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Review

Successful methylphenidate treatment of early onset extreme obesity in a child with a melanocortin-4 receptor gene mutation and attention deficit/hyperactivity disorder

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ABSTRACT

We present the case report of a 2 year old boy with early onset extreme obesity (body mass index (BMI) 34.2 kg/m²; body mass index standard deviation score (BMI-SDS) 5.4) who is heterozygous for a non-conservative functionally relevant *melanocortin MC_4 receptor* mutation (Glu308Lys) and who also showed severe symptoms of attention deficit/hyperactivity disorder (ADHD). Treatment with the stimulant methylphenidate led to a sharp decrease of BMI to 21.8 kg/m² (BMI-SDS 2.8) within 24 months. We discuss potential mechanisms for this unusually large weight loss and suggest a potential link between the melanocortinergic and the dopaminergic systems, and the sympathetic nervous system. The potential benefit of methylphenidate in obese *melanocortin MC_4 receptor* mutation carriers with and without co-morbid ADHD warrants further studies.

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1. Introduction

A 29 month old boy initially presented with early onset severe obesity (BMI 34.2 kg/m^2, BMI-SDS 5.4, Fig. 1) and pronounced symptoms of hyperactivity, inattention and impulsivity fulfilling the DSM-IV TR (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) (APA, 2000). Throughout the day he was restless

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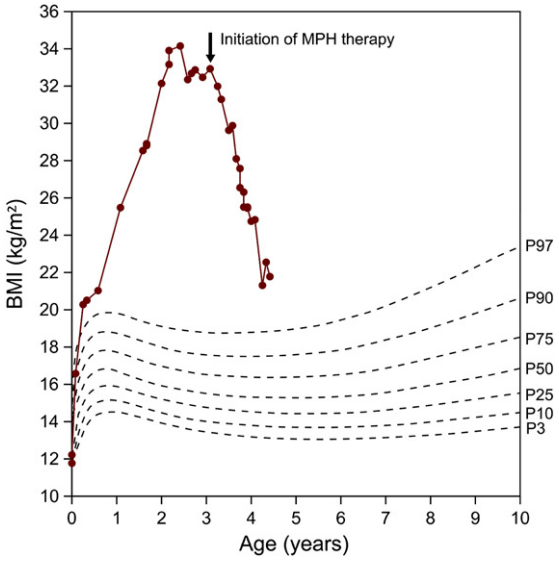

Fig. 1. Development of obesity and MPH induced BMI reduction: maximal weight of 37 kg (height 106 cm) upon initiation of MPH treatment; at age 53 months body weight and height were 28.8 kg and 115 cm. BMIs illustrated at different ages using the German reference BMI percentiles (www.mybmi.de).

and acted impulsively, especially when requests were denied. He was hardly able to perform age-appropriate activities which require attention (e.g. painting or listening to a story). He was heterozygous for a paternally inherited, functionally relevant non-conservative mutation (Glu308Lys; Santini et al., 2004) in the *melanocortin MC_4 receptor* gene; such mutations occur in 2–6% of extremely obese children and adolescents (Hinney et al., 2003; 2010; Hebebrand et al., in press). After birth at 2700 g in gestational week 36 the boy started to gain weight excessively. Upon presentation, the boy was not able to walk more than 15 steps without taking a break; he could not climb stairs without help and complained about painful ankles and knee-joints. He was permanently hungry and hyperphagic; he woke up hungry during the night. Temper tantrums occurred when food was denied. Dietary intervention had not resulted in weight reduction. Blood pressure and heart rate were within the upper normal range. Cognitive development was normal. His father recalled both hyperactive behavior and childhood onset obesity (current BMI 35 kg/m^2 at age 33 years). His hyperactivity remitted during early adulthood.

