Stimulants and growth in children with attention-deficit/hyperactivity disorder

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Abstract

Initial suggestions that suppression of growth may be an intrinsic characteristic of attention-deficit/hyperactivity disorder (ADHD) have now largely been disproven. Although controversy persists regarding the possible negative effect of adrenergic stimulants on growth in children with ADHD, the consensus that appears to be reached in the scientific literature is that stimulant usage may cause a manageable attenuation of growth in these children. Since it is known that stimulants increase the amount of dopamine and noradrenaline in the synapse, this writing suggests that these increases in dopamine and noradrenaline are responsible for the growth attenuation in these children. It appears that increased amounts of dopamine and noradrenaline have the ability to inhibit the secretion of growth hormone and growth-related hormones such as prolactin, thyroid hormones, sex hormones and insulin. Therefore, it would be reasonable to suggest that the increases in dopamine and noradrenaline caused by stimulant usage can disrupt the homeostasis of both growth hormone and growth-related hormones, generating the potential for the suppression of growth.

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Introduction

There is, as yet, no consensus on whether children with attention-deficit/hyperactivity disorder (ADHD), who are treated with adrenergic stimulants, experience growth inhibition, or not. In order to determine whether a relationship exists between stimulant intake and growth in children with ADHD, the first question to be asked is how un-medicated children with ADHD compare in size to control subjects. Although some studies found un-medicated children with ADHD to be of normal height [1–3], weight [1,2] and body mass index (BMI) [2,4]; several, in fact the majority, of studies indicated that un-medicated children with ADHD are actually taller [5–9] and heavier than normal [3,5–8,10]. These findings, therefore, contradict the initial suggestion [11] that height deficits in ADHD may be mediated by the disease itself.

Since the above-mentioned findings indicate that children with ADHD are generally average to above-average in height, weight and BMI, this suggests that growth retardation is not an intrinsic characteristic of ADHD. It, therefore, led to the next question, i.e. can the use of stimulant medication be associated with growth inhibition in children with ADHD? Although this topic is highly controversial, with some studies indicating that stimulant treatment has no effect on the growth of children with ADHD [2,3,12,13]; the overriding evidence in the scientific literature is that stimulant treatment can indeed cause an attenuation of growth. However, this problem seems to be manageable [5]. Most studies agree that stimulant medication causes an attenuation of height velocity, specifically during the first few years of treatment [1.6–8,14–24], with an estimated height deficit of about 1 cm/year for the first 3 years [8]. Although some studies suggest that, in most cases, this stunting of linear growth normalises after approximately 3 years of treatment and that adults with ADHD do not differ significantly in height from control subjects [1,4,8,12,22], others are of the opinion that no tolerance to the height suppressant effects of stimulants develops [19] and no evidence of growth rebound exists in these subjects [6].

Regarding the effect of stimulant medication on weight, the consensus appears to be that adrenergic stimulants can cause a significant decrease in weight, specifically during the first few months of treatment [3–8,10,14,15,19,21,22,24]. However, this effect appears to be more pronounced in children that are over-weight to begin with [10,12]. Moreover, it is believed that the weight suppressant effects of stimulants decrease over time and that these children re-gain the weight loss in later years [5,10,12,19,22]. Further indications regarding the relationship between stimulant usage and growth are that the effects of stimulant medication on growth are dosage dependent, with higher doses of stimulant medication causing greater growth deficits [5,19,21], and that amphetamines cause more growth suppression than methylphenidate [19,22]. However, it should be mentioned that the dosage dependent effects of stimulants on growth are not supported by all studies [10,20]. The effect of drug holidays on growth also remains controversial. Although there are some indications that drug holidays may reduce the potential growth-inhibitory effects of stimulants [19], scepticism regarding the effect of drug holidays...
still exists [3,14,25]. Pliszka et al. [25] specifically, found that drug holidays had no effect on change in height z scores in children with ADHD.

Since the overriding evidence is that stimulant medication has the potential to cause growth attenuation in children with ADHD, the question remains as to the possible mechanism/s by which stimulants may affect growth. Although the mechanism of action of the stimulants commonly used to treat ADHD, such as amphetamines and methylphenidate, is not completely understood, it is generally accepted that they function by increasing the amount of extracellular dopamine and noradrenaline in the synapse [26–29]. They accomplish this by increasing the efflux of dopamine into the synapse, with methylphenidate specifically shown to cause an increased transport of dopamine into vesicles [30] and, moreover, an increase in the release of dopamine from these vesicular stores [30,31].

