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# Reduced dopaminergic tone in hypothalamic neural circuits: expression of a "thrifty" genotype underlying the metabolic syndrome?

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**Abstract**

The thrifty genotype hypothesis postulates that the genetically determined ability to grow obese and insulin resistant in times of food abundance confers a survival advantage in times of famine. Obviously, this ability poses a major health threat in modern times, where food is always available in large quantities. In the last 10–15 years, many genes encoding pathways that orchestrate energy balance and fuel flux have been discovered. This paper summarizes the evidence that diminished dopaminergic tone in hypothalamic nuclei contributes to the "thrifty" genotype/phenotype. Reduced dopaminergic neurotransmission in the suprachiasmatic nucleus of seasonally obese animals appears to drive noradrenalin and NPY mediated transmissions in other nuclei to induce the obesity syndrome at the appropriate time of year. Treatment with dopamine $D_2$ receptor agonists can fully reverse the metabolic syndrome in these animals. Similar mechanisms are operative in non-seasonal obese animal models. In man, treatment with dopamine $D_2$ receptor antagonists induces obesity and type 2 diabetes mellitus, whereas dopamine $D_2$ receptor activation ameliorates the metabolic profile in obese nondiabetic and diabetic humans. Various loss of function mutations of the dopamine $D_2$ receptor gene are associated with overweight in humans. In concert, the data support the notion that diminution of dopaminergic (dopamine $D_2$ receptor mediated) transmission in relevant hypothalamic nuclei sets the stage for efficient partitioning of ingested nutrients to contribute to a phenotype that is not so thrifty anymore.


*Keywords:* Dopamine; Dopamine D2 receptor; Metabolic syndrome X; Insulin resistance; Obesity

## 1. Introduction

Insulin resistance, glucose intolerance, hypertension and combined hyperlipidemia (hypertriglyceridemia, hypercholesterolemia, low high density lipoprotein (HDL) cholesterol) often cluster. These metabolic anomalies have therefore been designated "the metabolic syndrome" (or syndrome X, insulin resistance syndrome). The syndrome is of major clinical importance, as it considerably increases cardiovascular risk and frequently proceeds to type 2 diabetes mellitus. Obesity strongly predisposes to the metabolic syndrome, but it is not a prerequisite for its generation. Caloric restriction and weight loss tend to restore the metabolic profile to normal in obese individuals (DeFronzo, 1988).

The cause of the syndrome remains elusive. The thrifty gene hypothesis postulates that, in prehistoric times, the genetically determined ability to grow obese and insulin resistant during periods of food abundance conferred a survival advantage in times of food scarcity (Neel et al., 1998). Efficient partitioning of ingested nutrients provides backup energy in less affluent periods. While insulin resistance of muscle and adipose tissue hampers glucose uptake in these tissues and thereby leaves glucose for use by the brain, it allows triglyceride breakdown to provide peripheral tissues with fatty acids as an alternative fuel. Hepatic insulin resistance enhances endogenous glucose and very low density lipoprotein production, which serves analogous metabolic goals. These advantageous metabolic adaptations, directed by thrifty genes and supposedly induced in the course of evolution by selection through environmental pressure, turn out to be a major health hazard in modern times, where food is always available in large quantities.

Which "thrifty" genes are involved in the pathogenesis of the metabolic syndrome and what are the regulatory pathways they encode? At present, we do not know. However, as the brain appears to be a key regulator of

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energy metabolism, it seems likely that candidate genes encode neurotransmitters and/or their receptors in relevant brain areas. Indeed, in recent years, a wealth of observations in (genetically modified) animals and humans has unveiled genes encoding constituents of neural circuits as pathogenetic foundations of obesity syndromes. In the present paper, I will summarize the evidence that reduced dopaminergic neurotransmission in hypothalamic nuclei may be involved in the pathogenesis of the metabolic syndrome.