We prescribed the stimulant methylphenidate off-label at this age in an attempt to ameliorate the severe ADHD symptoms and reduce the voracious appetite, appetite suppression being one of the most common side effects of stimulants. ADHD symptoms strongly decreased (initial methylphenidate dose = 0.41 mg/kg); to continuously control ADHD symptoms the dose was increased to 1.1 mg/kg (methylphenidate extended release) during the first two months of treatment. The appetite suppression was profound and severe weight loss ensued over the whole observation period. Upon the most recent presentation at age 53 months the methylphenidate (current dose: 1.4 mg/kg) effect was reported to wane seven hours after intake, so that excessive appetite and ADHD symptoms re-emerge during the evening. Blood pressure and heart rate were slightly lower than at initial presentation. The boy experiences difficulties falling asleep and wakes up 4–5 times per night complaining of painful knees and feet, caused by genua recurvata. The parents are unable to state whether or not he is hungry, because food after bedtime has long been denied.

2. Discussion

Although weight loss is a common side-effect of methylphenidate treatment (Poulton and Cowell, 2003; Barkley et al., 1990), to our clinical experience the steep and long-lasting BMI decline (see Fig. 1) in this obese *melanocortin MC_4 receptor* mutation carrier with comorbid ADHD appears rather unusual. The effect is stronger than the anorexic effect of methylphenidate normally observed in ADHD patients (with and without obesity). Hence, our observation raises the question, as to whether the altered melanocortinergic signalling due to reduced *melanocortin MC_4 receptor* activity specifically contributes to the marked effect of methylphenidate. Alternatively, our observation merely depicts the upper edge of the variability of weight loss following stimulant treatment.

2.1. Obesity and ADHD as comorbid conditions

During the last decade, compelling evidence substantiated the link between ADHD and obesity/overweight (for review see Davis, 2010). There is a growing number of clinical studies on adults (Altfas, 2002) and children (Holtkamp, 2004), as well as epidemiological studies comprising large population based samples (Pagoto et al., 2009; Waring et al., 2008). For example, Altfas et al. (2002) described a clinical sample of 215 adult bariatric patients (mean age 43.4 years, mean BMI before treatment 36.2 kg/m^2). The prevalence of ADHD was 27.4% in the whole sample. Most of these comorbid patients (42.6%) were found among the most obese individuals (BMI > 40 kg/m^2). Those with ADHD reduced their weight during treatment to a lesser extent than those without ADHD. In children a significantly higher BMI-SDS was reported in a clinical sample of 97 boys with ADHD (mean age 10 ± 2 years, mean BMI-percentile 57 ± 30; Holtkamp et al. 2004). In a clinical sample of 177 children and adolescents aged 8 to 15 years (mean BMI = 29.2 ± 4.33) high body weight was associated with high impulsivity, especially at younger ages (Pauli-Pott et al., 2010). This is in line with the observation of Tsukayama et al. (2010), who were able to show that low impulsivity predicted prospective decrease of BMI percentile rank during transition from childhood into adolescence. Population-based data based on 6,735 adult persons yielded a 1.6 odds ratio (95% confidence interval = 1.1, 2.4) for patients with ADHD to be overweight and a 1.8 odds ratio (95% confidence interval = 1.1, 2.6) to be obese (Pagoto et al., 2009).

ADHD medication might actually weaken the relationship between ADHD and obesity (Poulton and Cowell, 2003; Barkley et al., 1990). In this respect the findings of Waring et al. (2008) are of special relevance. In a population-based survey comprising 62,884 children and adolescents aged 5–17 years (5,680 with ADHD) children and adolescents with ADHD who did not take any medication at the time of assessment showed a higher rate of overweight. In contrast, those who were on medication for ADHD were more likely to be underweight than the children and adolescents without ADHD.

2.2. Link between reduced melanocortinergic tone and ADHD

Melanocortin MC_4 receptor mutation carriers could represent a subgroup of obese patients with comorbid ADHD. *Melanocortin MC_4 receptor* mutations that lead to a reduced receptor function have consistently been found to be associated with obesity (Hinney et al., 2006; Farooqi and O'Rahilly, 2006; Lubrano-Berthelier et al., 2003). Within a Palestinean consanguineous family homo- and heterozygous carriers of a functionally relevant *melanocortin MC_4 receptor* mutation (Cys271Arg; Agranat-Meged et al., 2008) presented with both obesity and ADHD. 29 subjects from 5 related nuclear families underwent thorough physical and psychiatric examination. ADHD was significantly more prevalent in the homozygous (80%) as well as in the heterozygous mutation carriers (21%) compared to the expected prevalence rates in the general population. Further, among the pedigree members the ADHD prevalence increased with the number of *melanocortin MC_4 receptor* obesity risk alleles. An impaired self-regulation and higher levels of impulsivity might indicate a common patho-mechanism both for ADHD and obesity due to a *melanocortin*