Furthermore, stimulants also decrease the re-uptake of dopamine and noradrenaline [28,29] by inhibiting dopamine and noradrenaline transporters [31–33], with high affinity [34]. Indeed, it has been shown in mice that enhanced dopaminergic neurotransmission is necessary for methylphenidate to exert its stimulating and rewarding effects, while enhanced noradrenergic neurotransmission is required to inhibit locomotor activity [34]. Areas in which methylphenidate-induced increases in dopamine have been shown to occur include the dorsal striatum [33], prefrontal cortex, nucleus accumbens and caudate-putamen [31]. Important receptors which appear to be involved in the therapeutic effects of methylphenidate in the prefrontal cortex include the noradrenergic α-2 adrenoreceptors and dopamine D1 receptors [27]. Although it is believed that amphetamines function by increasing the extracellular concentration of noradrenaline, dopamine and serotonin, indications are that methylphenidate has no effect on extracellular serotonin [35]. Therefore, the focus in this writing will be on the effects of dopamine and noradrenaline on growth. The question then is what impact do increases in dopamine and noradrenaline have on the growth axis?

**Stimulants and growth hormone**

Growth hormone (GH) stimulates protein synthesis in the body, resulting in enlargement of the skeleton, skeletal muscles and viscera. The effects of GH on skeletal growth are mediated by somatomedins produced by the liver such as insulin-like growth factor I (IGF-I) and insulin-like growth factor II (IGF-II) [36]. No recent studies which look at the effect of methylphenidate and related psychostimulants on GH could be found. Furthermore, older results on the effect of stimulant medication on GH secretion appear to be somewhat contradictory. Indications from a number of laboratories are that stimulant usage can cause a decrease in GH secretory activity [37–40], as well as a decrease in IGF levels [2,41]. A case study by Barter and Kramer [38] showed that methylphenidate is associated with suppression of sleep-induced GH release, while a case study by Holtkamp et al. [37] found a decrease in GH secretion in a child experiencing almost complete growth arrest following methylphenidate intake. Furthermore, Aarskog et al. [39] reported that methylphenidate results in a delayed GH response to l-3,4-dihydroxyphenylalanine (l-dopa), while Hunt et al. [40] found that methylphenidate causes a decreased GH response to the adrenergic agonist clonidine. Kilgore et al. [41], moreover, found that methylphenidate and related psychostimulants result in an inhibition of IGF bioactivity in cartilage tissue.

Although several studies indicated an inhibitory effect of stimulant medication on growth hormone and growth factor levels, some results are less supportive of the possibility. Indeed, a handful of older studies [42–44] have reported an increase in human GH levels with methylphenidate usage. Furthermore, Bereket et al. [2] reported methylphenidate to be associated with mild, but transient decreases in serum IGF-1 and IGF binding protein 3 (IGFBP-3) levels, while Toren et al. [45] found that boys with ADHD treated with methylphenidate do not differ from untreated boys, or from control subjects, with regards to fasting serum GH, GH binding protein (GHBP) or IGF-1 levels. More than the absolute serum levels are necessary to be able to assess the influence of these stimulants on growth hormone functioning and, as yet, not much has been done in this respect.

Since a relatively limited number of studies are available on the effects of dopamine and noradrenaline on growth hormone secretion in subjects with ADHD, the effects of these hormones on GH secretion in subjects other than individuals with ADHD is summarised in **Table 1**. The majority of studies have found that dopamine causes a decrease in GH concentrations [44–48,52]. In animals, dopamine has been found to decrease the secretion of GH by pituitary cells due to an increase in the release of somatostatin [57–59]. Similarly, it has been suggested that the increase in dopamine caused by stimulant administration in humans leads to a decrease in GH secretion [5] due to its effect on D2 dopamine receptors [60], which may have a direct inhibitory action on somatotropes [46].

