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The role of Sibutramine in the treatment of obesity and a hypothesis on its possible psychological effects

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TITOLO
Il ruolo della Sibutramina nel trattamento dell'obesità e di una ipotesi sui possibili effetti psicologici

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Summary
Sibutramine is known to be effective in the treatment of obesity and is used worldwide by millions. It acts on the central nervous system by inhibiting the neuronal reuptake of serotonin and noradrenaline; thereby also have possible psychologiocal effects. This article reviews animal studies as well as clinical trials done on the role of sibutramine in the treatment of obesity. Also, we hypothesise on possible psychological effects, focussing specific on the inhibition of the reuptake of serotonin in the brain, influencing depression. This article concludes with the hypotheses that patients who have a tendency for depression who uses sibutramine, might end up with ultimate low levels of serotonin in the brain. Also, we hypothesise on the possible potentiated effect of sibutramine and SSRI's on the neuronal reuptake of serotonin.

Riassunto
La sibutramina è nota per essere efficace nel trattamento dell'obesità ed è utilizzata in tutto il mondo da milioni di persone. Agisce sul sistema nervoso centrale inibendo la ricaptazione neuronale di serotonina e noradrenalina; perciò può anche avere possibili effetti psicologici. Questo articolo prende in esame studi su animali e trial clinici condotti sul ruolo della sibutramina nel trattamento dell'obesità. Inoltre, vengono proposte ipotesi sui possibili effetti psicologici che influenzano la depressione, concentrandosi in modo specifico sull'inibizione della ricaptazione della serotonina nel cervello. Concludiamo con l'ipotesi che i pazienti che usano la sibutramina, che hanno una tendenza alla depressione, potrebbero avere alla fine bassi livelli di serotonina nel cervello. Inoltre, si ipotizza il possibile effetto potenziato di sibutramina e SSRI sulla ricaptazione neuronale di serotonina.

Introduction

Body mass reduction methods have become a major part of our world, especially in the advertisement industry. Millions of different products are marketed as being the quick and easy way to losing the unwanted fat rapidly during a very short period. Howe-

ver, specific knowledge of the active constituents in many of these products is of utmost importance before taking it, since many of these products may have potential adverse affects. Also, often the necessary supervision and informed consent from either the seller or a health care professional may be lacking. To decrease body mass slowly is the safest way, since the rapid reduction in body mass has several adverse effects such as loss of fat-free mass (1, 2) Most of these products are specifically aimed at the obese population, since obesity has become the most prevalent metabolic disease in the world.

Obesity is a chronic disease characterized by the increase in body fat stores and is measured by the calculation of a person's Body Mass Index [BMI = weight (kg)/ height $(m)^2$]. Normal range of BMI would be between 18.5 and 24.9 whereas overweight is characterized by a BMI of more than or equal to 25. Pre-obesity is classified according to a BMI of between 25.0 and 29.9, obesity class 1 as 30.0-34.9, obesity class II as 35.0-39.9 and obesity class III as a BMI of above or equal to 40.0 (3, 4). Obesity is associated with a number of co-morbid conditions including hypertension, diabetes, dyslipidemia, atherosclerosis, osteoarthritis, cancer as well as chronic renal failure (5). An obese state will develop when the amount of energy intake of a person, chronically exceeds the total amount of energy burnt by the individual (6).

Sibutramine is an example of a weight-reducing agent and is known as an anti-obesity drug, since it acts by selectively inhibiting the neuronal reuptake of noradrenaline and serotonin.[7] This article focuses on the role of sibutramine in the treatment of obesity and provides a review on the animal and clinical studies conducted on sibutramine. We also hypothesise that it may have an effect on the psychological functioning of users due to its impact on serotonin.

