Prolactinoma-associated obesity treated with bupropion and methylphenidate

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Introduction

Obesity has been strongly associated with dopaminergic deficiency and dysfunctional reward processing [Wang *et al.* 2001; Johnson and Kenny, 2010]. Dopamine is proposed to regulate food intake by modulating food-related reward signals within the mesolimbic circuitry of the brain [Martel and Fantino, 1996] as well as peripherally regulating adipocyte function [Ben-Jonathan and Hnasko, 2001]. Increased food intake has been interpreted in terms of compensation for an underlying dopaminergic deficiency including reduced phasic reward signals to food stimuli. Consistently, patients receiving D2-receptor blocking compounds report increased appetite and weight gain [Baptista, 1999]. Conversely, drugs increasing brain dopamine levels promote reductions, both in weight and appetite. [Towell *et al.* 1988; Foltin *et al.* 1990]. Prolactin-secreting pituitary adenomas may serve as a mechanistically plausible example to investigate the role of dopamine in obesity. Prolactinomas suppress the dopaminergic tone and, consistently, have been shown to be associated with body weight gain and obesity [Greenman *et al.* 1998]. Similar brain lesions that lead to obesity have also been shown to be associated with a reduced dopaminergic tone, e.g. hypothalamic tumors such as craniopharyngioma [Elfers and Roth, 2011].

Still, the exact mechanism of the association of prolactinoma and obesity is insufficiently understood and studies on obesity after normalization of prolactin levels show inconsistent results [Greenman *et al.* 1998; Delgrange *et al.* 1999; dos Santos Silva *et al.* 2011]. However, both standard pharmacological treatments for prolactinoma and cognitive-behavioural treatment often fail to reduce patients' weight [Doknic *et al.* 2002; dos Santos Silva *et al.* 2011]. Overall, there is a considerable need for effective clinical options to address obesity associated with pituitary tumours and to elucidate the relationship between central and peripheral dopamine effects on adipogenesis

including the role of prolactin. The above-mentioned observations suggest the exploration of novel dopaminergic strategies.

Case description

We admitted a 35-year-old patient (NR) to our inpatient psychiatric unit, 1 year after the diagnosis of a prolactin-secreting adenoma (macroprolactinoma, see Figure 1).

The patient had suffered from obesity from his early adolescence and his physical development including the development of secondary sexual characteristics had been retarded since then. The educational track had been in deep contrast to the academic background of his family. There are no psychiatric or metabolic disorders known in the immediate family. It could be shown, that the adenoma had caused a hyperprolactinaemia, hyposomatotropinaemia and, secondary to that, hypogonadism with a lack of testosterone. Treatment with cabergoline, a dopamine D2-receptor agonist, was started soon after the diagnosis was confirmed. Prolactin, growth hormone and insulin-like growth factor 1 (IGF-1) quickly reached standard levels while testosterone levels only slowly began to rise. While sex hormone-binding globulin (SHBG) was within normal range, total testosterone and, consequently, free androgen index were lowered. A gonadotropin-releasing hormone (GnRH) test showed that a stimulation of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) was present but insufficient, supporting the diagnosis of secondary hypogonadism. A diagnostic sonography showed small testicles without other pathological findings. A substitution of testosterone was initiated. Following an insulin-induced hypoglycaemia test, a corticotropine deficiency was not observed.

MRI follow up showed a continuous volume decline of the pituitary gland. Consequently, the patient underwent two long-term inpatient treatments focused on weight reduction in different

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Figure 1. T1-weighted MRI slice showing NR's macroprolactinoma sized at 26 mm × 20 mm × 19 mm (left–right; cranial–caudal; anterior–posterior). Further inspection revealed that the hypophysis and pituitary stalk were displaced to the right. Sellar tissue proliferation extended to the suprasellar and left parasellar region, without compression of the optic chiasm. The left internal carotid artery was walled by the surrounding soft tissue. On the right-hand side, the tumour extended to the craniomedial part of the carotid artery.

hospitals with a cognitive–behavioural approach applied. Both treatments were ineffective, with no weight reduction after the first treatment and even a weight gain after the second treatment.

At admission, NR's body weight was 142.7 kg, with a body mass index (BMI) of 50.6. When exposed to food, he appeared impulsive and disinhibited, eating larger quantities without considering consequences. These events did not meet the criteria of binge attacks, however.

Overall, NR showed a deficit in sustained attention and patience when faced with unpleasant everyday tasks. Symptoms of affective lability included regular but short episodes of sadness, anger or happiness. Moreover, he revealed unrealistic and regularly changing plans for the future, for example becoming a professional tennis player. NR reported to suffer from the consequences of being overweight making it difficult to find friends or a partner. Structured clinical interview according to DSM-IV did not reveal evidence for a primary psychiatric disorder, particularly mood disorder, eating disorder or attention deficit hyperactivity disorder (ADHD). This was further supported by application of disorder-specific rating scales. We started our treatment focusing on the affective symptoms with 300 mg of bupropion, a norepinephrine and dopamine reuptake inhibitor. After 3 weeks, affective symptoms had improved; impulsive and inconsiderate behaviour remained

though. Moreover, the patient had lost 1.5 kg of his body weight.

At week 6, we added methylphenidate starting with 18 mg and increasing the dose to 36 mg at week 7. The combined medication was well tolerated, NR reported to have a longer and better ability to focus his attention or organize tasks. We observed less impulsive and more goal-directed behaviour with improved emotional stability. Furthermore, uncontrolled food intake and body weight decreased without any reported or observable effort to take control over the impulse to eat. We discharged NR with a body weight of 133 kg (BMI 47.1) after 10 weeks of treatment. At no point did we apply psychological treatment for obesity nor made the body weight a major issue in the therapeutic sessions and visits. NR clearly refused any efforts in losing weight.

