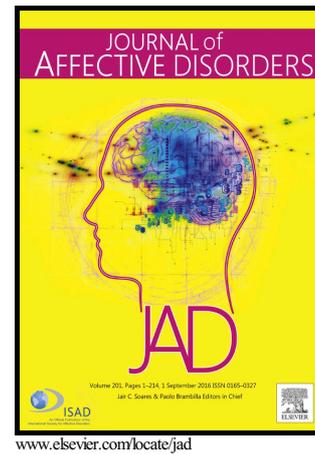


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## Sugars, Exercise and Health

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### Abstract

#### *Background*

There is a direct link between a variety of addictions and mood states to which exercise could be relieving. Sugar addiction has been recently counted as another binge/compulsive/addictive eating behaviour, differently induced, leading to a high-significance health problem. Regularly exercising at moderate intensity has been shown to efficiently and positively impact upon physiological imbalances caused by several morbid conditions, including affective disorders. Even in a wider set of psychiatric diseases, physical exercise has been prescribed as a complementary therapeutic strategy.

#### *Method*

A comprehensive literature search was carried out in the Cochrane Library and MEDLINE databases (search terms: sugar addiction, food craving, exercise therapy, training, physical fitness, physical activity, rehabilitation and aerobic).

*Results:*

Seeking high-sugar diets, also in a reward- or craving-addiction fashion, can generate drastic metabolic derangements, often interpolated with affective disorders, for which exercise may represent a valuable, universal, non-pharmacological barrier.

*Limitations*

More research in humans is needed to confirm potential exercise-mechanisms that may break the bond between sugar over-consumption and affective disorders.

*Conclusions*

The purpose of this review is to address the importance of physical exercise in reversing the gloomy scenario of unhealthy diets and sedentary lifestyles in our modern society.

**Graphical Abstract**

***Depicting of the brain reward cascade dysfunction.*** Sugar over-consumption alters the reward system resulting in a deficiency that preludes to a sugar addiction. This vicious circle may be attenuated by physical exercise via enhancement of the neurotrophic factor (BDNF) and the dopaminergic system.

**Abbreviations:**

Akt, protein kinase B; ACC, anterior cingulate cortex; ADHA, attention-deficit hyperactivity disorder; BED, binge eating disorder; BDNF, brain-derived neurotrophic factors; CREB, cAMP response element-binding protein; Ca<sup>2+</sup>MK, Ca<sup>2+</sup>-calmodulin-dependent protein

kinases; CVD, cardiovascular diseases; DA, dopamine; DD2R, dopamine receptors; DSM, diagnostic and statistical manual of mental disorders; ERK, extracellular signal-regulated kinase; fMRI, functional magnetic resonance; FNDC5, fibronectin type III domain containing 5; HbA1c, glycosylated hemoglobin; NCDs, noncommunicable diseases; PET, positron emission topography; PGC-1 $\alpha$ , peroxisome proliferator receptor  $\gamma$  coactivator 1 $\alpha$ ; PI3-kinase, phosphoinositide 3-kinase; POMS, profile of mood states; RCT, randomized controlled trial; OFC, orbitofrontal cortex; SSRI, selective serotonin reuptake inhibitors; SUD, substance use disorder; TrkB, tropomyosin-related kinase B; YFSA, Yale Food Scale Addiction.

**Keywords:**

Sugar addiction, Exercise therapy, binge/addictive eating behaviors

**1. Introduction**

Highly processed foods may be associated with “food addiction”, and therefore considered “addictive”, as they share common features with drugs of abuse (Schulte et al., 2015). In fact, due to the high concentrated doses and the rapid rate by which refined carbohydrates are absorbed into the system, highly processed foods, rich in sugar content, are implicated in addictive-like eating behavior (Henningfield and Keenan, 1993; Monteiro et al., 2010). A growing body of neurochemical and genetic evidence suggests that food addiction is similar to psychoactive drug addiction (Ahmed et al., 2013; Salamone and Correa, 2013). Some recent experimental research in laboratory rats has revealed that sugar and sweet reward can be even more addictive than traditional substances of dependence and abuse, like cocaine (Lenoir et al., 2007; Volkow et al., 2013). Rats allowed to choose between cocaine and sweet fluids (suchrose or saccharine solutions) in discrete trials procedures have a strong preference for the non-drug reinforcer (Cantin et al., 2010; Kendig,

2014). In addition, food has both homeostatic and hedonic components, therefore emerging as a potent, natural, conditioning stimulus to the brain's reward pathways (Rada et al., 2010; Volkow et al., 2011). However, there is a wide spectrum of overeating, ranging from casual overindulgences to pathological drives to consume palatable food. Either way, the resulting addictive appetite behaviour (up to bingeing) might be coupled to the contemporary obesity pandemic, with obesity being reinforced by this surge of palatable reward (Hone-Blanchet and Fecteau, 2014).