Sibutramine

Sibutramine (Meridia®, Reductil®), is a neuropharmacological drug that is widely used as a weight-loss stimulant to treat obesity. Sibutramine is currently the only centrally active FDA-approved drug for the long- term treatment of obesity (8). It acts on the central nervous system by inhibiting the neuronal re-uptake of the neurotransmitters, noradrenaline (NA) and serotonin (5-HT), in the brain (7, 9). These neurotransmitters are associated with the mechanism of satiety and hunger and the inhibition of these neurotransmitters causes an increase in the extracellular synaptic concentration, leading to an increased satiety and a consequent reduction in food intake. It was initially developed as an antidepressant drug in 1980 as it had similar properties than the tricyclic antidepressants, and was first administered to humans in 1984 (10). Sibutramine has two pharmacologically active metabolites, M1 and M2, (the demethylated secondary and primary amines respectively) and these are responsible for the observed hypophagic and weight-reduction effect via the inhibition of the reuptake of the neurotransmitters 5-HT and norepinephrine (11-13). It was also stated that sibutramine stimulates thermogenesis, but is it thought that this secondary action only plays a minor part in the weight reduction (12).

The typical dose of sibutramine is 10 or 15 mg per day and metabolism is mainly by hepatic cytochrome p450 3A4 enzymes and are mostly (77%) renally excreted (13).

Side effects of sibutramine that have been reported include insomnia, dry mouth, constipation, nausea and headache, but it has also been associated with hypertension, increased pulse rate, tachyarrythmias and angina pectoris (11, 13, 14).

A number of contraindications have been reported for sibutramine, these include patients with a history of coronary artery disease,

heart failure, arrhythmias and cerebrovascular disease. Sibutramine is also contraindicated in patients with inadequately controlled hypertension, bulimia and anorexia nervosa. Pregnant and lactating woman should also avoid using sibutramine, as well as patients with severe renal and liver dysfunction and also narrow angle glaucoma. Furthermore, it is contraindicated in patients treated with monoamine oxidase inhibitors (MAOI,s) and selective serotonin reuptake inhibitors (SSRI,s) (15).

Animal studies

A number of animal studies have been used over the years to study the effects of sibutramine. In a study done by Foltin in 2006, the author examined the effect of sibutramine on the appetite and food consumption in primates. The researcher used dexfenfluramine as positive control to compare to the effects of sibutramine. In this study it was found that subutramine causes a decrease in the consummatory behaviour in baboons, and with this they also reported a modest decrease in appetitive behaviour in these animals. The results of this study also suggested an inter-sex difference, with the female animals showing a greater response to a number of the sibutramine doses administered, than the males (16)

Many studies using rats as their rodent model of choice, reported on the reduction of food intake in these animals after oral or i.p. injection of sibutramine, revealing the role of this weight-loss product on satiety mechanisms (8, 17). The animals were fed a high fat/high sucrose diet, and were systemically treated with doses of sibutramine ranging from 0.5, 1.0 and 3.0 mg/kg. The authors found a dose-dependent reduction in food intake with no observable alteration in water intake and locomotor activity (8).

LeBlanc and Thibault in 2003 investigated the effect of sibutramine on macronutrient selection in male en female Wistar rats. Animals from both sexes were divided into three experimental groups and each group were on a different set of three sensorily contrasting macronutrient-specific diet rich in carbohydrates, fats and proteins. The authors administered sibutramine at a dosage of 10 mg/kg and found a decrease in carbohydrate and fat intake at all data points, regardless of diet and gender. Furthermore, they found the effect of sibutramine on protein intake to be diet- and gender- specific (18).

Clinical trials

In 2002, Luque and Ray reported on a number of clinical trials published on the role of sibutramine in the treatment of obesity. Many clinical trials consistently reported on the effective reduction in weight in patients treated with sibutramine in doses ranging from 10-20 mg/day (11).

In 2006, Lechin and co-workers investigated the neurochemical, neuroautonomic and neuropharmacological effects of 15mg oral dosage of sibutramine in healthy patients (9). The authors measured the levels of the circulating neurotransmitters, blood pressure and heart rate. The authors found an increase in NA and NA/Ad ratio as well as in increase in diastolic blood pressure. They also found a slight increase of DA during a specific time period. With regards to systolic blood pressure and heart rate, no significant increase could positively be correlated with the NA/Ad ratios. With these results the authors concluded that sibutramine stimulates neural sympathetic activity but not adrenal activity in healthy subjects (9).

A question that also arises is weather sibutramine has the ability to maintain weight loss in patients who have been on a low-calorie diet.