MC_4 receptor mutation (Agranat-Meged et al., 2008). In light of the evidence linking ADHD and obesity, the occurrence of ADHD in *melanocortin MC_4 receptor* mutation carriers might indicate a unique genetic subgroup of obese patients with comorbid ADHD. However, we can obviously not exclude a coincidental co-occurrence of ADHD and obesity in our patient.

An elevated occurrence of ADHD in *melanocortin MC_4 receptor* mutation carriers is further supported by both human and rodent studies pertaining to the brain-derived neurotrophic factor, which is released upon *melanocortin MC_4 receptor* activation and inhibits food intake (Xu et al., 2003). The mouse model of a homozygous *brain-derived neurotrophic factor* receptor tyrosine kinase receptor hypomorph, becomes severely obese and shows marked hyperphagia (Xu et al., 2003). Heterozygous *brain-derived neurotrophic factor* knock-out mice show an increased weight range compared to the wild-type with significant weight increase in a subgroup of the heterozygous knock-out mouse model (fat heterozygous *brain-derived neurotrophic factor* mutant mice), which increased their body weight markedly over time compared to non-fat *brain-derived neurotrophic factor* heterozygous mutants and wild-type. Further, *brain-derived neurotrophic factor* heterozygotes had increased rates of locomotor activity. (Kernie et al., 2000). *Brain-derived neurotrophic factor* conditional mutant mice lead to the deletion of *brain-derived neurotrophic factor* postnatally and thus provide a genetic tool to assess the role of this neurotrophin in the postnatal brain. Adult conditional mutant mice had substantially reduced brain-drived neurotrophic factor in the hypothalamus, hippocampus, and cortex. The transgenic mice were significantly more hyperactive after exposure to stressors compared to the controls. Baseline locomotor activity, however, was not significantly different (Rios et al., 2001). A girl with a *de novo* chromosomal inversion encompassing the *brain-derived neurotrophic factor* gene was also reported to be both severely obese and hyperactive (Gray et al., 2006).

2.3. Mechanisms related to methylphenidate induced weight loss

The use of stimulants is considered as first-line treatment in ADHD (NICE, 2008). Methylphenidate is a central nervous system stimulant. Pharmacologically, stimulants can be divided into amphetamine-stimulants (amphetamine, methamphetamine, methylphenidate) or 3,4-Methylendioxy-N-methylamphetamine (MDMA) and non-amphetamine stimulants (atomoxetine or modafinile; Stahl, 2008). They have in common that they induce enhanced alertness, wakefulness and locomotion. Hyperactivity in ADHD patients is however reduced. The pharmacodynamic effect by which methylpheniate reduces ADHD symptoms is not yet completely understood. A large number of pharmacological, genetic and neuroimaging studies suggest that methylphenidate increases intrasynaptic concentrations of dopamine and noradrenaline in subcortical brain regions which are associated with motivation and reward (Arnsten, 2006; Volkow et al., 2004) and in the prefrontal cortex. The prefrontal cortex is associated with attention and impulsivity (Arnsten, 2009). Proper functioning of the prefrontal cortex requires an optimal level of dopamine and adrenergic catecholamines. The size of the prefrontal cortex in ADHD is reduced as well as its functional activity (Rubia et al., 1999; Casey et al., 1997; Sowell et al., 2003; Seidman et al., 2005; Bush et al., 2005; Sheridan et al., 2007). Moreover, striatal dopamine release has been shown to be decreased in adult patients with ADHD (Volkow et al., 2007).