On a side, high glycemic food is coupled with postprandial hyperglycemia and hyperinsulinemia which, in turn, could trigger hunger and ultimately result in weight gain (Benedini et al., 2011). Despite multiple studies have questioned whether sugar is the unique cause of diabetes (not specifically addressed in any randomized-controlled-trial) or obesity (putatively resulting from high sucrose-, high-fructose corn syrup-, sweetened beverages consumption), most of them have failed in ratifying a sole linkage (Rippe and Angelopoulos, 2016). It is rather likely that the primary pathological event is excess energy intake leading to overweight, obesity, and type 2 diabetes. Neither sugar consumption *per se*, nor a single nutrient would uniquely cause these morbid conditions (Hall et al., 2012). Once adjustments for total energy intake are made, in fact, typically many published studies have shown no relation between sugar consumption and body weight. In meta-analyses of randomized controlled trials, when sugar is replaced with energy-equivalent macronutrients, no increase in body weight occurs (Kaiser et al., 2013; Malik et al., 2013; Te Morenga et al., 2013). Simply, especially in modern westernized countries, large availability (ubiquity, affordability) of any sort of palatable food becomes more and more responsible for the dramatically increasing rate of obesity. According to animal evidence, the sugar-bingeing model mimics addiction-like phenotype but does not

necessarily induce obesity (Avena, 2007; Colantuoni et al., 2002; Rada et al., 2005; Wideman et al., 2005). In this model, there is still presence of tolerance, withdrawal, cross-sensitization and neurochemical modulation (Hone-Blanchet and Fecteau, 2014). Both food and drug rewards foresee the activation of the dopamine-systems.

On the other extreme of the overeating continuum, in the *Reward Deficiency Syndrome*, genetic and epigenetic phenomena lead to impairment of the brain reward circuitry that causes hypo-dopaminergic function and abnormal craving behaviour (Blum et al., 2014). Dopamine (DA), a powerful neurotransmitter, controls feeling of well-being and it is activated by a variety of conditions like over-consumption of carbohydrates and alcohol, intake of crack cocaine, cocaine, opioids, abuse of nicotine, aggressive behaviours, sexual arousal. So too does physical exercise, especially sustained endurance exercise.

Animal studies (Colantuoni et al., 2002; Cottone et al., 2009; Hernandez and Hoebel, 1988) and fMRI in humans (Wang et al., 2001) support the hypothesis that similar brain circuits are disrupted in obesity and drug dependence, implicating a specific DA-modulation of reward circuits in pathological eating behaviors (Murray et al., 2014).

Compulsive overeating and binge eating disorders are treated with pharmacological (e.g. antidepressant, topiramate) and behavioral strategies, providing variable results. One approach is to increase the amount of physical activity.

In the last decades much evidence has been accumulated documenting the many health benefits of physical activity: regular exercise offers protection against all-cause mortality, primarily by lowering the atherogenic profiles (Blair et al., 2001), reduces rates of CVD, hypertension, metabolic syndrome, type 2 diabetes, breast cancer and colon cancer. Furthermore, physical training has been proved to be

effective in the treatment of several of these diseases, including ischemic heart diseases (Jolliffe et al., 2000) and heart failure (Piepoli et al., 2011).

Beyond its frank anti-inflammatory effects (Codella et al., 2015), exercise has been extensively debated as a natural anti-depressant. The psychological benefits of long-term exercise adherence in both clinical and community individuals are well established (Berger and Motl, 2008; Martinsen, 1994; Weyerer and Kupfer, 1994). Exercise can increase resistance to the development of depression and other stress-related psychiatric disorders, such as anxiety and stress itself (Greenwood and Fleshner, 2011). Central reward circuitry, including neurotransmitters and neurotrophic factors, are implicated in the pathophysiology and treatment of stress-related disorders (Nestler and Carlezon, 2006). Even though there is limited knowledge on the effects of physical activity as a treatment of psychological stress-related symptoms, multiple physiological and neuroendocrine mechanisms have been theorized (Greenwood and Fleshner, 2011; Trost and Hauber, 2014). Exercise was found to be a naturally reinforcing and rewarding activity (Trost and Hauber, 2014).