We saw the patient for follow up interviews at weeks 3 and 8 after discharge. NR's psychopathological status and his weight remained essentially stable, with a slight increase to 134.1 kg (+1.1). Medication remained unchanged and was well tolerated. Eight weeks after discharge NR's body weight had even further decreased to 131.8 kg.

Discussion

We present, to the best of the authors' knowledge, the first report on combined treatment with bupropion and methylphenidate as added to an

established therapy with cabergoline in a patient with a prolactin-secreting pituitary adenoma. We report a subsequent improvement of neuropsychiatric symptoms and a sustained reduction of obesity. This improvement was not observed during a preceding 1 year's treatment with cabergoline, despite normalization of prolactin, somatotropin and testosterone levels. This observation suggests no direct influence of this D2 agonist on the reward processing system and no indirect influence on weight through normalization of prolactin levels.

Notably, abnormalities of the circadian rhythm of prolactin secretion rather than the baseline prolactin level has been associated with weight increase [Doknic *et al.* 2002], which might explain some inconsistencies in the literature mentioned above [Greenman *et al.* 1998; Delgrange *et al.* 1999; dos Santos Silva *et al.* 2011]. As the somatotropin levels were normalized at the point of treatment, we did not substitute this hormone. The normalization of somatotropin levels without any impact on the body weight suggested that a substitution of somatotropin would not have led to a significant impact on the body weight. Furthermore, hyposomatotropinaemia has been rather associated with selectively elevated visceral fat than with obesity. Still, a significant effect of a substitution is clearly possible.

In contrast to cabergoline more selectively acting on D2 receptors in the tuberoinfundibular system, we suggest that the weight-reducing effect of bupropion and methylphenidate may be, at least in part, due to a modulation of other dopaminergic pathways involved in reward processing, especially the mesolimbic system. This results in a decreased reward-seeking behaviour given the evidence for a dysfunctional reward processing in obesity, for example those using measurements of neural responses to food *versus* nonfood stimuli using functional neuroimaging [Wang *et al.* 2001; Stoeckel *et al.* 2008; Johnson and Kenny, 2010]. Bupropion is effective in smoking cessation and its neural effects on stimulus processing within the reward system has been shown [Weinstein *et al.* 2010]. Another track showing the influence of dopamine and, thus, bupropion on food intake is the activation of pro-opiomelanocortin (POMC)-producing neurons in the arcuate nucleus of the hypothalamus (ARH). The anorectic effect of POMC is mediated by α -melanocyte-stimulating hormone (α -MSH) and limited by autoinhibitory feedback of β -endorphin [Cowley *et al.* 2001]. Animal models show that the expression of POMC-mRNA is regulated by dopamine, especially the activation of D2-receptors of the

ARH [Tong and Pelletier, 1992]. Bupropion appears to increase the activity of hypothalamic POMC-producing cells [Greenway *et al.* 2008, 2009]. Previous studies have shown that methylphenidate can amplify dopaminergic signalling within the mesolimbic circuitry when humans are exposed to food stimuli [Volkow *et al.* 2002]. Conversely, there is a lack of comparable evidence for effects of cabergoline on reward processing [Gibson *et al.* 2012] and especially the induction of psychiatric disorders involving the mesolimbic system, e.g. psychosis [Chang *et al.* 2008].

Other reasons for weight reduction should be taken into account, however. The consequences of hospital admission itself should be considered. However, both lack of weight reduction during two earlier therapies aiming at weight reduction as well as the maintenance of weight reduction 8 weeks after discharge render a largely environmental explanation unlikely. Finally, we cannot distinguish between a direct pharmacological effect on food regulation and indirectly reduced food intake due to clinical improvement associated with improved control and inhibition of behaviour.

Although other contributions cannot be excluded, there is no hint on other causal factors for the patient's obesity. He had previously gone through a detailed diagnostic process including a wide range of laboratory parameters (including a GnRH-test and an insulin-induced hypoglycaemia test), repetitive MRI brain scans, a genetic analysis at the gene and chromosome level, showing no aberrations beyond those already mentioned. Moreover, the patient's biography is free of traumatic events or even major challenges in the context of a very good parental care, with no family history of overweight or obesity. Taken together, the patient's prolactinoma may be regarded as sufficient to produce the observed deficits and in the present case offers the most likely explanation.

The question of the relative contribution of bupropion and methylphenidate including their possible synergy cannot be resolved in the present case. The slight weight loss observed already with bupropion alone suggests that this drug contributed to the effect observed after the addition of methylphenidate. Nevertheless, the observed sustained weight reduction renders a combination of bupropion and methylphenidate a promising strategy, worthy of further investigation. This holds at least for therapy refractory obesity related to pituitary brain tumours, which may be insufficiently treated with cabergoline or bromocriptine regarding weight aspects.

Moreover, the combination of these three dopaminergic drugs (cabergoline, bupropion and methylphenidate) was well tolerated and led to no specific side effects, which has not been described in the literature, to date. Definite information about safety cannot be derived from this case report, however. Particularly effects on lowering the seizure threshold in patients with epilepsy but also effects on other comorbid conditions have to be taken into account. Overall, our results support the role of dopaminergic deficiency and dysfunctional reward processing in this still insufficiently understood condition [Greenman *et al.* 1998].

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