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AMPHETAMINES, GROWTH HORMONE AND NARCOLEPSY

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1 Plasma amphetamine and growth hormone levels have been measured in eight normal and twenty-six narcoleptic subjects following a single dose of (+)-amphetamine (20 mg) or (–)-amphetamine (20 mg) by mouth.

2 Peak plasma levels and the shape of the plasma amphetamine–time curve were similar with both isomers in normal and narcoleptic subjects.

3 In most normal subjects both (+)- and (–)-amphetamine (20 mg) caused an increase in the plasma concentration of growth hormone. The two isomers were approximately equipotent in this respect. Neither (+)- nor (–)-amphetamine (20 mg) caused an increase in plasma growth hormone concentration in narcoleptics.

4 Following amphetamine (30 mg), two of six narcoleptic subjects had an increase in plasma growth hormone concentration.

5 Levodopa (250 mg) with (–)- α-methyldopa hydrazine 25 mg (Sinemet) by mouth, caused a rise in plasma growth hormone concentration in most normal subjects. The magnitude of the Sinemet-induced rise in plasma growth hormone concentration in narcoleptics was less than in normal subjects.

Introduction

Amphetamine injected intravenously causes immediate arousal from sleep. An intact reticular formation is necessary for this effect, and amphetamine does not cause arousal after mid-brain transection in animals (Moruzzi & Magoun, 1949). The alerting effect of amphetamine is likely to be due to the actions of this drug on brain catecholamine systems (Van Rossum, 1972). Amphetamine has a close structural similarity with catecholamines (Alles, 1933), and applied topically, it alters the firing rate of noradrenaline and dopamine neurones (Graham & Aghajanian, 1971; Bunney, Aghajanian & Roth, 1973). Many of the behavioural effects of amphetamines in animals are prevented by drugs having the pharmacological property of causing catecholamine receptor blockade, and in particular by the specific dopamine receptor blocking drug, pimozide (Gunne & Änggård, 1973). It is not certain however, to what extent dopamine and noradrenaline neurone systems are involved in the regulation of the normal sleep-walking cycle, or the alerting effect of amphetamine in man. The alerting effect of (+)-amphetamine is two to four times greater than that of (–)-amphetamine (Parkes & Fenton, 1973).

Amphetamine derivatives cause an increase in the concentration of growth hormone (GH) in the plasma (Rees, Butler, Gosling & Besser, 1970). Levodopa and dopamine infusion also cause a rise in plasma GH concentration (Boyd, Lebovitz & Pfeiffer, 1970; Wilcox, Aminoff, Keenan, Millar & Kremer, 1973) which can be prevented by pretreatment with drugs that cause dopamine receptor blockade (Mims, Scott, Modebe & Bethune, 1975). The amphetamine-induced rise in plasma GH concentration is likely to result from the effects of this drug on catecholamine neurone systems in the hypothalamus.

In normal subjects, not given drugs, a major stimulus to GH release occurs during sleep. People with narcolepsy have a mistiming of different sleep phases, and the pattern of GH release during a 24 h cycle is different from that of normal subjects (Takahashi, Takahashi & Azumi, 1971). Because of this, the GH response to amphetamines may be different in normal and narcoleptic subjects, although drug metabolism is probably similar in both groups.

We have investigated the effects of (+)- and (–)-amphetamine in normal and narcoleptic subjects, to determine whether arousal is accompanied by evidence of catecholamine-receptor stimulation, as shown by an increase in plasma GH levels.

Methods

Normal and narcoleptic subjects

Eight normal subjects, five male and three female, aged 24–41 years (mean 29) and twenty-six patients with narcolepsy, fourteen male and twelve female, aged 25–65 years (mean 45) were investigated. All subjects with narcolepsy also had cataplexy. The duration of narcolepsy was 1–52 years (mean 21) and cataplexy, 3–50 years (mean 19). The sleep-walking cycle of control subjects was normal (mean total sleep time approximately 8 h per 24 h), and that of narcoleptic subjects severely interrupted, with frequent day-sleep periods and nocturnal awakenings (mean total sleep time approximately 9 h per 24 h).

