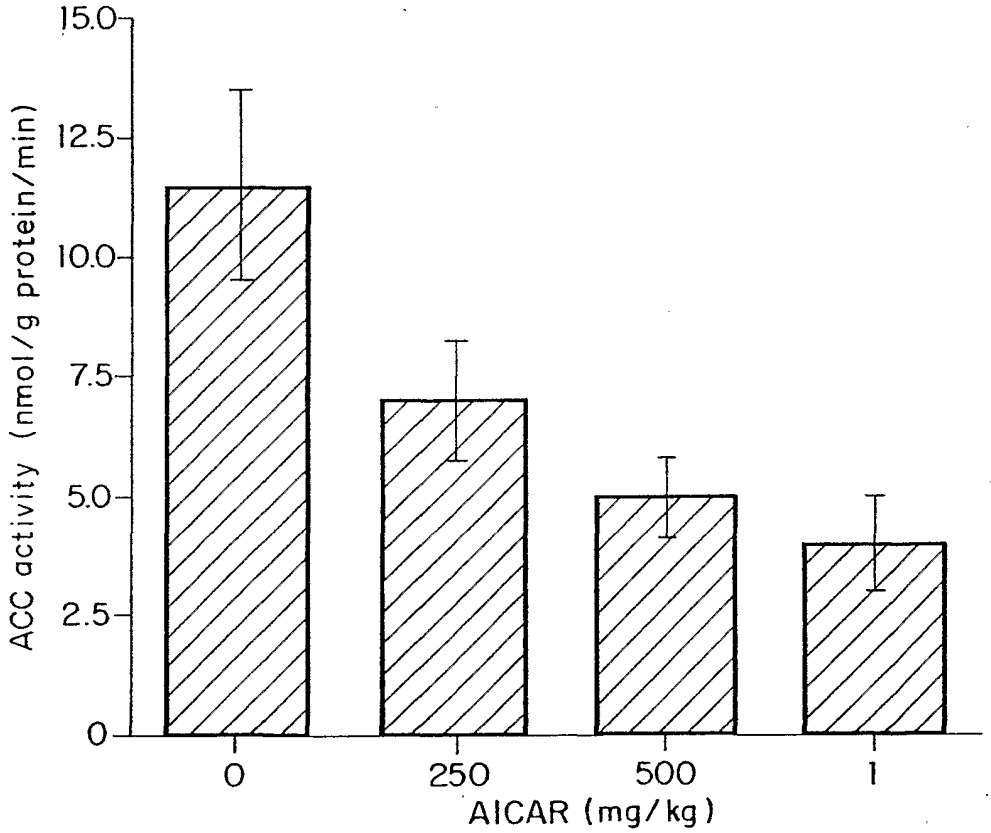

15.0
12.5
10.0
7.5
5.0
2.5
0
ACC activity (nmol/g protein/min)
0
250
500
1
AICAR (mg/kg)