## 2. Dopaminergic neurotransmission

Dopamine is the predominant catecholamine neurotransmitter in the mammalian brain. It is involved in the regulation of a broad range of biological functions, including locomotor activity, cognition, food intake and (pituitary) hormone secretion. Dopamine signal transduction is mediated by at least five distinct G-protein coupled receptor subtypes, classified as $D_1$-like ($D_1$ and $D_5$) and $D_2$-like ($D_2$, $D_3$ and $D_4$) receptors. The dopamine $D_1$-like receptors couple to the G-protein $G_s$ and activate adenylyl cyclase, whereas the dopamine $D_2$-like subfamily inhibits adenylyl cyclase through interaction with $G_i$ proteins (Missale et al., 1998). The dopamine $D_1$ receptor is the most widespread dopamine receptor. It has been found in the striatum, nucleus accumbens, olfactory tubercle, limbic system, hypothalamus and thalamus (Dearry et al., 1990; Fremeau et al., 1991). The dopamine $D_2$ receptor is also abundant in the mammalian brain. It has been detected in many areas, including the hypothalamus (reviewed by Missale et al., 1998), where it exists as two alternatively spliced variants, the $D_2$L and $D_2$S isoforms (Giros et al., 1989). The short $D_2$S isoform mainly serves presynaptic inhibitory autoreceptor functions and the long $D_2$L isoform acts primarily at postsynaptic sites (Usiello et al., 2000).

## 3. Dopaminergic neurotransmission in animal models of the metabolic syndrome

### 3.1. Lessons from studies in seasonally obese animals

Many vertebrate species are subjected to seasonal changes in food availability in the wild and many of these species can develop the obese insulin resistant state at precisely the appropriate time of year (i.e. winter time, when food is no longer readily available). Thus, it appears that (inborn) circannual adaptations allow these animals to store fat and become insulin resistant even in the face of *reduced* (but not absent) nutrient availability. This intriguing observation suggests that nutrients are partitioned in a fundamentally different way in summer than in winter in these seasonally obese animals. How does this come about? Dopaminergic neural activities in distinct parts of the brain change profoundly at the turn of the seasons in Syrian hamsters and experimental simulation of these changes produces the appropriate seasonal condition. For example, dopamine and serotonin metabolites are reduced in suprachiasmatic nuclei of seasonally obese vs. lean hamsters (Luo et al., 1998, 1999c), reflecting diminished monoaminergic transmission in winter conditions. Selective destruction of dopaminergic neurons in the area of the suprachiasmatic nucleus severely impairs insulin sensitivity and promotes body fat accretion in lean animals (Luo et al., 1997). The suprachiasmatic nuclei, harboring the biological clock in mammals, communicate with various other hypothalamic nuclei that play a pivotal role in the guidance of fuel flux and energy homeostasis (i.e. the paraventricular and ventromedial hypothalamic nuclei; Luiten et al., 1987; Nagai and Nakagawa, 1992). Diminished dopaminergic tone in the suprachiasmatic area may therefore affect neural circuits in these hypothalamic nuclei to impact metabolism. Indeed, reduced dopaminergic tone in the suprachiasmatic nuclei is associated with markedly enhanced noradrenergic transmission in the ventromedial hypothalamic nuclei of seasonally obese vs. lean hamsters (Luo et al., 1998) and noradrenalin infusion into this brain area promotes body fat accretion, hyperinsulinemia, insulin resistance and hypertriglyceridemia without producing sustained hyperphagia in various animal models (Cincotta et al., 2000; Luo et al., 1999b; Shimazu et al., 1986). The fact that enhanced food intake is not a prerequisite for the development of the metabolic syndrome in these animals suggests that altered partitioning of nutrients rather than caloric intake per se is responsible for the marked phenotypic changes. Notably, it remains to be established whether withdrawal of dopaminergic inputs into the suprachiasmatic nuclei directly drives enhanced noradrenergic activities in the ventromedial nuclei. However, the fact that activation of inhibitory dopamine $D_2$ receptors can reduce noradrenaline release from nerve terminals (Ziegler et al., 1979) suggests that this receptor is directly involved.