The eight normal subjects had not taken central stimulant drugs, hypnotics or other medication in the week before trial. Twelve subjects with narcolepsy were on regular treatment with (+)-amphetamine (total daily dosage 5–30 mg), and one took (–)-amphetamine 20 mg daily. The duration of amphetamine treatment was 1–35 years (mean 10). Tolerance to amphetamines (defined as a doubling of amphetamine dosage to produce an equal alerting effect, occurring over 4 weeks; after initial 3 month period of treatment) had occurred in five subjects. Twelve narcoleptics took ephedrine, methylphenidate, or both drugs, but not amphetamines, and one was on no treatment. Twenty narcoleptics took clomipramine 10–75 mg daily (mean 35) in addition to central stimulant drugs.

Amphetamine load test

The responses to (+)-amphetamine (20 mg) (eight control subjects and twelve narcoleptics), (–)-amphetamine (20 mg) (eight control subjects and twelve narcoleptics), (+)-amphetamine (30 mg) (six narcoleptics) and levodopa (250 mg) combined with (–)-α-methyldopa hydrazine (25 mg, Sinemet) (eight control subjects and thirteen narcoleptics) were determined. All drugs were given by mouth. The eight normal subjects were each given (+)- and (–)-amphetamine (20 mg) on separate occasions at a one week interval. Two subjects with narcolepsy were given (+)- and (–)-amphetamine (20 mg) on separate occasions, five were given (+)-amphetamine (20 mg) and levodopa (250 mg) plus (–)-α-methyldopa hydrazine (25 mg) on separate occasions, four were given (–)-amphetamine (20 mg) and levodopa (250 mg) plus (–)-α-methyldopa hydrazine (25 mg) on separate occasions, two were given (–)-amphetamine (20 mg) and (+)-amphetamine (30 mg) on separate occasions, five (+)-amphetamine (20 mg) alone, four (–)-amphetamine (20 mg) alone, and four (+)-amphetamine (30 mg) and levodopa (250 mg) plus (–)-α-methyldopa hydrazine (25 mg) on separate occasions.

In narcoleptics, all previous treatment was stopped 24 h before test. On the day of test, normal and narcoleptic subjects remained fasting until 09.00 h when a single dose of amphetamine or (–)-α-methyl hydrazine was given as detailed above, followed by a meal containing carbohydrate 30 g, fat 19 g and protein 17 g. Venous blood was taken by indwelling forearm catheter before and after drugs were given, at 30 min intervals over a 4 h period. The degree of alertness (increased, normal, drowsy or asleep), pulse rate and blood pressure (erect) were recorded at the time of each blood sampling.

Amphetamine growth hormone and dopa determination

The plasma concentrations of amphetamine, dopa and GH were determined by the methods of Campbell (1970), Curzon, Kantamanini & Trigwell (1972), and Schalch & Parker (1964), respectively. The behavioural and hormonal changes observed were related to the plasma concentration of amphetamine or dopa.

Results

Plasma concentration of amphetamine in normal subjects

The mean plasma concentration of amphetamine in normal subjects, following either (+)- or (–)-amphetamine (20 mg) given orally, is shown in Figure 1. The shape of the plasma amphetamine curve, and peak plasma amphetamine levels were similar after both isomers (Table 1). There was a rapid rise in plasma amphetamine concentration following the oral administration of either isomer, peak levels

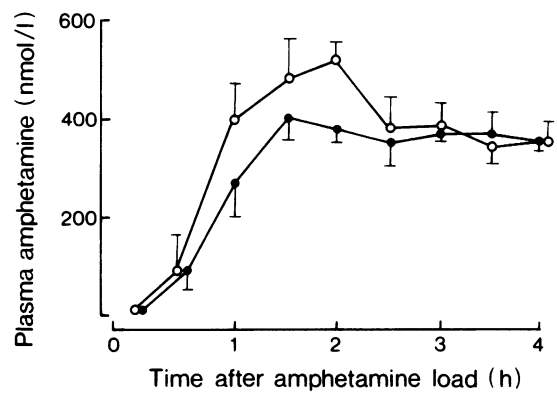

Figure 1 The mean plasma amphetamine concentration (±1 s.e. mean) in eight normal subjects following the oral administration of (+)-amphetamine (20 mg, ●) and (–)-amphetamine (20 mg, ○).