FIG. 5B

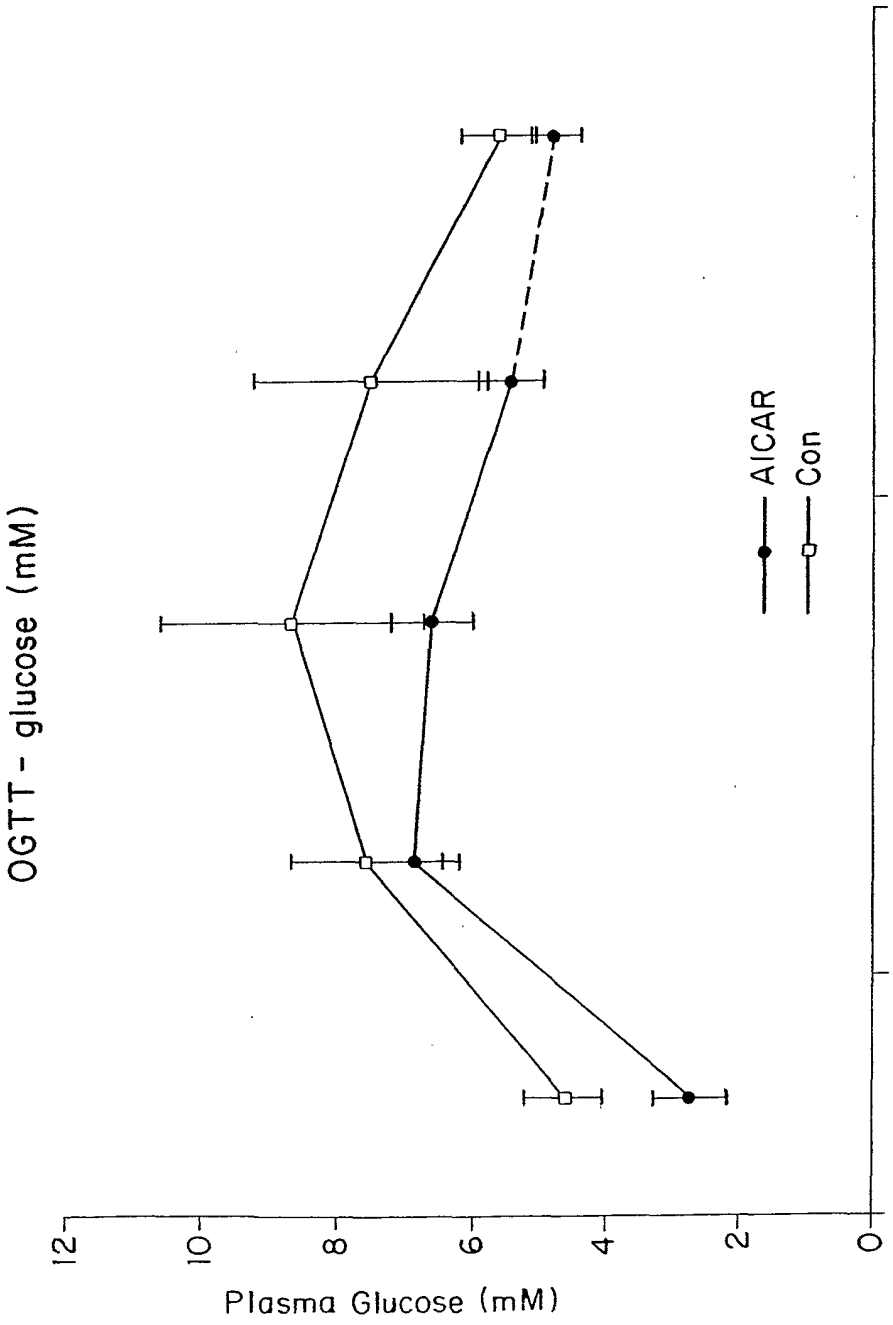
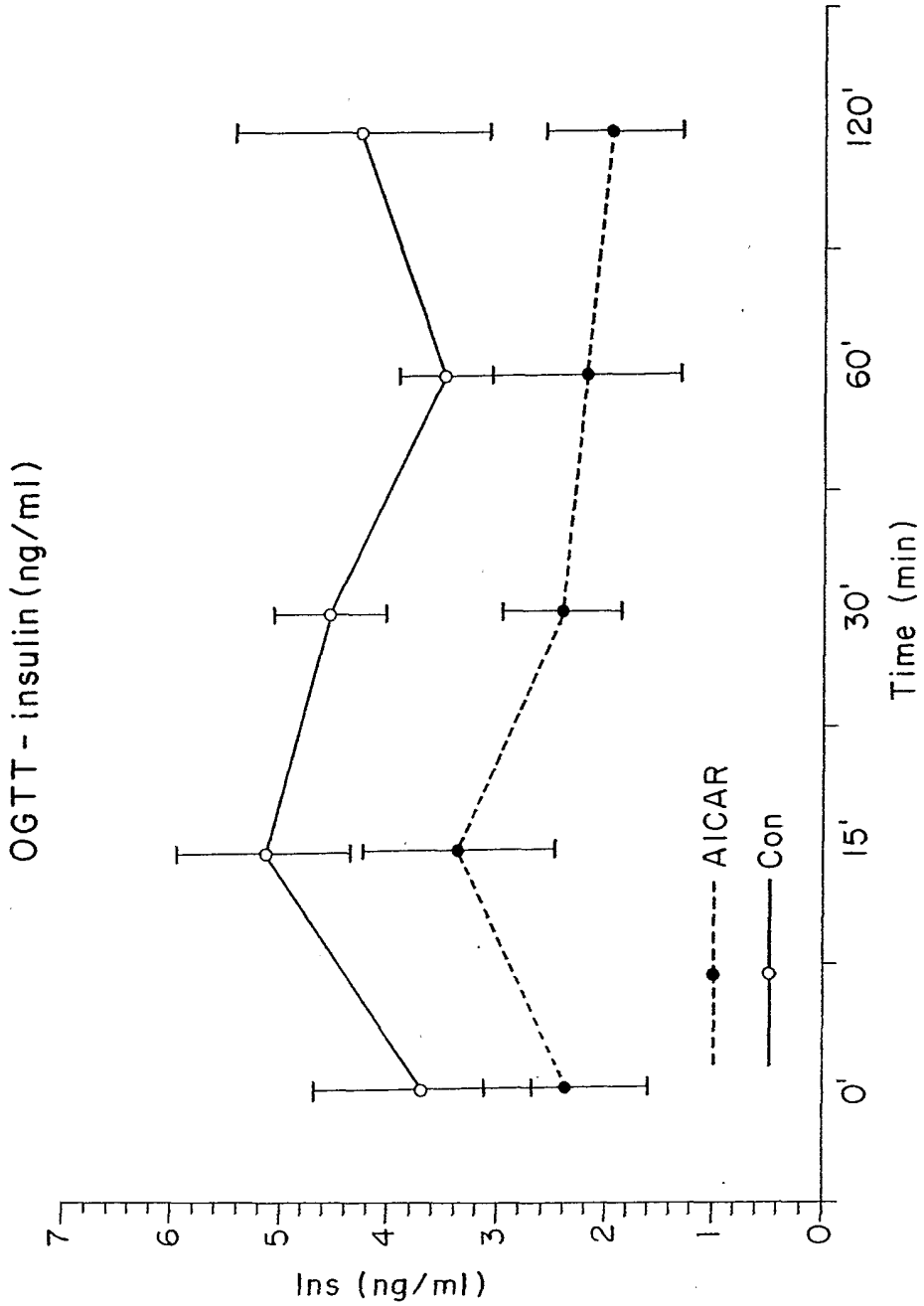