Here, we want to review how physical exercise might exert a number of health benefits that can promote positive well-being, particularly by neuromodulation, so to counter many of the negative addictive behaviours, specifically over-consumption of refined carbohydrates.

## **2. Methods**

A systematic literature search was carried out in the Cochrane Library and MEDLINE databases for studies published in English (1996 January to 2016 June) combining the terms “sugar addiction”, “food craving”, “exercise therapy”, “training”, “physical fitness”, “physical activity”, “rehabilitation and aerobic”. We examined reference lists

in original articles and reviews. Study search was performed both electronically and by following up references quoted in relevant paper. We have primarily identified systematic reviews and meta-analyses and thereafter selected additional controlled trials. Case reports, expert opinions, article unavailable in English were excluded.

### **3.Results**

#### **3.1 Study selection**

The initial electronic database search yielded 1.284 hits. Three additional studies were found from other sources. Following first screening, 788 studies were excluded: 311 were duplicated; 473 focused on other subjects; 4 case-reports.

Thereafter, 499 remaining studies were further examined for final consideration: 2 studies were removed because unavailable in English and 2 studies were not located. Finally, 495 studies were selected (Figure 1). A synoptic table of the studies analyzed is offered (Table 1).

#### **3.2 Added-sugars food consumption and addictive-like eating behaviours**

##### *3.2.1 Sugar consumption*

World Health Organization (WHO) defines overweight and obesity as abnormal or excessive fat accumulation that may impair health (“WHO | Obesity and overweight,” 2016). Diverse causes may contribute to the obesity pandemic: energy over-intake, easy availability to hyper-palatable foods, physical inactivity amongst others. In the past, sugars and refined carbohydrates were proposed, with modest evidence, as more obesogenic than other nutrients (Yudkin, 1971), however it seems reasonable that certain foods such as added-sugars food may be capable of triggering

addictive responses in some individuals, leading at last to compulsive and obsessive overeating (Gearhardt et al., 2009a).

Several fallacious convictions on sugar consumption have been generated in the previous decade (Rippe and Angelopoulos, 2016), raising concerns among a number of international organizations, granting agencies and public health policymakers (Moran et al., 2016). Nevertheless, a number of recent studies ascertained the lack of a substantial, unique causative role of sugar in the increasing rates of chronic-degenerative diseases (Kahn and Sievenpiper, 2014; Welsh et al., 2011). Despite the introduction of new caloric sweeteners, fructose intake has not massively increased since 1920; it has been decreasing since 1999 and there is no correlation with obesity (Lowndes et al., 2014; White, 2013). Consumption of added sugars has not augmented disproportionately as the modern diet expanded over the past 40 years; on the contrary it has been declining for more than a decade (Marriott et al., 2009; White, 2013). This is supportive for another real contributor to the pandemic “diabesity”: the imbalance between energy intake and expenditure.

Although glucose is the dominant sugar in the human diet, diverse research protocols biased biochemical outcomes by using large dosages of fructose or glucose, consumed in isolation, and delivered atypically (e.g. intravenously) (Rippe and Marcos, 2016; Rippe and Tappy, 2016). Caloric sweeteners, instead, show a composition in which glucose and fructose are consumed together and in a relatively equal amounts from high-fructose corn syrup, sucrose, honey, and grape-juice concentrate. Extreme dosing (from 30 up to 60% of total energy intake) and overfeeding studies clearly provoke metabolism abnormally, therefore resulting “non-physiological” to assess risks in humans (White, 2013). According to up-to-date systematic reviews and meta-analyses, levels up to 30% of energy from added sugars

do not increased risk of obesity, diabetes, CVD, provided that sugars are isocalorically replaced by other carbohydrates (Lowndes et al., 2015, 2014). Within a hypercaloric global scenario, some studies identify 20% of energy or more from added sugar as a plausible upper limit of recommendation, considering that  $\geq 20\%$  of energy from sugar induce a significant rise in triglycerides (US Department of Agriculture, 2010). Current guidelines of WHO advise that sugar comprise  $\leq 5\%$  of total energy intake, beyond the previous stated upper limit of 10% introduced in 2003 guidelines. WHO is particularly concerned on consumption of free sugars, in the form of sugar-sweetened beverages, that may result in both reduced intake of foods containing more nutritionally adequate calories and an increase in total caloric intake, leading to an unhealthy diet, weight gain and increased risk of noncommunicable diseases (NCDs). WHO is likewise greatly preoccupied by the role played by free sugars play in the development of dental diseases, particularly dental caries, which accounts for 5-10% of health budgets in industrialised countries (“WHO | Obesity and overweight,” 2016).