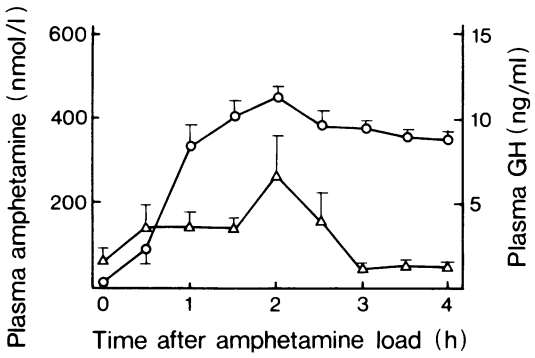

Figure 2 Mean plasma amphetamine (both (+)- and (−)-amphetamine, O) and GH concentration (△) (±1 s.e. mean) following the oral administration of (+)-amphetamine (20 mg) and (−)-amphetamine (20 mg) in eight normal subjects.

occurring after 30–120 min. After 4 h, the level of (+)- or (−)-amphetamine was only slightly lower than at the time of peak concentration. There was a two-fold variation in the peak level of amphetamine in the plasma in different subjects after each isomer (range of peak plasma concentration; after (+)-amphetamine, 289–526 nmol/l, and after (−)-amphetamine, 363–689 nmol/l).

Plasma concentration of amphetamines in narcoleptics

In eight of thirteen patients with narcolepsy, on regular (+)- or (−)-amphetamine treatment, despite withdrawal of all medication for a 24 h period, low concentrations of amphetamine were detected in blood samples taken before the amphetamine load was given. Following (+)- or (−)-amphetamine (20 mg), the plasma amphetamine curve (Figure 2) and peak plasma amphetamine levels (Table 1) were similar to those of normal subjects. In both normal and narcoleptic subjects, peak amphetamine levels in the blood occurred 30–120 min after oral dosage.

Peak plasma amphetamine levels were higher following (+)-amphetamine 30 mg than 20 mg. Peak levels occurred at approximately the same time with each dosage.

Effect of previous amphetamine treatment

Previous amphetamine treatment did not appear to alter the absorption of amphetamines. Peak plasma levels following (+)-amphetamine (20 mg) were closely similar in the single patient who had never received amphetamines, in seven patients treated with amphetamines for less than 5 years, and in four patients treated for over 20 years.

Amphetamine tolerance

Peak plasma amphetamine levels following (+)-amphetamine (20 mg) were similar in five patients who had developed tolerance to (+)-amphetamine during chronic treatment, and in seven patients who had not become tolerant.

Amphetamine-clomipramine interaction

Peak plasma amphetamine concentration following (+)- or (−)-amphetamine (20 mg) was slightly, but not

Table 1 Mean peak plasma amphetamine and growth hormone concentration (±1 s.e. mean) in normal and narcoleptic subjects following the oral administration of (+)- and (−)-amphetamine.

	Plasma concentration	
Normal subjects	*amphetamine (nmol/l)*	*growth hormone (ng/ml)*
(+)-amphetamine (20 mg) ($n=8$)	444 ± 50	6.6 ± 3.1
(−)-amphetamine (20 mg) ($n=8$)	533 ± 75	11.3 ± 4.4
Narcoleptics		
(+)-amphetamine (20 mg) ($n=12$)	630 ± 48	2.9 ± 1.3
(−)-amphetamine (20 mg) ($n=12$)	515 ± 66	1.2 ± 0.5*
(+)-amphetamine (30 mg) ($n=6$)	889 ± 59	4.9 ± 4.5
(+)-amphetamine (20 mg); previous treatment		
(+)-amphetamine-tolerant ($n=5$)	665 ± 96	1.8 ± 0.4 *
(+)-amphetamine non-tolerant ($n=7$)	598 ± 43	3.4 ± 1.6
(+)-amphetamine alone ($n=4$)	559 ± 41	4.2 ± 1.8
(+)-amphetamine plus clomipramine ($n=8$)	655 ± 65	2.3 ± 1.6

* The difference between normal and narcoleptic subjects significant, $P<0.01$, Student's t-test.

significantly ($P > 0.1$), higher in patients previously given clomipramine, than in those not on clomipramine.

Growth hormone response to amphetamines in normal subjects

Fasting blood GH concentration was low (< 3 ng/ml) in all eight normal subjects. Following the oral administration of (+)-amphetamine (20 mg), there was a rise in plasma GH concentration in six subjects (mean peak plasma GH concentration, ± 1 s.e. mean) of 9.6 ± 4 ng/ml, and following (−)-amphetamine (20 mg), a rise in five subjects (mean peak, 17.5 ± 5 ng/ml). The difference in mean peak concentration with both isomers was not statistically significant ($t = 0.7$, $P > 0.1$). Peak plasma GH concentration occurred 30–150 min after oral administration of amphetamines, at approximately the same time as peak plasma amphetamine concentration (Figure 2). An increase in plasma GH concentration occurred in both males and females, and in the youngest and oldest subject.