Regarding the effect of an increase in noradrenaline on GH secretion, it has been shown that, in goldfish, noradrenaline decreases the release of GH due to its effect on α-2 adrenoreceptors [61]. Interestingly, this effect was found to be dosage dependent and reversible [61]. Although quite a far stretch, if extrapolated to humans, this could provide a possible explanation for the perception that an increase in stimulant dosage causes greater growth deficits, as well as the belief that discontinuation of stimulant usage leads to a surge in growth [62]. In humans, it has been found that stimulation of α-2 adrenoreceptors can exert a dual effect on GH by either inhibiting [55] or stimulating its release [53,54,63]. Furthermore, it has been shown that stimulation of β-receptors can inhibit GH release via stimulation of hypothalamic somatostatin [63].

The overriding evidence therefore supports the potential of stimulant medication to inhibit growth via its effects on GH, be it directly on its secretion or on the somatomedins or via cellular actions. Therefore, it would appear that increases in both dopamine and noradrenaline have the potential to decrease GH-related functions. This could result in a decreased enlargement of the skeleton, skeletal muscles and viscera and would, therefore, cause decreases in both height and weight gain.

**Stimulants and prolactin**

Besides its effects on mammary development and lactogenesis, prolactin is believed to act as an autocrine/paracrine cytokine or growth factor [64], with stimulatory effects on cellular growth and proliferation believed to resemble those of GH [65]. These effects appear to be mediated by an intermediary growth molecule called synlactin, which is synthesised and released by the liver [65]. Although the effect of synlactin on growth in humans has not been documented, synlactin has been associated with crop-sac mucosal growth in rats, mice and pigeons [66], and a substantial increase in the height of the tail fin in bullfrog tadpoles [67]. Furthermore, a non-lactogenic factor believed to be related to synlactin, which has been shown to synergistically enhance the growth of rat lymphoma cells, has been found in human serum [68]. It is interesting to note that a correlation (r = 0.88) between suppression of growth in stature and prolactin levels was found in a study on hyperkinetic children [1], while a highly significant correlation between loss of expected height percentile and reductions in mean sleep-related prolactin secretion was found in a
study by Puig-Antich et al. [69] on hyperkinetic children taking stimulants.

Dopamine is a well known prolactostatin which inhibits prolactin secretion [51,70–83], as well as the prolactin response to thyroid releasing hormone (TRH) [84–86]. It has been shown that slight elevations of plasma dopamine are sufficient to inhibit prolactin secretion, suggesting that dopamine is a major physiological prolactin-inhibiting factor [80]. The effect of dopamine on prolactin is believed to be due to the direct inhibition of the high-secretory tone of the anterior pituitary lactotroph [87]. This is believed to be due to the binding of dopamine to D2 receptors, which results in a reduction in prolactin gene expression and exocytosis through intracellular signaling mechanisms [87]. D1 receptor stimulation, on the other hand, has been shown to increase prolactin levels [50,88,89]. Although not much research has been done into the effect of noradrenaline on prolactin release, it has been shown that noradrenaline causes prolactin suppression in both adenaomatous and nonadenaomatous pituitary cells [60], and that it decreases prolactin secretion via ovine pituitary cell adrenoreceptors [90]. However, unlike dopamine, noradrenaline is believed not to be a physiologically important prolactin-inhibiting factor [90].

Therefore, increases in dopamine and noradrenaline both have the potential to exert an inhibitory effect on prolactin secretion, resulting in a deficiency in prolactin-related cellular growth functions.

Stimulants and thyroid hormones

The main function of the thyroid hormones is the stimulation of cellular metabolism, which in itself can have an effect on the physical characteristics of the body. Direct effects of thyroid hormones on growth include the stimulation of endochondral ossification, linear bone growth, maturation of epiphyseal bone centres and an increase in the maturation and activity of chondrocytes in the cartilage growth plate [65].

Although not much work has been done on the effect of stimulants on thyroid hormone secretion, stimulant medication has been shown to cause a statistically significant drop in thyroxine (T4) in children with ADHD [2]. Similarly, repeated amphetamine exposure has been shown to cause a decrease in rat plasma T4 levels [91]. Regarding the effect of dopamine on thyroid hormones (see Table 2), studies have shown that dopamine decreases the levels of thyroid stimulating hormone (TSH) in the body [50,82,92,93], and causes a suppression of thyroidal iodine release and serum T4 and triiodothyronine (T3) levels [93]. Moreover, it appears that dopamine infusion decreases the response of TSH [84–86,94] and T3 [84] to TRH. Some studies suggest that dopamine inhibits TSH at the hypothalamic level [50], while others suggest that there is a direct inhibition of pituitary TSH with a secondary effect on thyroid gland secretion [93].