Bromocriptine, a dopamine $D_2$ receptor agonist with sympatholitic properties (Di Chiara et al., 1978), was shown to inhibit seasonal fattening in a variety of species without altering food intake (Cincotta and Meier, 1989). It suppresses lipogenesis and abolishes seasonal hyperinsulinemia and glucose intolerance in the Syrian hamster (Cincotta et al., 1991). Indeed, bromocriptine treatment can fully redirect the seasonally obese insulin resistant state towards the lean insulin sensitive state in these animals. It reduces body fat stores, lipolysis and plasma free fatty acid and triglyceride levels, while it promotes protein turnover, lean body mass accretion and insulin stimulated glucose disposal (Cincotta et al., 1993). Furthermore, it inhibits free fatty acid oxidation and endogenous glucose output in seasonally obese hamsters (Cincotta and Meier, 1995). Although the mechanisms by which bromocriptine produces these favourable metabolic changes in seasonal obesity have not been fully elucidated, the central nervous system appears to be a critical target. Intracerebroventricular injections of bromo-

criptine at a very low dose completely reproduce the metabolic effects of high dose i.v. administration (Luo et al., 1999a). It seems reasonable to infer from these data that dopaminergic neural circuits within the area of the suprachiasmatic nuclei (i.e. the biological clock) may be involved in the seasonal changes of bodyweight and metabolism that characterizes animals undergoing these changes. In particular, diminished dopamine $D_2$ receptor activation may stimulate other (catecholaminergic) neural circuits to promote fat accretion and insulin resistance. Are dopaminergic circuits also involved in the regulation of fuel flux in non-seasonal animals and humans?

### 3.2. Dopaminergic activity in non-seasonal obesity

Several animal models of non-seasonal obesity are marked by reduced dopaminergic activity in relevant brain areas.

Leptin deficient *ob*/*ob* mice have low dopamine levels in the arcuate nucleus and increased noradrenalin (Lorden et al., 1975; Oltmans, 1983) and neuropeptide Y (Schwartz et al., 1996) activity in the paraventricular nucleus. Neuropeptide Y is critically involved in the regulation of food intake and energy balance. Chronic intracerebroventricular administration of neuropeptide Y induces obesity and insulin resistance in rats (Sainsbury et al., 1997a,b), metabolic features that are reminiscent of those induced by chronic noradrenalin infusion (Cincotta et al., 2000; Shimazu et al., 1986). Noradrenalin colocalizes with neuropeptide Y in hypothalamic neurons that project to the paraventricular nucleus (Sawchenko et al., 1985) and dopamine (through dopamine $D_2$ receptor activation) was shown to inhibit both neuropeptide Y and noradrenalin gene expression (Carey et al., 1983; Li and Pelletier, 1986; Pelletier and Simard, 1991; Ziegler et al., 1979). The fact that combined dopamine $D_2$ and dopamine $D_1$ receptor agonism reverts elevated hypothalamic neuropeptide Y levels and bodyweight and hyperglycemia in obese *ob*/*ob* mice (Bina and Cincotta, 2000; Cincotta et al., 1997) suggests that reduced dopaminergic tone is directly involved in the pathogenesis of the metabolic features of these animals.

The Zucker rat grows obese as a result of a loss of function mutation in the gene encoding the leptin receptor (Phillips et al., 1996). Homozygous animals are massively obese, whereas heterozygous rats have normal bodyweight. Fasting dopamine levels are reduced (Meguid et al., 2000) and dopamine $D_2$ receptor expression is diminished in the ventromedial and lateral hypothalamic nuclei of obese vs. lean Zucker rats (Fetissov et al., 2002). The cause of this neurochemical anomaly is unknown. It is likely, however, to contribute to the metabolic phenotype of the obese Zucker rat, given the profound effects of dopamine $D_2$ receptor signaling on glucose and lipid metabolism as delineated above. Moreover, bromocriptine treatment was shown to reduce body fat stores in obese Zucker rats (Cincotta and Meier, 1989).

One half of male Sprague–Dawley rats fed a high energy diet develop diet-induced obesity, hyperinsulinemia and insulin resistance, whereas the other half is diet resistant (Levin, 1995; Levin and Dunn-Meynell, 1997). The animals that are prone to become overweight differ in various ways from those that are not, even before the onset of obesity. In particular, they have reduced dopamine turnover in the mediobasal hypothalamus, while norepinephrin levels (Levin, 1995) and neuropeptide Y gene expression are elevated in this area (Levin and Dunn-Meynell, 1997). It is important to recognize that these neurochemical features are present *before* the onset of obesity and that neuropeptide Y gene expression remains elevated even when the animals grow obese and hyperinsulinemic (which suggests that neuropeptide Y neurons are somehow insulin resistant in obesity-prone rats, as insulin normally downregulates neuropeptide Y expression Schwartz et al., 1992). Also, obesity-prone animals develop their phenotype only when given access to a palatable, high energy diet, which renders this model of particular relevance for the study of the obesity syndrome in humans.