Growth hormone response to amphetamines in narcoleptics

Fasting plasma GH concentration was low (< 3 ng/ml) in twenty-four, and high in two narcoleptic subjects (6 and 7 ng/ml, respectively). Following (+)-amphetamine (20 mg) (twelve subjects) or (−)-amphetamine (20 mg) (twelve subjects), no patient with narcolepsy had an increase in plasma GH concentration greater than 3 ng/ml. The difference in mean peak plasma GH concentration following amphetamine (20 mg), between normal and narcoleptic subjects was highly significant ($t = 3.5$, $P < 0.005$).

Following (+)-amphetamine (30 mg), two of six subjects with narcolepsy had an increase in plasma GH concentration, to 14 and 20 ng/ml respectively (in these two subjects, peak plasma amphetamine concentration was 850 nmol/l and 1030 nmol/l respectively).

Relation between plasma growth hormone and amphetamine concentration

In normal subjects, there was no clear correlation between peak plasma amphetamine and peak plasma GH concentration ($r = 0.4$, $P > 0.05$, NS). In the normal subject with the highest peak plasma amphetamine concentration (689 nmol/l), the rise in plasma GH concentration was 4 ng/ml, and in the subject with the lowest peak amphetamine level (289 nmol/l), the rise in GH concentration was 26 ng/ml. Mean peak plasma amphetamine levels were similar in normal subjects who did have a rise in plasma GH concentration, and those who did not.

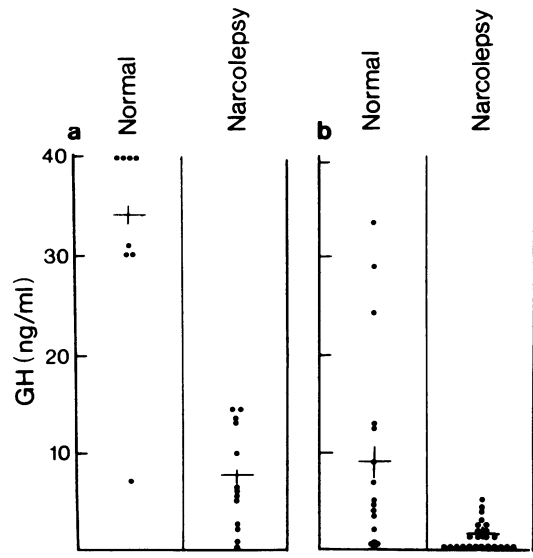

Figure 3 Individual peak human growth hormone (GH) concentration following (a) levodopa (250 mg) plus (−)-α-methyldopa hydrazine (25 mg) in eight normal and thirteen narcoleptic subjects, and following (b) amphetamine (20 mg) (either (+)- or (−)-amphetamine) in eight normal (sixteen determinations) and twenty-four narcoleptic subjects. The mean peak GH response to both amphetamines and levodopa plus (−)-α-methyldopa hydrazine is significantly reduced in narcoleptics as compared with normal controls ($P < 0.005$, Student's t-test).

Changes in plasma GH concentration in narcoleptic subjects given (+)- or (−)-amphetamine (20 mg) were minor, less than 3 ng/ml over a 4 h period, and no obvious relationship between plasma amphetamine and GH levels could be determined.

Growth hormone response to levodopa plus (−)-α-methyldopa hydrazine in normal subjects

Levodopa (250 mg) combined with (−)-α-methyldopa hydrazine (25 mg) caused a rise in plasma GH concentration in all eight normal subjects. Nausea and vomiting occurred in three of these subjects. The mean peak plasma dopa concentration was 7.1 ± 0.7 μmol/l and the mean peak plasma GH concentration was 35 ± 2.9 ng/ml (Figure 3). There was no significant relationship between the increase in plasma dopa and GH levels.