Decreased appetite, headache, stomach ache and insomnia are the most common side-effects of stimulant medication (Barkley et al., 1990). However, daily methylphenidate doses of 0.6 and 1.0 mg/kg decreased the appetite only mildly in 83 children with ADHD (Barkley et al., 1990). Major weight loss has however been observed upon use of ADHD stimulant medication in adult obese patients with comorbid ADHD (Levy et al., 2009). In detail, mean weight loss in 65 (mean age 41.3 years $\pm$ 12.1, mean BMI 42.7 kg/m^2 $\pm$ 9.3) comorbid subjects was 15.05 kg ($\pm$10.35) as compared to 13 untreated comorbid controls (mean age 38.8 years $\pm$ 9.4, mean BMI 41.7 kg/m^2 $\pm$ 8.2). Controls gained 3.26 kg ($\pm$7.03) of body weight ($p<0.001$) after an average observational period of 466 days ($\pm$260).

In children, pretreatment weight is a predictor of weight loss during methylphenidate treatment, with heavier children being more likely to decrease their height adjusted weight and BMI than thinner children (Schertz et al., 1996). Besides, methylphenidate has been shown to significantly reduce intake of highly palatable food in obese adults (Leddy et al., 2004). Therefore, the exceedingly high pretreatment weight of our index case can in itself be viewed as a positive predictor for the therapeutic outcome in regard to weight loss. The extreme pharmacological response of our patient bears resemblance to the effects observed upon leptin treatment of leptin deficient children (Farooqi et al., 1999, 2002; Licinio et al., 2004).

2.4. Dopaminergic mechanisms related to methylphenidate induced weight loss

The strength of the methylphenidate response could depend on the dopamine transporter binding efficacy. The dose of oral methylphenidate required to block 50% (ED_{50}) of the dopamine transporter corresponds to 0.25 mg/kg as investigated via a positron emission tomography study designed to estimate dopamine transporter occupancies after different doses of oral methylphenidate in seven healthy adult subjects (Volkow et al., 1998).The percentage of dopamine transporter occupancy was not significantly correlated with individual differences in extracellular dopamine increase. It was suggested that the therapeutic efficacy of methylphenidate also depends on the dopaminergic tone in the brain, i.e. the activity of dopaminergic cells in target neurons (Volkow et al., 2002). This would imply that methylphenidate induced increase in dopamine will be lower in a subject with low dopamine cell activity than in an individual with high dopamine cell activity.

Eating behavior and weight control seem to be moderated by brain dopamine activity. Reducing dopamine activity by the use of dopamine antagonists increases food consumption and leads to weight gain (Baptista, 1999). Increased brain dopamine activity induced via dopamine agonists has been shown to lead to a reduction in eating and subsequent weight loss (Schertz et al., 1996; Leddy et al., 2004). Additionally, neuroimaging studies in obese subjects detected a decrease in dopamine D_2 receptor density, that correlated inversely with the BMI (Wang et al., 2001). It has been proposed that impaired inhibitory control over food intake, in addition to enhanced food reward and motivation for food consumption, may represent behavioral consequences of impaired dopaminergic circuitry in obesity (Vucetic and Reyes, 2010).

In sum, higher levels of the central nervous system dopamine activity are likely to predict a reinforced methylphenidate effect, compared to lower levels. Reduced control over food intake seems to be associated with low levels of dopamine activity. Methylphenidate displays anorexigenic properties in increasing dopamine levels in brain regions involved in food intake circuitries.

2.5. Link between the melanocortinergic and dopaminergic systems

Because methylphenidate affects dopamine signalling, it is worthwhile to explore a potential link between the dopamine and the melanocortin system. The two systems overlap anatomically. Dopaminergic neurons are localized in the substantia nigra pars compacta, the ventral tegmental area and the hypothalamus, where they have been shown to occur in the arcuate nucleus (Jaber et al., 1996; Ershov et al., 2001). Messenger RNA (mRNA) of the most widespread dopamine D_1 receptor in the human brain is found in the striatum, nucleus accumbens, olfactory tubercle, the limbic system,

hypothalamus and in the thalamus (Jaber et al., 1996). *Melanocortin MC_4 receptor* mRNA was detected in the ventral tegmental area and in the hypothalamus in addition to other sites in virtually every brain region, including the cortex, the thalamus, the brainstem, and the spinal cord. Pro-opiomelanocortin seems to be expressed almost exclusively in two subcortical brain structures: the hypothalamic arcuate nucleus and the nucleus of the solitary tract of the brainstem (Mountjoy et al., 1994; Cone, 2005). Neurons in the arcuate nucleus contain dopamine D_2 receptors and dopamine D_3 receptors (Doron et al., 2006; Liang and Pan, 2001). The nucleus of the solitary tract of the rat brain was shown to express dopamine D_2 receptors (Qian et al., 1997).