Therefore, it would appear that the increase in dopamine caused by stimulant usage could very well result in an attenuation of thyroid hormone release and thereby a stunting of growth. The inhibitory effect of stimulants on thyroid functioning, as mentioned before, has already been shown [2,91].

### Stimulants and sex hormones

Testosterone stimulates protein synthesis and, therefore, muscular development and is, moreover, involved in the stimulation of linear or skeletal growth [95]. Similarly, oestrogen is responsible for protein synthesis and is also involved in skeletal growth and the maintenance of the structural integrity of the skeletal system [95]. The release of testosterone and oestrogen is controlled by lutropin (LH), which in turn is regulated by hypothalamic luteinising hormone (GnRH) [95].

### Table 1

The effect of dopamine and noradrenaline on growth hormone levels.

<table>
<thead>
<tr>
<th>Author</th>
<th>Effect</th>
<th>Subjects</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Van den Bergh et al.</td>
<td>Dopamine decreases mean serum GH concentrations, amount of GH per secretory burst and secretory burst amplitude</td>
<td>Critically ill adult polytrauma patients (n = 11)</td>
<td>Duša Trčev et al.</td>
<td>α-2 Adrenergic agonists clonidine and guanfacine increase the release of GH in 82.4% and 47% of cases respectively</td>
<td>Children with short stature (n = 17)</td>
</tr>
<tr>
<td>Svetić et al. [47]</td>
<td>Dopamine agonist CV 205-502 decreases plasma GH concentrations</td>
<td>Patients with acromegaly (n = 10)</td>
<td>Hoehe et al.</td>
<td>α-2 Adrenergic agonist clonidine induces a significant dose-dependent GH increase</td>
<td>Healthy male volunteers (n = 12)</td>
</tr>
<tr>
<td>De Zegher et al. [48]</td>
<td>Dopamine virtually abolishes GH secretion</td>
<td>Neonates with symptomatic polycythaemia (n = 3)</td>
<td>Struthers et al. [55]</td>
<td>α-2 Adrenergic antagonist (idazoxan) augments the exercise-induced increase in GH</td>
<td>Normal volunteers (n = 6)</td>
</tr>
<tr>
<td>Miell et al. [49]</td>
<td>Dopaminergic agonist CV 205-502 causes an increase in GH secretion</td>
<td>Healthy, male volunteers (n = 18)</td>
<td>Lechin et al. [56]</td>
<td>α-2 Adrenergic agonist clonidine induces no changes in GH levels</td>
<td>Patients with depression (n = 50)</td>
</tr>
<tr>
<td>Boesgaard et al. [50]</td>
<td>Dopamine D1 receptor agonist fenoldopam causes no change in basal GH levels</td>
<td>Normal men (n = 9)</td>
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<tr>
<td>Ferrari et al. [51]</td>
<td>Potent, dopaminergic agent dihydroergokryptine does not affect GH levels</td>
<td>Healthy women (n = 6)</td>
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<tr>
<td>Camannì et al. [52]</td>
<td>Dopamine fails to induce an increase in plasma GH</td>
<td>Normal subjects (n = 9)</td>
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<tr>
<td></td>
<td>Dopamine causes a marked fall in GH</td>
<td>Patients with acromegaly (n = 15)</td>
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GH, growth hormone.
The effect of dopamine on thyroid hormone levels.