### *3.2.2 Addictive-like eating behaviours*

Volkow and O’Brien were among the first to question whether obesity should be included as a brain disorder (Volkow and O’Brien, 2007). Many others have reported that highly palatable, added-sugars foods, could be authentically “addictive”, at least in a correspondent ratio of exposed people (Avena et al., 2008). The Yale Food Addiction Scale (YFSA) estimates that nearly 10-20% of people would present addiction-like symptoms toward hyperpalatable foods (Gearhardt et al., 2009b) - a quota not dissimilar from that one of cocaine or heroin users, which become indeed “dependent”. A substantial body of research supports the

neurobiological leverage of natural rewards implicated in the development of addictive disorders (Avena, 2007; Gearhardt et al., 2011; Volkow et al., 2013; Ziauddeen et al., 2012).

*Animal models* – Rats have been shown to develop most of the behavioral signs of addiction, after prolonged self-administration of drugs, including cocaine and sugar (Lenoir et al., 2007). When rats are offered an exclusive choice, self-administered, between sucrose or saccharin and cocaine, they mature a robust preference for sugar. That scenario persisted when the exclusive choice was between nicotine and sucrose (Lesage, 2009): rats go for sugar, likewise. These findings might suggest that sugar and its sweet reward not only substitute substances of abuse but it might be even more rewarding and attractive than the latter. It is also true that added-sugars food may modulate brain activity via more natural routes than drugs of abuse: not only through brain postabsorptive glucose signaling (Grayson et al., 2013) but also via the stimulation of peculiar sweet taste cells in the mouth and the gut (Brown and Rother, 2012; Yarmolinsky et al., 2009).

One could argue that sugar and sweet reward are though less potent than classical drugs in brain dopamine signaling (Lenoir et al., 2007). However, when mice were offered to choose between high concentration of sucrose and optogenetic stimulation of dopaminergic neurons, mice preferred sucrose again (Adamantidis et al., 2011). Although optogenetic stimulation of dopaminergic neurons can be rewarding alone, there it might be some competitive drives that make sugar more rewarding than brain dopamine (Adamantidis et al., 2011; DiLeone et al., 2012; Lenoir et al., 2007).

Remarkably, animal evidence indicated that sugar consumption can induce negative effects on cognitive function, precisely spatial learning and memory,

even when sugar doses are comparable with human ones (and without weight gain, besides) (Kendig et al., 2013). In rodent models, anxiety and mood appeared not to be affected by long-term sugar consumption (Cao et al., 2007; Chepulis et al., 2009). It remains harsh to extrapolate cognitive effects of sugar from animal models and transferring them into the real human world. First, it is difficult to deal with several procedural factors such as amount of sugar ingested, age, animal strain and which aspect of behavioral measures is investigated (and expected to be affected, proportionally to the sugar consumed). Secondly, it is important to consider the extent by which cognitive effects of sugar might be connected with putative metabolic impairments (Kendig, 2014).

*Human studies* – Considering that food addiction encompasses symptoms ascribable to binge-eating-disorders (BED) and obesity, several studies investigated the neural common substrates of sugar reward by means of functional magnetic resonance imaging (fMRI) and positron emission topography (PET). Food cravings in response to food cues have demonstrated to boost brain activity in the caudate and insula, as it occurs in drug addicts (Teegarden and Bale, 2008, 2007; Wang et al., 2004). These areas are also activated in cravings observed in substance use disorder (SUD) (Goldstein and Volkow, 2011). In a fMRI of 48 females drinking a chocolate milkshake, YFSA scores were positively correlated with food cues (Ng et al., 2011). Moreover, subjects with higher YFSA scores showed increased activation of anterior cingulate cortex (ACC) and medial orbitofrontal cortex (OFC) (Ng et al., 2011; Stice et al., 2008), which was previously associated with a response induced by the presentation of food items (Goldstein and Volkow, 2011). Decreased reward experience after receiving a food reward was found to be associated with the “tolerance” registered in SUDs.

Imaging studies in obese individuals have shown that high BMI and overeating entail neurobiological reward pathways similarly seen in SUDs (Volkow et al., 2012). Increased food reward (viewing high palatable food stimuli) and diminished satisfaction after ingestion of palatable food (reduction of striatal DA signal) could promote weight gain and overeating in obese people. However, obesity remains a very complex problem as indicated by controversial data existing on the association between obesity and low density of DA receptors (DD2R) (Volkow et al., 2008): some authors have argued that this might be producing differences in personality rather than as an indication of physical addiction (Benton and Young, 2016).