FIG. 6

1.7 mg glucose/g body weight as a 35% solution was given by gavage. Blood samples were taken from the tail vein. Data are means ± SE. n=5 for each group.



1.7 mg glucose/g body weight as a 35% solution was given by gavage. Blood samples were taken from the tail vein. Data are means ± SE. n=5 for each group.

FIG. 7

	Weight (grams)			Gastroc/Plantaris Triglyceride (umol/g)
	Epididymal	Perirenal	Mesenteric	
Control	4.11 ± 0.93 (6)	7.13 ± 1.08 (6)	6.96 ± 1.16 (6)	8.25 ± 0.84 (6)
AICAR	3.15 ± 0.19 (7)	4.29 ± 0.48* (7)	4.89 ± 0.71 (7)	6.18 ± 0.82 (7)

Fed rats were sacrificed between 11 AM and 1PM, 24 hours after last injection. Values are means ± SE. * Significantly different from control ($p < 0.05$).

FIG. 8

	Weight (grams)					
	Body	Liver	Heart	Kidneys	Soleus (1)	Gastroc/ Plantaris
Control	475 ± 23 (6)	15.3 ± 0.5 (6)	1.75 ± 0.13 (6)	3.3 ± 0.1 (6)	0.20 ± 0.01 (6)	3.0 ± 0.1 (6)
AICAR	478 ± 24 (7)	16.0 ± 0.8 (7)	1.87 ± 0.02 (7)	3.4 ± 0.1 (7)	0.21 ± 0.02 (7)	3.3 ± 0.1 (7)

Fed rats were sacrificed between 11 AM and ! PM, 24 hours after last injection. Initial weight of the Controls was 385g ± 14 and initial weight of the AICAR-treated group was 386g ± 13. Values are means + SE.

FIG. 9

	AICAR dose (mg/kg)			
	0	250	500	1000
Glucose (mM)	10.2 ± 0.6 (2)	9.6 ± 0.3 (4)	11.1 ± 0.7 (4)	8.2 ± 0.5 (4)
Lactate (mM)	2.4 ± 0.1 (2)	2.3 ± 0.2 (4)	6.4 ± 0.5*** (4)	7.3 ± 0.3*** (4)
Insulin (ng/ml)	2.2 ± 0.5 (4)	2.0 ± 0.5 (4)	1.4 ± 0.4 (4)	0.7 ± 0.1 (4)
Leptin (ng/ml)	0.58 ± 0.06 (4)	0.73 ± 0.10 (4)	0.80 ± 0.16 (4)	0.65 ± 0.02 (4)
FFA (mEq/L)	0.31 ± 0.01 (4)	0.35 ± 0.02 (4)	0.29 ± 0.02 (4)	0.24 ± 0.02* (4)
Triglyceride (mg/dl)	52 ± 10 (4)	53 ± 4 (4)	44 ± 4 (4)	57 ± 11 (4)

Fed rats (weight 331 g ± 3) were anesthetized and sacrificed between 11 AM and 1 PM, 2 hours after AICAR injection. Blood was collected from the orbital sinus. Results are means ± SE. Significantly different from control: * $p < 0.05$; *** $p < 0.001$.

