

TREATMENT OF LIPID AND GLUCOSE METABOLISM DISORDERS WITH DOPAMINE AND SEROTONIN AGONISTS

This application claims priority pursuant to 35 U.S.C. 5
119 from U.S. Provisional Application Ser. No. 60/019,209
filed Jun. 6, 1996, the entire disclosure of which is hereby
incorporated by reference.

FIELD OF THE INVENTION

This invention relates to novel, improved methods for
modifying or regulating in a subject (vertebrate animal or
human) at least one of body weight, body fat, food
consumption, lipid metabolism, and glucose metabolism. 15

BACKGROUND OF THE INVENTION

Obesity and Lipid Metabolism Disorders—Body Fat Loss

In humans, obesity can be defined as a body weight
exceeding 20% of the desirable body weight for individuals
of the same sex, height and frame (Salans, L. B., in *Endo-
crinology & Metabolism*, 2d Ed., McGraw-Hill, New York
1987, pp. 1203–1244; see also, R. H. Williams, *Textbook of* 25
Endocrinology, 1974, pp. 904–916). In other animals (or
also in humans) obesity can be determined by body weight
patterns correlated with prolactin profiles given that mem-
bers of a species that are young, lean, and “healthy” (i.e.,
free of any disorders, not just metabolic disorders) have 30
daily plasma prolactin level profiles that follow a pattern
characteristic of the species. This pattern is highly repro-
ducible with a small standard deviation. Members of a
species suffering from lipid and/or metabolism disorders,
however, have aberrant prolactin profiles that depart from 35
the normal (or healthy subjects’) pattern by at least 1 SEM
in at least two spaced apart time points or by at least 2 SEM
(standard error of the mean) in at least one time point.

Obesity, or excess fat deposits, correlate with and may
trigger the onset of various lipid and/or glucose metabolism 40
disorders, e.g. hypertension, Type II diabetes,
atherosclerosis, retinopathy etc.

Even in the absence of clinical obesity (according to the
above definition) the reduction of body fat stores (notably 45
visceral fat stores) in man, especially on a long-term or
permanent basis would be of significant benefit, both
cosmetically, physiologically and psychologically.

The reduction of body fat stores in domestic animals (as
well as pets), especially on a long-term or permanent basis, 50
would also obviously be of considerable economic benefit to
man, particularly since farm animals supply a major portion
of man’s diet; and the animal fat may end up as de novo fat
deposits in man.

Whereas controlled diet and exercise can produce modest 55
results in the reduction of body fat deposits, prior to the
cumulative work of the present inventors (including the
prior co-pending patent applications and issued U.S. patents
referred to below), no truly effective or practical treatment
had been found for controlling obesity or other lipid metabo- 60
lism disorders.

Hyperlipoproteinemia is a condition in which the concen-
tration of one or more of cholesterol- or triglyceride-
carrying lipoproteins (such as chylomicrons, very low den-
sity lipoproteins (“VLDL”), and low-density lipoproteins 65
 (“LDL”) in plasma exceeds a normal limit. This upper limit
is generally defined as the ninety-fifth percentile of a random

population. Elevated levels of these substances have also
been positively correlated with atherosclerosis and the often
resulting cardiac infarction, or “heart attack”, which
accounts for approximately half of all deaths in the United
States. Strong clinical evidence has been presented which
correlates a reduction in plasma lipoprotein concentration
with a reduced risk of atherosclerosis (Noma, A., et al.,
Atherosclerosis 49:1, 1983; Illingworth, D. and Conner, W.,
in *Endocrinology & Metabolism*, McGraw-Hill, New York
1987). Thus, a significant amount of research has been
devoted to finding treatment methods which reduce levels of
plasma cholesterol and triglycerides. High LDL and/or
VLDL accompanied by high triglyceride levels in the blood
constitute most important risk factors for atherosclerosis.
Reduction of one or both of lipoproteins and triglycerides
in the blood would reduce the risk of atherosclerosis and
cardiac arrest, or retard their development.

Another subset of the plasma lipoproteins found in ver-
tebrates are high density lipoproteins, HDL (“HDL”). HDL
serve to remove free cholesterol from the plasma. A high
HDL concentration, as a percentage of total plasma
cholesterol, has been associated with a reduced risk of
atherosclerosis and heart disease. Thus, HDL are known in
the lay press as “good” cholesterol. Therefore, therapeutic
strategies involve attempts both to reduce plasma LDL and
VLDL content (that is, reduce total plasma cholesterol), and
to increase the HDL fraction of total plasma cholesterol.
Several lines of research indicate that simply increasing
HDL is of benefit even in the absence of LDL or VLDL
reduction: Bell, G. P. et al., *Atherosclerosis* 36:47–54, 1980;
Fears, R., *Biochem. Pharmacol.* 33:219–228, 1984;
Thompson, G., *Br. Heart J.* 51:585–588, 1989; Blackburn,
H. *N.E.J.M.* 309:426–428, 1983.

Current therapies for hyperlipoproteinemias include a low
fat diet and elimination of aggravating factors such as
sedentary lifestyle. If the hyperlipoproteinemia is secondary
(i.e., incident to e.g., a deficiency of lipoprotein lipase or
LDL receptor, various endocrine pathologies, alcoholism,
renal disorders, or hepatic disorders) then control of the 35
underlying disease is also central to treatment. Hyperlipo-
proteinemias are also treated with drugs, which usually alter
the levels of particular components of the total plasma
cholesterol, as well as reduce the total plasma lipid compo-
nent. Among the most recently introduced drugs to treat
hyperlipoproteinemia is lovastatin (MEVACOR®) which
selectively inhibits an enzyme involved in cholesterol
production, 3-hydroxy-3-methylglutaryl coenzyme A
(HMG-CoA) reductase. This drug specifically reduces total
cholesterol and can cause a modest (5–10%) increase in
HDL concentrations. However, benefits from these therapies
vary from subject to subject.

Moreover, use of the HMG-CoA enzyme inhibitor is
sometimes accompanied by side effects such as liver
toxicity, renal myoglobinuria, renal shutdown, and lenticular
opacity. The risk of such side effects necessitates close
monitoring of the patients (e.g., liver function is tested
monthly).

Another drug prescribed against hyperlipoproteinemia is
clofibrate. The effectiveness of clofibrate also varies from
subject to subject and its use is often accompanied by such
side effects as nephrotic syndromes, myalgia, nausea, and
abdominal pain.

Type II Diabetes (NIDDM) and Glucose Metabolism Disorders

Type II diabetes, also known as non-insulin dependent
diabetes mellitus (NIDDM), is one of the most insidious of