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<tbody>
<tr>
<td>Van den Berghe et al. [84]</td>
<td>Dopamine decreases the response of TSH and T3 to TRH</td>
<td>Critically ill patients (n = 15)</td>
</tr>
<tr>
<td>De Zegher et al. [92]</td>
<td>Dopamine inhibits the release of TSH</td>
<td>Neonates</td>
</tr>
<tr>
<td>Boesgaard et al. [50]</td>
<td>Dopamine D1 receptor agonist fenoldopam causes a decrease in basal TSH</td>
<td>Normal men (n = 9)</td>
</tr>
<tr>
<td>Connell et al. [86]</td>
<td>Dopamine decreases the response of TSH to TRH</td>
<td>Normal males (n = 6)</td>
</tr>
<tr>
<td>Kaptein et al. [93]</td>
<td>Dopamine infusion causes a suppression of thyroidal iodine release, serum TSH, serum T3 and serum T4</td>
<td>Healthy euthyroid males (n = 6)</td>
</tr>
<tr>
<td>Köbberling et al. [94]</td>
<td>Dopamine agonist bromocriptine does not alter the TSH response to TRH at 100 μg, but significantly blunts it after 200 μg</td>
<td>Normal volunteers (n = 6)</td>
</tr>
<tr>
<td>Massara et al. [82]</td>
<td>Dopamine decreases TSH levels</td>
<td>Normal subjects (n = 5), women with galactorrhea (n = 7), patients with acromegaly (n = 9) and patients with primary hypothyroidism (n = 4)</td>
</tr>
<tr>
<td>Besses et al. [85]</td>
<td>Dopamine decreases the response of TSH to TRH</td>
<td>Normal males (n = 10)</td>
</tr>
</tbody>
</table>

TSH, thyroid stimulating hormone; T3, triiodothyronine; TRH, thyroid releasing hormone; T4, thyroxine.

With regards to the effect of the sex hormones on GH secretion, oestrogen has been found to cause increases in the pulsatile secretion of GH in healthy women [96], while testosterone is believed to stimulate the GH-axis at the hypothalamic level by promoting GH releasing hormone (GHRH) functioning in adult men [97]. Furthermore, testosterone has been shown to cause an increase in nocturnal GH concentration and pulsatile GH secretion, as well as morning serum IGF-1 levels in healthy older men [98].

Indications are that methylphenidate can flatten testosterone diurnal rhythms in children [99] and markedly decrease levels of rat testicular [100], as well as plasma [101], testosterone. Repeated amphetamine administration, similarly, has been shown to cause decreases in basal [91,101,102] and human chorionic gonadotropin-stimulated levels of testosterone in rats [102]. With regards to oestrogen, indications from studies on rats are that methylphenylpionate can adversely affect ovarian folliculogenesis, perturb pubertal onset and adversely affect maturation of the female reproductive axis by inhibiting pituitary LH release [103].

Studies show that dopamine inhibits the release of LH [70,73,74,104–110], as well as the LH response to GnRH [105] (see Table 3). Furthermore, the D1 receptor agonist fenoldopam has been shown to cause a decrease in basal and stimulated testosterone [50] (see Table 3).

The increase in dopamine concentration, caused by stimulant usage, could therefore result in decreases in both testosterone and oestrogen production, which in turn would lead to decreases in both muscle synthesis and skeletal growth, resulting in both decreases in weight and height gain. In addition, the decreases in testosterone and oestrogen production would then result in a decrease in GH secretion, accentuating the already present growth attenuation.

### Table 2

<table>
<thead>
<tr>
<th>Effect</th>
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<tbody>
<tr>
<td>Dopamine decreases mean serum LH concentration, LH secretion amplitude, amount of LH secreted per burst and the number of LH pulses</td>
<td>Adult male polytrauma patients (n = 9)</td>
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<tr>
<td>Dopamine D-1 receptor agonist fenoldopam increases the LH response to GnRH</td>
<td>Normal men (n = 9)</td>
</tr>
<tr>
<td>Low doses of dopamine do not achieve a significant suppression of LH release</td>
<td>Euprolactinemic (n = 15) and hyperprolactinemic (n = 15) women</td>
</tr>
<tr>
<td>Dopamine causes no suppression of serum gonadotropin levels but reduces the LH response to GnRH</td>
<td>Normal and amenorrheic hyperprolactinemic women</td>
</tr>
<tr>
<td>Dopamine causes a significant decrease in LH levels</td>
<td>Ovulatory women (n = 15)</td>
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<tr>
<td>Dopamine produces a significant decrease in serum LH levels</td>
<td>Subjects with polycystic ovarian disease (n = 16)</td>
</tr>
<tr>
<td>Dopamine decreases LH levels</td>
<td>Castrated men (n = 4) and normal men (n = 4)</td>
</tr>
<tr>
<td>Dopamine causes a significant reduction in LH levels</td>
<td>Healthy women (n = 8), patients with hyperprolactinaemic amenorrhea (n = 12), patients with premature ovarian failure (n = 5) and patients with polycystic ovarian disease (n = 8)</td>
</tr>
<tr>
<td>Dopamine lowers circulating LH levels and reduces spontaneous LH fluctuations</td>
<td>Normal ovulatory women</td>
</tr>
<tr>
<td>Dopamine suppresses elevated LH levels</td>
<td>Subjects with polycystic ovarian syndrome (n = 8)</td>
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<tr>
<td>Dopamine decreases levels of LH</td>
<td>Ovariectomized and normal women</td>
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### Table 3