FIG. 10

	Control	AICAR (250 mg/kg)
Glucose (mM)	11.7 ± 0.4 (5)	10.8 ± 0.2 (7)
Lactate (mM)	2.4 ± 0.2 (5)	2.3 ± 0.4 (7)
Insulin (ng/ml)	3.6 ± 0.4 (6)	2.5 ± 0.3* (7)
Leptin (ng/ml)	1.40 ± 0.16 (6)	0.87 ± 0.13* (7)
FFA (mEq/L)	0.40 ± 0.01 (6)	0.40 ± 0.03 (7)
Triglyceride (mg/dl)	82 ± 15 (6)	51 ± 6 (7)

Fed rats (weight 477 g ± 16) were sacrificed between 11 AM and 1 PM, 24 hours after last injection. Blood was collected at sacrifice from the orbital sinus. Results are means ± SE. Significantly different from control: * $p < 0.05$.

FIG. 11

	Mesenteric	Epididymal	Perirenal	M + E + P	Brown Adipose
AICAR	4.0 ± 0.3 #	6.9 ± 0.6 **	7.8 ± 0.8 #	18.7 ± 1.0 **	0.31 ± 0.02 *
Con	6.9 ± 0.7	10.5 ± 0.4	13.1 ± 0.9	30.5 ± 1.4	0.41 ± 0.03

Rats (fed ad lib) were injected with 250 mg/kg AICAR or saline 3 times/week for 16 weeks. Fed rats were sacrificed approximately 24 hours after last injection between 11 AM and 1 PM. Results are means ± SE (n=3). Significantly different from control: * $p < 0.05$; # $p < 0.02$; ** $p < 0.01$.

FIG. 12A

	Muscle (g)					Adrenals (g)	Kidney (g)	Liver (g)
	Soleus	EDL	Gastroc	Plantaris	Total			
AICAR	0.34 ± 0.02	0.33 ± 0.01	3.75 ± 0.08 *	0.80 ± 0.07	5.22 ± 0.07 *	0.059 ± 0.005	1.9 ± 0.1	15.6 ± 0.8
Con	0.28 ± 0.02	0.28 ± 0.02	3.36 ± 0.09	0.73 ± 0.03	4.66 ± 0.14	0.045 ± 0.004	1.8 ± 0.2	15.5 ± 1.4

Rats (fed ad lib) were injected with 250 mg/kg AICAR or saline 3 times/week for 16 weeks. Fed rats were sacrificed approximately 24 hours after last injection between 11 AM and 1 PM. Results are means ± SE (n=3).
Significantly different from control: * $p < 0.05$.

FIG. 12B

	Weight (g)			Blood		Plasma		
							Cholesterol	
	Initial	Final	Gain	Glucose (mM)	Lactate (mM)	FFA (mEq/L	Total (mg/dl)	HDL (mg/dl)
AICAR	461 ± 10	632 ± 32	171 ± 21	10.2 ± 0.1 #	3.5 ± 0.4	0.33 ± 0.03	40.0 ± 4.6	13.1 ± 2.6
Con	465 ± 10	622 ± 23	158 ± 14	8.2 ± 0.5	2.6 ± 0.1	0.34 ± 0.03	53.9 ± 4.5	26.2 ± 3.8

Rats (fed ad lib) were injected with 250 mg/kg AICAR or saline 3 times/week for 16 weeks. Fed rats were sacrificed approximately 24 hours after last injection between 11 AM and 1 PM. Orbital sinus blood was collected from anesthetized rats prior to sacrifice. Results are means ± SE (n=3). Significantly different from control: # $p < 0.02$.

FIG. 13

	Weight (g)			Total Food Consumed (g)
	Initial	Final	Gain	
AICAR	486 ± 10	629 ± 21	143 ± 13	1349 ± 63
Con	482 ± 14	657 ± 12	175 ± 11	1409 ± 23

Results are means ± SE for 5 rats per group and are from the AICAR III study. AICAR (250 mg/kg) was administered s.c. on Mon., and Fri. of each week.

FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/18467

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/70; C07H 19/052.
US CL : 514/46, 43, 45, 886; 536/26.9, 28.6.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/46, 43, 45, 886; 536/26.9, 28.6.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,912,092A (GRUBER) 27 March 1990, see abstract and claims.	1-12
Y	US 5,817,640A (GRUBER ET AL) 6 October 1998, see abstract and claims.	1-12
Y	US 4,575,498A (HOLMES ET AL) 11 March 1986, see abstract and claims.	1-12
Y	US 5,658,889A (GRUBER ET AL) 19 August 1997, see abstract and claims.	1-12
Y	US 5,777,100A (BULLOUGH ET AL) 7 July, 1998, see abstract and claims.	1-12
Y	US 5,082,829A (GRUBER ET AL) 21 January 1992, see abstract and claims.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search
07 August 2001 (07.08.2001)

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/18467

Continuation of B. FIELDS SEARCHED Item 3:
CAS on line, EAST. Search terms used: AICAR, 5-Amino-1-ribosyl-4-imidazolecarboxamide, 5-Amino-4-imidazolecarboxamide riboside, acadesine, AICA-riboside, treatment of obesity and prophylaxis(prophylactic).