## 4. Clues linking dopaminergic circuits and the metabolic syndrome in humans

Antipsychotic drugs, blocking the dopamine $D_2$ receptor among other monoaminergic receptors, promote weight gain in rodents and humans (Jones et al., 2001; Kaur and Kulkarni, 2002). For example, olanzapine was shown to induce an average gain of 6 kg in 573 patients during 2.5 years of follow-up (Kinon et al., 2001). Recently, numerous case reports have linked novel antipsychotics to the development of diabetes mellitus and hyperlipidemia (Bettinger et al., 2000; Fertig et al., 1998; Popli et al., 1997; Procyshyn et al., 2000; Rigalleau et al., 2000; Wirshing et al., 1998, 2001). Several systematic studies have confirmed these observations. In one prospective study, as many as 30 out of 82 subjects (36%!) were diagnosed with new-onset diabetes within 5 years after clozapine initiation (Henderson et al., 2000). In a recent large survey, the incidence of type 2 diabetes among young (<40 years) patients using antipsychotic medication was six to eight times as high as compared with the general population in the same age range (Sernyak et al., 2002). Although it is tempting to postulate that the disruption of glucose metabolism in patients treated with antipsychotics is caused by weight gain, this was not the case in most studies that evaluated this possibility (Henderson et al., 2000; Popli et al., 1997). Moreover, cases of new-onset diabetes mellitus in the absence of weight gain were also reported (Henderson et al., 2000; Popli et al., 1997; Wirshing et al., 1998), and in the majority of cases, glycemic control appears to normalize within weeks after discontinuation of treatment (Koller et al., 2001; Ober et al., 1999; Rigalleau et al., 2000). A few studies have looked at the metabolic and endocrine profile of non-diabetic patients

using antipsychotic drugs. The results consistently show that these drugs induce (euglycemic) hyperinsulinemia, insulin resistance, increased plasma leptin levels and impaired glucose tolerance in response to an oral glucose load (Melkersson et al., 1999, 2000; Melkersson and Hulting, 2001; Newcomer et al., 2002).

Although the association between the use of antipsychotics and (type 2) diabetes mellitus has been firmly established, the underlying neural mechanisms are unclear. All classes of antipsychotic drugs share affinity for dopamine $D_2$ receptor as a common pharmacologic feature which appears to be mandatory for antipsychotic action (Strange, 2001). However, a novel class of antipsychotics (designated as ''atypical'') is distinguished from the classic drugs (designated as ''typical'') on the basis of their adverse effect profile and intrinsic pharmacologic properties. In particular, atypical drugs have relatively low affinity for the dopamine $D_2$ receptor, but exhibit potentially important additional affinities for other dopamine receptor subclasses (D3 and D4) and distinct monoamine receptor subtypes (i.e. 5-$HT_{2A/C}$ and histamine $H_1$ receptors) (Arnt and Skarsfeldt, 1998). The majority of cases of type 2 diabetes mellitus described earlier have been linked with the use of atypical antipsychotics, whereas relatively few reports on typical drugs and type 2 diabetes mellitus have appeared. It is conceivable that simultaneous antagonism of the various monoaminergic receptor subtypes exerts synergistic effects on glucose and lipid metabolism, as all these particular receptors have been implicated in the regulation of fuel fluxes (for review, see Leibowitz and Alexander, 1998; Sakata et al., 1997). However, although the incidence of new-onset type 2 diabetes mellitus is generally somewhat higher in individuals on atypical antipsychotics, the two recent studies that have systematically compared the incidence of type 2 diabetes mellitus among typical vs. atypical drug users found a considerably increased risk (6 ×) in typical drug users as well (Lund et al., 2001; Sernyak et al., 2002). Thus, dopamine $D_2$ receptor antagonism may be the common denominator that is central to the adverse metabolic effects of all antipsychotic drugs.