Growth hormone response to levodopa plus (−)-α-methyldopa hydrazine in narcoleptics

The mean peak plasma dopa level (± s.e. mean) in thirteen patients with narcolepsy following oral administration of levodopa (250 mg) combined with

(−)-α-methyldopa hydrazine (25 mg), was 4.6 ± 0.5 μmol/l. Ten of these thirteen patients had an increase in plasma GH concentration 30–90 min following levodopa, the mean fasting and peak GH concentration being 3 ± 1 ng/ml and 10 ± 2 ng/ml respectively. The mean peak plasma dopa concentration was similar in narcoleptic subjects who had an increase in plasma GH concentration, and in those who did not. No patient reported arousal following levodopa, which caused nausea in six narcoleptic subjects. The two of six narcoleptic subjects who had, following (+)-amphetamine (30 mg), a rise in plasma GH concentration (peak levels 14 and 20 ng/ml, respectively), also had an increase in plasma GH concentration following levodopa plus (−)-α-methyldopa hydrazine (peak levels 14 and 40 ng/ml, respectively).

Alertness, plasma amphetamine and growth hormone

Some or all of the following symptoms occurred in all normal subjects given (+)-amphetamine (20 mg), and in five of eight given (−)-amphetamine (20 mg); talkativeness, wakefulness, alertness, euphoria, increased confidence with a sense of increased ability to solve problems, elation, tenseness, slight motor weakness and unsteadiness, sweating, flushing of the face, suppression of appetite, and restlessness. These symptoms lasted 3–8 h. Three normal subjects described fatigue and depression, with no other symptoms, following (−)-amphetamine (20 mg).

The response to amphetamines in narcoleptics was probably influenced by previous drug withdrawal, which resulted in frequent narcolepsy in all subjects. After a 24 h period on no drugs, all narcoleptic subjects reported increased arousal following (+)- or (−)-amphetamine (20 mg), with some or all of the above symptoms. As far as could be determined by clinical observation, the alerting effect of a given amphetamine dosage was similar in narcoleptic and normal subjects.

Peak plasma amphetamine concentration (± 1 s.e. mean) was slightly greater in those five normal subjects who reported symptoms of arousal following (−)-amphetamine (20 mg) than in the three subjects who were not aroused (580 ± 70 and 441 ± 85 nmol/l, respectively). The mean peak increase in plasma GH concentration was 9.2 ± 1 and 14.5 ± 8 ng/ml, respectively.

Cardiovascular and other effects of amphetamines

In normal subjects, following (+)-amphetamine (20 mg), there was a mean increase in erect mean arterial pressure (diastolic blood pressure plus one-third pulse pressure) of 13.5 mm Hg, and following (−)-amphetamine (20 mg), of 17.3 mm Hg at the time of peak increase. In patients with narcolepsy, corresponding values were 13 mm Hg and 24 mm Hg. In normal subjects, there was an increase in mean peak pulse rate following (+)-amphetamine (20 mg) of 23 beats/min, and following (−)-amphetamine, 10 beats/min: corresponding figures for narcoleptics, 21 and 17. The maximum increase in blood pressure and pulse rate occurred 30–120 min following the oral administration of amphetamine.

Sweating occurred in three normal subjects and in five narcoleptics after (+)- or (−)-amphetamine (20 mg). Involuntary movements, muscle jerks and oro-facial dyskinesia, did not occur in any subject given amphetamine.

Discussion

Amphetamines increase alertness to approximately the same extent in normal and narcoleptic subjects. This increased arousal is likely to result mainly from the effects of amphetamines on noradrenaline and dopamine systems in the brain. Behavioural changes of arousal due to amphetamines in animals are prevented when catecholamine synthesis is prevented by *p*-amino-methyl tyrosine (Wolf, Rollins, Rowland & Reigle, 1969). However, the dopamine precursor levodopa, the noradrenaline precursor dihydroxyphenylserine, the dopamine agonists bromocriptine and apomorphine, and the noradrenergic agonist clonidine, do not in our experience cause arousal in normal or narcoleptic subjects (Parkes, Baraitser, Marsden & Asselman, 1975). These drugs all have multiple actions distinct from those of amphetamines. However, the alerting action of amphetamine may be partly due to non-catecholamine effects of amphetamines on brain glycogen, fatty acids, and possibly protein synthesis (Hajos & Garattini, 1973; Nahorski & Rogers, 1975; Dewar & Winterburn, 1973).