### **3.3 Treatments for food addiction**

#### *3.3.1 Diagnosis*

Literature is not cohesive in considering food addiction as an authentic dependence disorder with a proper, genuine phenotype (Carlier et al., 2015; Rippe and Marcos, 2016; Westwater et al., 2016). For diagnostic criteria we should refer to the YFSA scale (Davis et al., 2011; Gearhardt et al., 2009b) and the fifth edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) (American Psychiatric Association, 2013). The former, validated for food addiction, shows several similarities with SUD symptoms and criteria included into the DSM-5. Some addiction-traits (like food cravings and binges) are detectable in BED and obesity (Brownell and Gold, 2012), but both conditions are not mutually inclusive. Food addiction, despite genetic similarities between compulsive overeating and addiction phenotypes (Carlier et al., 2015), has not been univocally recognized as a valid, real phenotype (Hone-Blanchet and Fecteau, 2014; Westwater et al., 2016). Food

addiction fits DMS-5 criteria of SUD and shares SUD brain reward networks. However, withdrawal symptoms (dysphoria, distress) are clinically unconvincing in human food addiction and, besides, “tolerance” foresees a different concept for intoxication rather than satiety (Hone-Blanchet and Fecteau, 2014).

After all, within a broad spectrum of specific phenotypes like obesity and BED, food addiction, as such, might elucidate the complex risk factors (neuropsychiatric, psychological and environmental) of obesity.

### *3.3.2 Therapeutic approaches*

The empirical base regarding therapy for BED, food/sugar addiction, and obesity remains quite elusive and it is still in its early stages. Nonetheless, additional research is stimulated to offer cutting-edge solutions and promising insights.

Psychological-behavioral approaches integrated with medical support yield superior outcomes as compared with acute pharmacotherapy-only and over long-term follow-up.

Among formal eating disorders, BED is more prevalent than anorexia and bulimia nervosa, homogeneously widespread regardless of gender, ethnicity and age (Hudson et al., 2007; Kessler et al., 2013). BED is robustly associated with rapid weight gains, obesity and related psychiatric comorbidities, and it shares traits with other eating disorders, including sugar/food addiction (Grilo et al., 2009, 2008).

Current treatments for BED comprise antidepressants (SSRIs), antiepileptics (topiramate), “attention-deficit hyperactivity disorder” (ADHD) medications, “anti-craving” medications and anti-obesity medications, most of which were withdrawn from the market (sibutramine, rimonabant) due to dangerous side-effects (Reas and Grilo, 2015). The limited number of RCTs (mostly performed in US, funded by

pharma-industry) and investigators involved, small size samples (excluding many potential BED patients with psychiatric comorbidities), very few follow-ups, represent a meaningful *caveat* to the research conducted so far in the field. Finally, a quite considerable number of patients, even in pharmacotherapy-only studies, did not achieve the expected results in terms of abstinence from binge eating, weight loss even in the short-term (Reas and Grilo, 2015).

In closing, larger and longer studies with comprehensive assessments of psychopathology and metabolic changes are warranted in order to reach generalizability in diverse clinical settings.

### **3.4 Effects of exercise**

Depending on intensity, type and duration, physical exercise is a potent inducer of physiological changes at different levels, pertaining stress hormones, energy crisis and oxidative stress. Beyond its physiological action, exercise has been shown to modulate mood states so to gain psychological benefits in both clinical and community individuals (Yeung, 1996).

#### *3.4.1 Hypoglycemic effects via insulin mimetic/sensitizing action*

Physical exercise induces glucose-lowering effects by ameliorating insulin sensitivity thus enabling the achievement of better positions on the glucose-tolerance curve in any subject. Mechanisms cover augmented postreceptor insulin signaling (Dela et al., 1993), increased glucose transporter (GLUT4)mRNA and protein (Dela et al., 1994), elevated glucose synthesis activity (Ebeling et al., 1993) and hexokinase activity (Coggan et al., 1993), lower release and higher clearance of free fatty acids (Ivy et al., 1999), increased glucose delivery to the muscles via an inflated muscle