In some studies researchers have combined pharmacotherapy with low-calorie diets, as was done by Apfelbaum and co-workers in 1999. They investigated the efficacy and tolerability of sibutramine in the long-term maintenance

of weight loss after the patients has been on a very-low calorie diet for four weeks. Patients with a BMI of greater than 30 were included in the study and those individuals who lost 6kg or more during a four week trial on a very-low calorie diet were assigned to treatment with 10mg/ day sibutramine for 1 year. With the results obtained the authors concluded that sibutramine is indeed effective in the maintenance of weight loss in patients for up to 1 year, after the very-low calorie diet (19).

In another double-blind, randomised, placebo-controlled study in 2005, the authors investigated the effects of sibutramine-induced weight loss on the cardiovascular system in obese patients. Sibutramine was administered at a dosage of 15 mg, and patients with a BMI of between 30 and 40 kg/m^2 were included in the study. Their body weight, BMI, blood pressure, echocardiographic LV mass, cardiac output and diastolic function were monitored. They found that, in combination with a hypocaloric diet, sibutramine increases weight loss in the obese patients and these weight changes positively affects reduction in blood pressure and reduction in LV mass which are markers of preclinical cardiovascular diseases (20).

The impact of sibutramine on the cardiovascular system has also been investigated extensively by many researchers since the inhibition of noradrenalin uptake by sibutramine is thought to increase blood pressure as well as pulse rate (15). Blood pressure increases were found after treatment with sibutramine in patients with and without previous history of hypertension. In 2008, Florentin and co-workers suggested that sibutramine is not contraindicated in well-controlled hypertensive patients but that these patients must be monitored frequently to monitor their blood pressure (15).

Psychological aspect and hypotheses

The fact that sibutramine acts on the central nervous system by inhibiting the neuronal re-uptake of the neurotransmitters, noradrenaline (NA) and serotonin (5-HT) in the brain, makes it relevant to investigate its role in possible psychological events. Therefore, aside from its weight-reduction effects, recurrent seizures, psychotic episodes and catatonic symptoms, related to the use of sibutramine, have also been reported on by some researchers (21-24).

Figures 1-6 are schematic representations of the synaptic cleft, explaining the secretion and reuptake of serotonin and factors influencing the latter. Under normal conditions, 5-HT is released from the presynaptic neuron into the synaptic cleft, and reuptake takes place via the 5-HT receptors (Fig. 1). Sibutramine blocks the reuptake of serotonin, which will lead to an increase in the concentration of 5-HT in the synaptic cleft (Fig. 2). Depressive patients (Fig. 3) have low levels of 5-HT in the synaptic cleft due to low levels in the presynaptic neuron, which causes a lowered auto receptor uptake of 5-HT and ultimately leads to desensitization of the auto receptors (25). When patients who have a tendency to become depressive uses sibutramine, it will lead to very low levels of 5-HT in the synaptic cleft as indicated in Figure 4. Depressive patients have low levels of 5-HT, and with sibutramine blocking the reuptake of 5-HT, it can be hypothesised that the autoreceptors will become even more desensitized as the already low concentration of 5-HT in the synaptic cleft might decrease even more.

Figures 5 and 6 show a hypothesis of neuronal reuptake of serotonin in patients on SSRI treatment and patients on SSRI treatment together with sibutramine use.

Conclusion

Weight-loss products have become a major part of our everyday lives, and numerous different products are available on the market for specifically the treatment of

Figure 1- Neuronal reuptake of serotonin under normal conditions

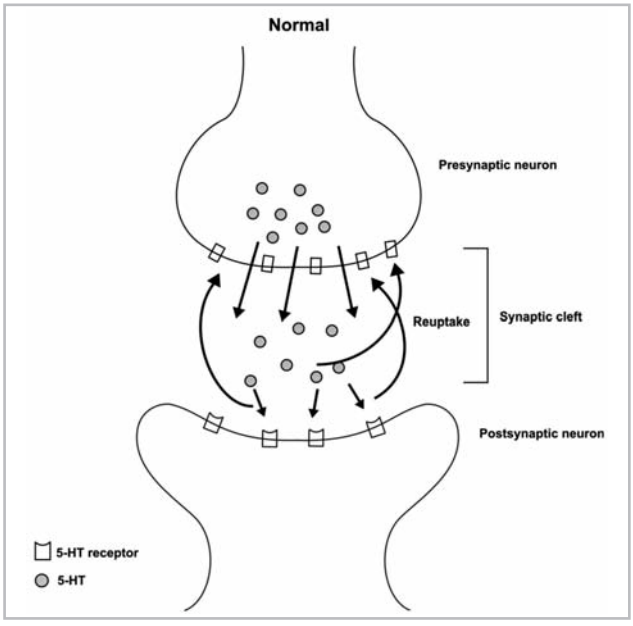


Figure 2 - Blocking of neuronal reuptake of serotonin when on sibutramine treatment