Amphetamines cause a rise in plasma GH levels in normal subjects. Both isomers are equipotent in this respect. The increase in plasma GH concentration is likely to be due to the action of amphetamines on hypothalamic dopamine systems, but also may result partly from changes in stress, mobility, alertness, blood pressure and blood glucose concentration. The action of amphetamines on dopamine systems is likely to be more important than the action on noradrenaline systems, in respect of GH release. It has proved difficult to determine the role of noradrenaline in GH control in man; however, adrenergic stimulation by clonidine or blockade with propranolol causes a minor rise in circulating GH levels, and phentolamine inhibits the levodopa-induced rise (Imura, Kato, Ikeda, Morimoto & Yawata, 1971). Amphetamine appears to be a less potent stimulator of GH release than levodopa, although the effect of large doses of amphetamine has not been determined owing to the possibility of side effects. (+)-Amphetamine in low oral dosage (10 mg) does not cause an increase in

plasma GH levels; methyl-amphetamine (15 mg i.v.) is as potent as (+)- or (−)-amphetamine (20 mg orally), causing a mean rise in plasma GH concentration of approximately 9 ng/ml in normal subjects (Besser, Butler, Landon & Rees, 1969).

All normal subjects do not respond to either amphetamines or levodopa plus (−)-α-methyldopa hydrazine, but the latter drug causes approximately four times as great a rise in plasma GH levels than amphetamine (20 mg). This difference is likely to result from the different pharmacological properties of amphetamines and levodopa. Receptor stimulation following amphetamines is dependent upon the release of existing catecholamine stores with reuptake blockade, whilst enzymic decarboxylation of levodopa to dopamine within the brain will greatly increase such stores. Levodopa is a much more effective antiparkinsonian drug than amphetamine (Parkes, Tarsy, Marsden, Bovill, Phipps, Rose & Asselman, 1975) which also may indicate that the degree of dopamine receptor stimulation following levodopa is greater than that which results, indirectly, from amphetamine.

Following the oral administration of either (+)- or (−)-amphetamine (20 mg) in both normal and narcoleptic subjects, peak amphetamine blood levels are achieved in 1–2 h, at approximately the same time as maximum arousal occurs. Blood levels remain relatively high for 4 h following dosage, although this is probably dependent upon the rate of amphetamine excretion by the kidney, which is pH dependent (Beckett, Rowland & Turner, 1965). The different behavioural effects of (+)- and (−)-amphetamine cannot be attributed to different concentrations of amphetamine achieved in the plasma, and the brain is readily penetrated by both isomers (Axelrod, 1970). During long term treatment, approximately a third of patients with narcolepsy become tolerant to the alerting effect of amphetamines, and require progressively higher doses. The mechanisms of amphetamine tolerance are not well understood. In the narcoleptic patients we studied who had previously become tolerant, peak blood amphetamine levels following a standard oral amphetamine load were similar to those of non-tolerant subjects. Also, in all subjects, peak plasma amphetamine levels did not vary with the duration of treatment. However, in a different patient group, amphetamine addicts, Gunne & Ånggård (1973) showed that the plasma elimination rate for amphetamines was increased in dependent as compared with drug-naive subjects.

Narcoleptics appear to be fairly unresponsive to the effect of amphetamines and levodopa plus (−)-α-methyldopa hydrazine on plasma GH levels. We have not investigated GH responses in narcoleptics to other stimuli, such as stress or insulin hypoglycaemia. The human pituitary contains around 5 mg GH (Tanner, 1972), and only 1–2% of this is released in a single burst sufficient to elevate blood levels to around 30 ng/ml (Frohman & Bernadis, 1970). It is unlikely, therefore, that GH stores are depleted in narcoleptics either as a consequence of the sleep disturbance accompanied by periodic GH release during a 24 h cycle, or treatment. The chronic treatment of parkinsonism with levodopa does not cause failure of GH release (Parkes, Debono & Marsden, 1976): by analogy, the chronic treatment of narcoleptics with amphetamine, a less potent releasing drug, would seem unlikely to deplete GH stores. The cause of the failure of catecholamine-GH response in narcoleptics is uncertain. Were a catecholamine receptor defect to blame, if this was widespread, other clinical signs, such as dwarfism, hyperprolactinaemia or parkinsonism, might be expected. These do not occur. Most narcoleptics have a normal spontaneous GH rise accompanying slow-wave sleep throughout the 24 h cycle. Catecholamine-stimulation and slow-wave sleep stimulation of GH release may depend on two different mechanisms, only one of which is abnormal in narcolepsy.

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