capillary network and blood flow (Coggan et al., 1993; Saltin et al., 1977). Enlarged blood flow is in turn accompanied by sheer stress on the vessel wall, which stimulates endothelial nitrogen oxide, ultimately resulting in muscle cell relaxation and vasodilation (McAllister et al., 1995). An exercise-induced hypoglycemic effect can be expected as a result of a heightened glucose uptake in insulin-sensitive tissues with a lower consumption of insulin. A decrease in hyperinsulinemia has been also observed with (Yamanouchi et al., 1995) and without dietary intervention (Dela et al., 1995). Aerobic- and resistance training are both beneficial for people with type 2 diabetes, although a combination of both may be even more efficacious in these individuals (Church et al., 2010). Glycemic control (HbA1c) seems to be even more ameliorated by high-intensity exercise rather than low-intensity exercise. Resistance and aerobic exercise are also recommended as effective treatments for metabolic syndrome. Physical training augments energy expenditure and induces lipolysis, therefore reducing fat mass, if energy balance is not compensated by an even-up caloric intake (Pedersen and Saltin, 2015). For weight loss, a considerable amount of moderately intense aerobic exercise ( $\geq 60$  min/day) is encouraged, especially in combination with strength training.

In all these morbid conditions, recommendations must be tailored *ad hoc*.

#### 3.4.2 Favorable alteration of mood states

Both physiological and psychological mechanisms have been proposed for the mood-enhancing effects of exercise. A reduction of negative mood states has been registered for most forms of aerobic exercise as well as anaerobic exercise (weight lifting, yoga). Profile of mood states (POMS) has been measured, with variable outcomes, in different-intensity exercise settings (Berger and Motl, 2008; Yeung,

1996). Although several studies accounted greater mood effects only for very active people, exercise-enhanced mood usually lasts for 3-4 hours post-exercise within general population (Dyer and Crouch, 1988; Molloy et al., 1988). Moreover, certain effects may persist for as long as 24 hours following an acute, single bout of exercise (Maroulakis and Zervas, 1993). Much interest has been given to the actions of endorphins within the central nervous system (Steinberg and Sykes, 1985; Thorén et al., 1990). Among other psychological theories, the “distraction” argues that enhanced mood would not be induced by a specific action of exercise, but rather by a relieving break that diverts from one’s negative and troublesome thoughts (Bahrke and Morgan, 1978; Hallgren et al., 2010). The mastery hypothesis (Simons et al., 1985) and the self-efficacy theory (Bandura, 1989) focus on the post-exercise sense of revitalization and achievement, thereby promoting positive moods.

### *3.4.3 Treatment for psychiatric disorders*

Modest evidence supports a positive effect of exercise on depression symptoms (Josefsson et al., 2014). Cross-sectional and prospective studies document an inverse relationship between levels of physical fitness and depression (Tolmunen et al., 2006). Depression incidence is lower in regularly physical activity practitioners (Paffenbarger et al., 1994). Exercise has been found to be preventive of depression, although a causative-role remained unestablished. Possible mechanisms include: a) virtuous cycle of an healthy lifestyle made up of physical exercise and sociality (Pedersen and Saltin, 2015); b) the amount of beta-endorphins and monoamine concentrations (Mynors-Wallis et al., 2000); c) stimulated growth of nerve cells in the hippocampus by brain-derived neurothopic factors (BDNF) (Pedersen et al., 2009).

Multifactorial explanations have been drawn for the positive effect of exercise in the treatment of anxiety, as outlined for depression treatments (healthy lifestyle, distraction). Recommendations point at low-intensity aerobic exercise for the beginners, then a steadily progressive increase in intensity (moderate) and duration is expected (Herring et al., 2010).

Other studies indicate that physical activity is capable of “distracting” patients affected by psychological stress and schizophrenia, diverting their attention and alleviating their problems (negative-, abnormal thoughts, hallucinations). Again, intense physical training was shown to increase BDNF levels in the brain, leading to an increase of the hippocampus volume, which is low in these psychiatric patients (Pedersen et al., 2009).

#### *3.4.4 Neuromodulation: BDNF and dopaminergic activity*

BDNF is a member of the neurotrophin family of growth factors along with nerve growth factor; it serves as a neurotransmitter modulator, essential in neuroplasticity as it supports differentiation, maturation and survival of neurons in the nervous system (Bathina and Das, 2015). Furthermore, emerging evidence suggests that BDNF serves widespread roles in the regulation of energy homeostasis by governing food intake and physical activity, and by modulating glucose metabolism in peripheral tissues: in skeletal muscle, increasing insulin sensitivity; in hepatocytes, decreasing glucose production; in pancreatic  $\beta$ -cells, increasing insulin production (Marosi and Mattson, 2014). BDNF serum levels were found critically diminished in mood disorders (Martinowich and Lu, 2008), depression, schizophrenia (Lu and Martinowich, 2008) and in people under great psychological stress (Knaepen et al., 2010; Marosi and Mattson, 2014). Mice lacking BDNF die shortly after birth due to