A nonselective melanocortin receptor agonist stimulates and a melanocortin MC_3 receptor and *melanocortin MC_4 receptor* antagonist were shown to inhibit dopamine metabolite 3,4-dihydroxyphenylacetic acid levels in the nucleus accumbens and in the striatum, but not in the prefrontal cortex of rats (Yang and Shieh, 2005).

Activation of *melanocortin MC_4 receptor* by α-melanocyte stimulating hormone in the rat ventral tegmental area causes increased release of dopamine in the nucleus accumbens. This effect on dopamine was completely blocked, when the animals were pretreated with a *melanocortin MC_4 receptor* selective antagonist. Thus, the effect of α-melanocyte stimulating hormone on dopamine signalling may be mediated by the *melanocortin MC_4 receptor* (Lindblom et al., 2001). Chronic intracerebroventricular melanocortin receptor agonist treatment in rats caused a statistically significant increase in the dopamine D_1 receptor binding in the nucleus accumbens and caudate putamen. Dopamine D_2 receptor binding was increased in the ventral tegmental area, the periaqueductal grey and in the compact area of the substantia nigra, and decreased in the caudate putamen. Further, melanocortin receptor activation leads to compensatory changes of dopamine receptor expression in the nigrostriatal and in the mesolimbic dopamine pathways (Lindblom et al., 2002).

Dopamine and melanocortin signalling are likely to interact reciprocally. Perfusion of rat hypothalamic slices with a dopamine D_2 receptor agonist led to the reduction of α-melanocyte stimulating hormone release. Respectively, treatment with an antagonist induced a significant increase of α-melanocyte stimulating hormone. Neither dopamine D_1 receptor stimulation nor inhibition had any effect on α-melanocyte stimulating hormone release (Tiligada and Wilson, 1989). Female dopamine D_2 knockout mice showed an increase in circulating α-melanocyte stimulating hormone and hypothalamic α-melanocyte stimulating hormone content. Furthermore, hypothalamic orexin precursor protein mRNA expression was significantly decreased. No differences were found in hypothalamic neuropeptide Y, melanocortin MC_3 receptor or *melanocortin MC_4 receptor* concentration. Because male dopamine D_2 receptor knock-out mice were unaffected, these results could point to a sex-dependent mechanism of food intake regulation (García-Tornadú et al., 2009).

Chronic cocaine treatment, which is known to exert its effects via the dopamine system, up-regulates *melanocortin MC_4 receptor* mRNA in the striatum and downregulates *pro-opiomelancortin* mRNA in the arcuate nucleus (Alvaro et al., 2003). Additionally, antagonizing dopamine D_1 receptor completely blocks cocaine induced up-regulation of *melanocortin MC_4 receptor* mRNA, whereas chronic dopamine D_2 receptor blockade increased the *melanocortin MC_4 receptor* mRNA expression in the striatum (Alvaro et al., 2003).

Taken together, these studies reveal a bidirectional interaction between the dopaminergic and melanocortinergic systems whereby changes in one system can lead to functional changes in the other. Methylphenidate might be especially beneficial for individuals with a mutation in the *melanocortin MC_4 receptor* gene that leads to a reduced *melanocortin MC_4 receptor* function and thus potentially reduced dopamine levels, because methylphenidate might increase dopamine levels in these patients.