<table>
<thead>
<tr>
<th>Effect</th>
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<tbody>
<tr>
<td>Dopamine increases serum PRL</td>
<td>Euprolactinemic (n = 15) and hyperprolactinemic (n = 15) women</td>
</tr>
<tr>
<td>Dopamine decreases LH levels</td>
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<td>Castrated men (n = 4) and normal men (n = 4)</td>
</tr>
</tbody>
</table>

GnRH, gonadotropin releasing hormone.
amine causes no discernable changes in rat plasma insulin levels [117].

Studies show that dopamine and its agonists inhibit glucose-stimulated insulin release [118–121] (see Table 4). Although this effect was initially believed to be mediated via D2 receptors [119–121], a recent study by de Leeuw van Weenen et al. [118] has indicated that the inhibitory effect of dopamine on insulin release is actually mediated via pancreatic α2 adrenoceptors. Although a study by Shankar et al. [120] found that low concentrations of dopamine increase the secretion of insulin, it is interesting to note that, in addition, this study found that noradrenaline can then inhibit dopamine’s stimulatory effects on insulin secretion. Noradrenaline itself is, moreover, believed to be a major physiological inhibitor of insulin secretion [122–124]. Indications are that noradrenaline acts via pertussis toxin-sensitive G proteins, thereby activating protein acyltransferase, which results in acylation and therefore inhibition, of proteins critical to the exocytosis of insulin [124].

Increases in both dopamine and noradrenaline concentrations, due to stimulant usage, could therefore result in decreases in basal and glucose-stimulated insulin release, contributing to the inhibition of amino acid absorption, protein synthesis, lipogenesis and growth.

Discussion

It is fairly obvious that adrenergic stimulants can influence most hormones involved in the growth process, with growth hormone possibly playing a central role. This would be in line with writing by Poulton [22] suggesting that stimulants activate mechanisms adapted for acute starvation in order to conserve energy stores and that the resultant negative energy balance could lead to a decrease in growth.

Although the situation is generally not of major concern, there do appear to be cases where the effects of stimulants on growth are significant. Such as in the study by Gross [12], where 2 patients experienced a substantial deficit in expected height while on stimulant medication, and in the study by Millichap [13] where 2 out of the 36 boys studied experienced a significantly decreased rate of growth. It appears that “there may be an important subgroup whose growth is permanently attenuated” [22]. We are thus left with the question as to which risk factors determine whether a child will be affected.

In summary we can say that stimulants appear to have the ability to cause an attenuation of growth in height and weight by increasing the amount of noradrenaline and dopamine in the synapse. We hypothesize that dopamine and noradrenaline may attenuate growth by affecting growth hormone activity and possibly that of other growth-related hormones such as prolactin, thyroid hormones, sex hormones and insulin. Furthermore, these growth-related hormones could very well have an additional influence through their effect on growth hormone itself.

Clinical implications

- Although growth suppression appears to occur in a minority of children taking adrenergic stimulants, it is necessary that clinicians are aware of the possibility.
- Until otherwise proven, clinicians should be aware of indications that increases in dopamine and noradrenaline could result in decreases in basal and glucose-stimulated insulin release, and may therefore influence glucose metabolism.
- Stimulants prescribed for individuals with ADHD may have a far more comprehensive effect on the endocrine system, and therefore on the internal homeostasis, of these individuals than is generally assumed.

Limitations of the study

A number of questions could not be answered, including:

- Whether drug holidays have an effect on growth, and if so, what the effect is.
- Which risk factors determine whether growth will be affected by stimulant usage.

Conflicts of interest statement

The authors declare that there is no conflict of interest.
References