abnormalities in the nervous system, they develop obesity (Kernie et al., 2000) and anxiety disorders (Rios et al., 2001). BDNF haploinsufficient mice are hyperphagic, obese and diabetic, but if they are intermittently fasted they improve insulin resistance, obesity as well as their behavioral abnormalities (Duan et al., 2003). BDNF administration peripherally or intracerebroventricularly induces dose-dependent appetite suppression and weight loss in rats (Naert et al., 2006). Consistently with animal observations, inherited BDNF deficiency induces obesity in humans (Gray et al., 2006). Plasma BDNF levels were inversely correlated with fasting glycemia in another human study (Krabbe et al., 2007). Moreover, elevated glucose levels diminished the BDNF produced and released from the brain into the bloodstream.

Interestingly, endurance exercise (running) and other forms of aerobic exercise augment serum BDNF levels (Griffin et al., 2011) and enhance cognitive performance (Winter et al., 2007), also alleviating anxiety and depression in humans (Sartori et al., 2011). Elderly subjects exercising for 4 months exhibited expanded hippocampal blood flow and greater functional connectivity with respect to age-matched controls, suggesting that exercise may hamper age-related cognitive decline (Burdette et al., 2010). In another review, moderate-intensity exercises appeared to be effective in promoting the increase of peripheral serum levels of BDNF in the elderly (i.e.: 55-80 years, walking, 60%VO<sub>2</sub>max/40min/52weeks) (Leckie et al., 2014). This increase has been observed even in elderly with Alzheimer's disease, following acute aerobic exercise (Coelho et al., 2014). A single session of aerobic exercise (running or cycling at 40-60% VO<sub>2</sub>max for 20-90 min) heightens BDNF levels whereas frequent aerobic training amplifies this increment (running or cycling, from 45 min three times a week for 12 weeks, to 60 min five times a week for 6 months, with a range of VO<sub>2</sub>max of 60-90%) (Huang et al., 2014). Thus, exercise seems to enhance both

baseline and end-exercise circulating levels of BDNF (Knaepen et al., 2010), which were found decreased in obesity and type 2 diabetes mellitus.

From a cellular and molecular point of view, running promotes BDNF expression in neurons by activating CREB via  $\text{Ca}^{2+}$  influx- and CaMK-mediated mechanism (Figure 1). Yet, exercise stimulates another muscle protein – FNDC5 – which mediates upregulation of BDNF in neurons, once FNDC5 is provoked by exercise indeed (Marosi and Mattson, 2014).

BDNF also activates TrkB so to enhance synaptic plasticity (learning, memory) (Bathina and Das, 2015) by multiple mechanisms including PI3-kinase-Akt pathway and other extra cellular signal regulated kinases (ERKs 1 and 2) (Figure 1). PI3-kinase and Akt are activated by 2 weeks of running-wheel in the hippocampus of the rats whereas even shorter bouts of exercise augment spatial learning, memory, hippocampal Akt, and CREB activities (Chen and Russo-Neustadt, 2005)(Chen et al., 2006).

As it was described for the reward mechanisms hijacked by drugs of abuse and addictive eating behaviors, dopaminergic system is also mediated by physical exercise (Greenwood and Fleshner, 2011). Rewarding effects of exercise could include diverse DA pathways (nigrostriatal and mesolimbic) (Herrera et al., 2016) (Figure 3). Continuous stimulation of these circuits (training) might lead to exercise-mediated resistance to stress (Foley and Fleshner, 2008). Rodents perceive exercise as a naturally reinforcing and rewarding activity (Trost and Hauber, 2014). In some models, rats found both voluntary and forced running as a natural reward, independently of exercise controllability (Herrera et al., 2016). Animal studies support the facilitated DA neurotransmission elicited by exercise (Petzinger et al., 2015). In a mouse model of Parkinson's disease, intensive daily treadmill training led