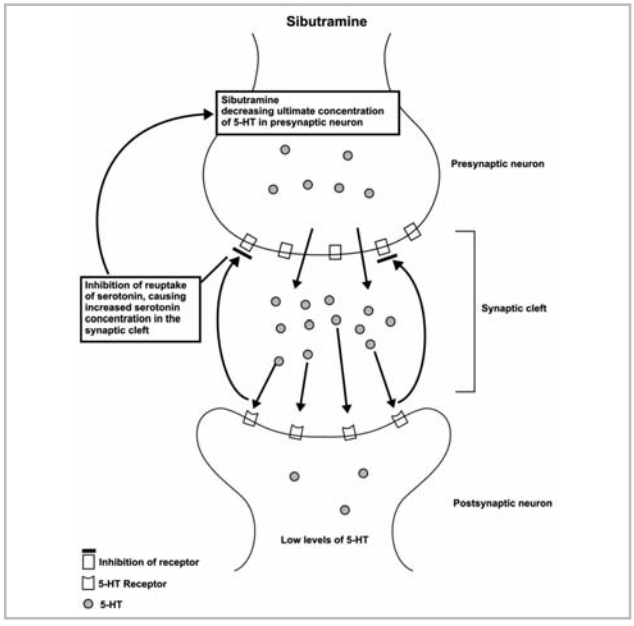


Figure 3 - Neuronal reuptake of serotonin in depressive patients

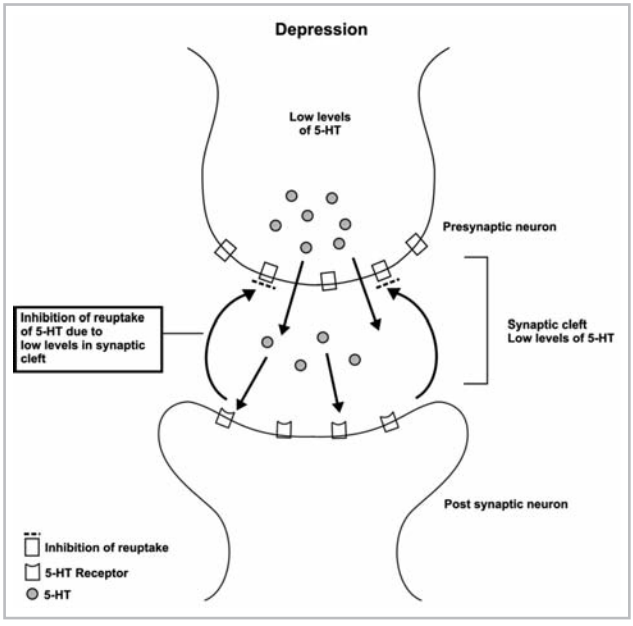


Figure 4 - Neuronal reuptake of serotonin in depressive patients on sibutramine treatment