2.6. Sympathetic nervous system and melanocortinergic system

Emerging evidence indicates that the central melanocortinergic system has stimulatory effects on the sympathetic nervous system, thus contributing to the regulation of thermogenesis (Voss-Andreae et al., 2007), energy expenditure, lipid metabolization (Nogueiras et al., 2007) and cardiovascular parameters (Humphreys, 2007). Therefore, a reduced sympathetic nervous tone could lead to a reduced energy expenditure and thus substantially contribute to the obesity seen in carriers of *melanocortin MC_4 receptor* gene mutations entailing an impaired receptor function. This is in line with the findings of Ste Marie et al. (2000) who showed that leptin did not lead to diet-induced thermogenesis via the expression of uncoupling protein 1 in brown adipose tissue of young lean female *melanocortin MC_4* receptor-null mice. Further, oxygen consumption of *melanocortin MC_4* receptor-null mice with similar body weights as wildtype controls was significantly reduced. Thus, sympathetic nervous system dependent metabolic efficiency in energy homeostasis seems to be regulated by the *melanocortin MC_4* receptor. Further, it has been demonstrated that *melanocortin MC_4* receptor deficient individuals (heterozygous carriers of loss of function mutations) had significantly lower mean systolic and diastolic blood pressure and lower urinary catecholamines, when compared to obese individuals without *melanocortin MC_4* receptor mutation (Greenfield et al., 2009). Investigation of central sympathetic nervous outflow through vasoconstrictive muscle sympathetic nerve activity in adult *melanocortin MC_4 receptor* mutation carriers compared to healthy controls (matched for age, BMI and gender) revealed an inverse correlation between muscle sympathetic nerve activity, BMI and leptin levels (Sayk et al., 2010). Additionally, in these mutation carriers diastolic pressure was lower and heart rate reduced (Sayk et al., 2010). A similar effect has been demonstrated in a hypertensive rat model (da Silva et al., 2008). Antagonizing melanocortin $MC_{3/4}$ receptor activity led to increased feeding, markedly elevated weight gain, insulin resistance and hyperleptinemia while the heart rate was concomitantly reduced and the mean arterial pressure lowered. Thus, the hypothesis was supported that central melanocortinergic signalling decreases sympathetic nervous system driven hemodynamic and metabolic functions.

In summary, *melanocortin MC_4 receptor* mutation carriers might conceivably profit from the sympathomimetic effect of methylphenidate.

3. Conclusion

It is unclear whether the marked effect of methylphenidate on weight loss in our patient is related to the reduced melanocortinergic tone due to a functionally relevant *melanocortin MC_4 receptor* mutation. In light of the sympathomimetic action of methylphenidate and its dopaminergic effects, we have discussed likely mechanisms which include interaction of the melanocortinergic and the dopaminergic systems and the influence of the melanocortinergic system on the sympathetic nervous system.

Because hypo-dopaminergic activity occurs as a result of down-regulated melanocortinergic signalling, we hypothesize, that this mechanism could account for or at least enhance the ADHD symptoms, which are also associated with low dopaminergic signalling. Accordingly, the use of the stimulant methylphenidate in our patient whose obesity and ADHD are potentially related to hypo-dopaminergic activity, could increase the dopaminergic tone.

The co-occurrence of early onset obesity and ADHD and the frequency of ADHD among *melanocortin MC_4 receptor* mutation carriers need to be studied further. We ourselves have not previously observed this comorbidity in mutation carriers. However, we had not systematically screened obese mutation carriers for ADHD, which has a frequency of approximately 5–10% in the general population (NICE, 2008). In light of the pedigree reported by Agranat-Meged et al. (2008) and our case report ADHD may occur with a higher frequency in obese *melanocortin MC_4 receptor* mutation carriers. Our case report

justifies further evaluation of stimulants in the treatment of obese *melanocortin MC_4 receptor* mutation carriers with and without ADHD; obviously, stimulants would need to be prescribed off label if ADHD is not comorbid. In addition, such patients should be monitored closely for medication related side effects.

We are aware of the fact that a single case report does not allow any conclusion as to the effects of methylphenidate in *melanocortin MC_4 receptor* mutation carriers. Nevertheless, in light of the strong effect of methylphenidate on both ADHD symptoms and body weight in our patient and the theoretical background as discussed above we deem our observation of interest to the scientific community. Only few groups worldwide have access to *melanocortin MC_4 receptor* mutation carriers. Potentially, further case studies can be conducted in order to follow-up this initial report.

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