Conversely, a number of clinical experiments suggest that activation of the dopamine $D_2$ receptor has favourable effects on body composition and fuel metabolism in obese humans with the metabolic syndrome. Bromocriptine treatment without concurrent dietary advises reduced body fat stores by approximately 12% in obese nondiabetic postmenopausal women (Meier et al., 1992). Body fat was reduced by 11% and blood glucose by 28% in an additional group of obese patients with type 2 diabetes mellitus on oral hypoglycemic drugs (Meier et al., 1992). Bromocriptine treatment as an adjunct to moderate caloric restriction results in loss of approximately 14% (vs. 4% on placebo) of body fat in obese patients (Cincotta and Meier, 1996). In addition, bromocriptine improves oral glucose tolerance in this setting (Cincotta and Meier, 1996). Another study in obese nondiabetic hyperinsulinemic women showed a decline of fasting and postprandial plasma glucose, triglyceride and free fatty acid concentrations in response to bromocriptine (Kamath et al., 1997). A modified insulin suppression test failed to show any impact of bromocriptine on insulin sensitivity in this study (Kamath et al., 1997). In two large, randomized placebo-controlled trials, bromocriptine significantly reduced hemoglobin $A1_C$, fasting and postprandial plasma glucose, free fatty acids and triglycerides in obese diabetic subjects with or without oral anti diabetic agents (Cincotta et al., 1999). One study in humans attempted to unravel the mechanisms underlying the beneficial metabolic effects of bromocriptine in patients with type 2 diabetes mellitus (Pijl et al., 2000). Although bromocriptine significantly reduced plasma hemoglobin $A1_C$ levels and other measures of glucoregulation in obese type 2 diabetic patients, endogenous glucose production and total body glucose disposal in response to physiological hyperinsulinemia were not affected (Pijl et al., 2000). In apparent contrast to these observations, a distinct bromocriptine formula failed to impact metabolic measures in obese patients with type 2 diabetes mellitus (Wasada et al., 2000).

## 5. Genetic markers of impaired dopaminergic ($D_2$) signaling and obesity in humans

The human dopamine $D_2$ receptor gene has been mapped to chromosome 11q23 (Eubanks et al., 1992). It contains eight exons and spans at least 52 kb (Gandelman et al., 1991). The evidence linking mutations of the gene and obesity syndromes is limited. In particular, the metabolic profile of carriers of functional polymorphisms of the dopamine $D_2$ receptor gene has been poorly studied. In general, loss of function mutations associates with overweight. A Ser311Cys mutation, which impairs dopamine $D_2$ receptor function (Cravchik et al., 1996), is linked with obesity and reduced energy expenditure (Comings et al., 1993; Jenkinson et al., 2000; Tataranni et al., 2001). Also, the Taq1A1 allele, which is associated with diminished receptor density in the brain (Jonsson et al., 1999; Noble et al., 1991), appears to be associated with obesity (Blum et al., 1996; Comings et al., 1996). Several other papers have also reported associations between dopamine $D_2$ receptor variants and human obesity (Blum et al., 1996; Comings et al., 1991; Jenkinson et al., 2000). Moreover, the number of dopamine $D_2$ receptor binding sites in the brain, as determined by in vivo positron emission tomography (PET) scan analysis, is considerably reduced in obese humans and inversely associated with body mass index (Wang et al., 2001).

## 6. Conclusions

A plethora of data from animal models of obesity syndromes supports the notion that reduced dopaminergic

neurotransmission in hypothalamic nuclei sets the stage for efficient partitioning of ingested nutrients, leading to obesity, insulin resistance and hyperlipidemia. These metabolic features allow survival in times of food scarcity. The fact that obesity and type 2 diabetes mellitus appear to be important side effects of pharmacological blockade of the dopamine $D_2$ receptor and dopamine $D_2$ receptor agonism ameliorates the metabolic profile of obese insulin resistant humans is in keeping with a similar function of dopaminergic neural circuits in humans. It is tempting to speculate that genetic modulation of the dopaminergic neural circuitry contributes to the ''thrifty'' genotype that has evolved in the course of evolution to survive famine. Indeed, loss of function mutations of the dopamine $D_2$ receptor gene associates with obesity in man. However, data on the metabolic impact of diminished dopamine receptor function are relatively scarce. Also (brain site specific), regulation of receptor expression and/or postreceptor signaling cascades may alter dopaminergic neurotransmission without mutation of receptors themselves. It seems worthwhile to further investigate the exact role of dopaminergic circuits in the regulation of energy balance and fuel metabolism in humans to clarify its contribution to a phenotype that is not so thrifty anymore.

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