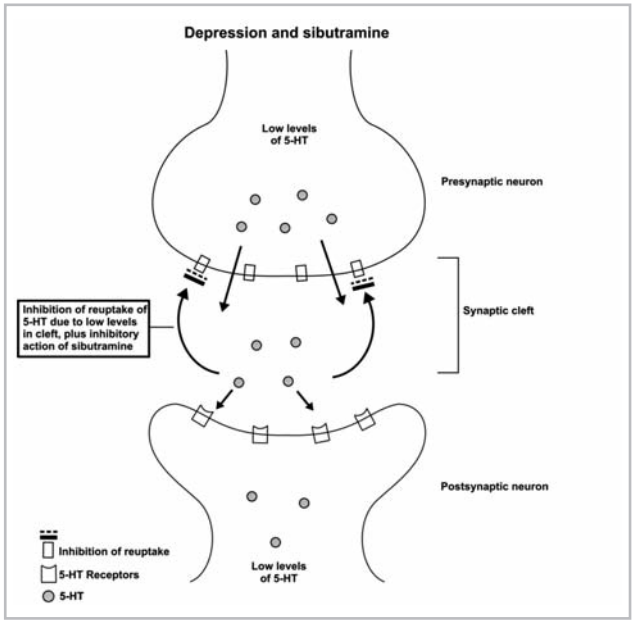


Figure 5 - Neuronal reuptake of serotonin in patients on SSRI treatment

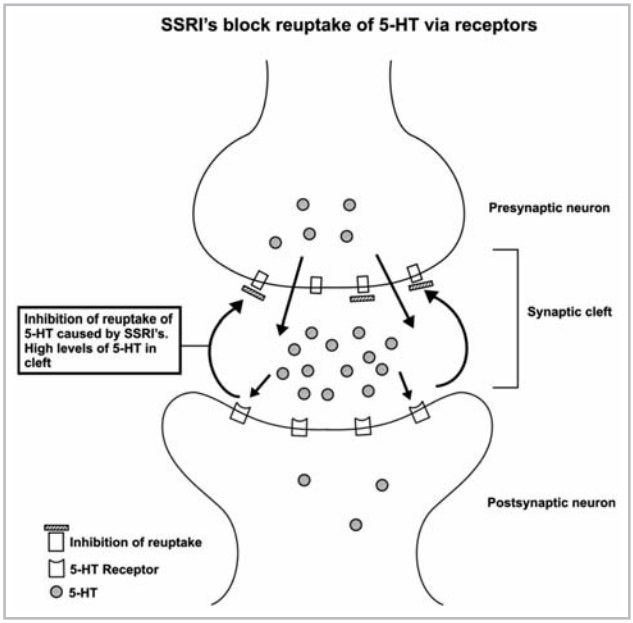
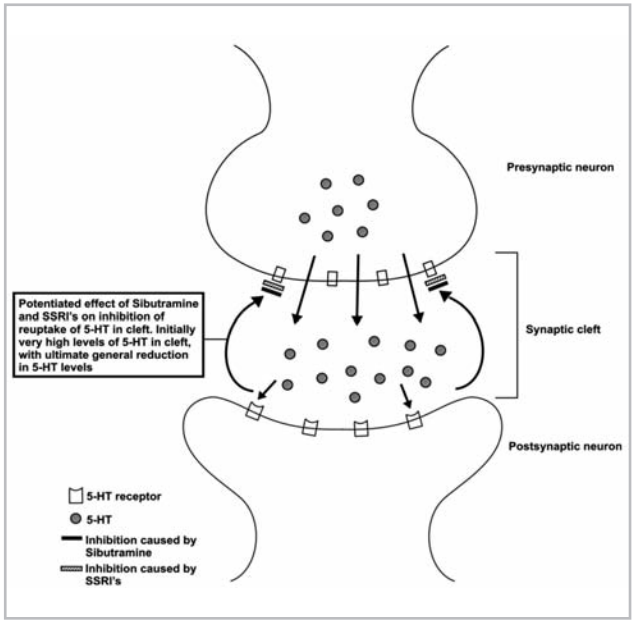


Figure 6 - Neuronal reuptake of serotonin in patients on SSRI treatment with simultaneous use of sibutramine



obesity as obesity has become the number one metabolic disease in the world. This review focussed on the role of sibutramine in the treatment of obesity as well as its possible side effects and contraindications as stated in the literature over a period of time. Numerous animal studies and clinical trials have been conducted to investigate the different properties of this product where it's proven to be effective in the treatment of obesity as well as in the maintenance of weight loss for a period of time. Another important aspect to consider when looking at the effects of sibutramine is its possible psychological effects. In this article we hypothesise on the possible effects on the neuronal reuptake of serotonin when used by depressive patients or patients on SSRI treatment and with this emphasising the importance of specific control in prescribing this product. Also, we hope to make the general, over-the-counter buyer, more aware of what might happen psychologically when using products containing sibutramine.

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