to improved motor function and increased DA neurotransmission with respect to non-exercise mice (Petzinger et al., 2007). Access to running-wheels for 6 weeks prevented acute stress in rats, elevating DA in the dorsal striatum (Clark et al., 2015). DA neurotransmission is also facilitated by an exercise-induced increment in DA receptor expression (DD2R) (Fisher et al., 2004). This exercise-induced increment was registered either in the aforementioned mouse model (Petzinger et al., 2007) or in individuals newly diagnosed with Parkinson's disease (Fisher et al., 2013). DA and DD2R modulate a range of behaviors, including reward seeking behaviour, motivation, expectation of a reward (Blum et al., 2014). Alteration in the DA reward system may lead to abnormal eating behavior (Benton and Young, 2016). DD2R down-regulation is thought to de-sensitize reward, providing an extra-stimulus to overeat. As previously indicated (Wang et al., 2001), a negative correlation between BMI and the number of DD2R has been registered in obese individuals: lower striatal DD2R may pose a risk factor for overeating.

To conclude, all these conditions are not mutually inclusive and exercise may offer tremendous benefits in neuroplasticity and psychological behaviors.

#### **4. Discussion**

An increasingly influential notion supports that hyperpalatable foods, particularly those high in sugar content, can induce reward and craving that are at least similar to addictive drugs (Ahmed et al., 2013; Hone-Blanchet and Fecteau, 2014). Sugar overconsumption may lead, in turn, to a variety of health problems entailing metabolic and psychiatric disturbances in the context of a sedentary lifestyle. Exercise has the capability to break this vicious circle by competing with other deleterious reward drives. As such, exercise may represent a natural pillar against a

multifaceted thread of chronic-degenerative and affective disorders which threaten nowadays society.

The sugar addiction model refers to a neurobiological framework in which excessive intake of highly processed foods may be appreciated as drug addiction (Avena et al., 2008; Hernandez and Hoebel, 1988). However, some differences exist: neural system is hijacked by food and drugs in processing rewards, although in a dissimilar fashion. First, different populations of nucleus accumbens neurons respond to cocaine and natural rewards (Carelli and Wondolowski, 2003). Second, the dopaminergic response to sugar becomes rapidly tolerated whereas DA response to cocaine does not habituate and it is boosted by anticipating cues (Di Chiara, 2005). On the contrary, DA response to sugar is attenuated by predictive cues (e.g. smell). Furthermore, in the case of sugar, the DA level rapidly returns to baseline after repeated consumptions of sucrose (Roitman et al., 2004), whereas in cocaine the boost of DA does not return to baseline but further increases after extra drug intakes (Phillips et al., 2003).

Another intriguing issue arises as to any pharmacodynamic effect exerted by sucrose in the development of neuroadaptive changes elicited by addiction, like drugs critically do (Westwater et al., 2016). Emerging findings from animal research seem to support that addictive behaviours originate from the palatability rather than caloric content. Second, these addiction-like behaviors, such as bingeing, occur in animals specifically when they have intermittent access to sugar (Colantuoni et al., 2002; Cottone et al., 2008).

Although controversial, an important relationship exists between dopamine and glucose. With regard to DA, aerobic exercise has been shown to increase DA levels in the striatum, hypothalamus, midbrain, and brainstem in several

animal studies, therefore supporting the positive exercise-effects on memory and mood (Foley and Fleshner, 2008). A part from the improvement of cognitive function and motor learning shown in animals, exercise induces changes in brain connectivity that drive neuroplasticity: neurotransmission, neurogenesis and synaptogenesis (Figure 3). This might be the key to counteract and reverse the deleterious habits of overfeeding, hijacking the competing reward drives coming from the hedonic *milieu* (palatability). In other words, exercise might represent a strategy for activating reward circuits therefore improving the hypodopaminergic function observed in obesity or reward deficiency syndrome.

There is also a synergistic, exercise dragging-effect on healthy sociality (Salmon, 2001): people who exercise regularly can await positive feedback from their environment and social interaction. In western societies physical activity is a sign of a healthy lifestyle, and a person engaging in physical exercise feels normal and satisfied despite his/her fitness achievements. All this leads to a virtuous cycle that promotes physical well-being, diverting people's attention from worrying thoughts and, potentially, from those frustrations causing addictive behaviours.

Each time one exercises, BDNF levels increase in the brain, blood and muscles (Pedersen et al., 2009). Seifert et al. (Seifert et al., 2010) showed that endurance training in obese subjects increases basal BDNF concentration in the brain. Data from animal and human studies support the BDNF-protection against metabolic syndrome and obesity, by suppressing appetite, increasing insulin sensitivity and cardiovascular tone (Marosi and Mattson, 2014). Given the major role played by BDNF as a neuromodulator (neurogenesis, synaptic plasticity) and a controller of central (interacting with leptin through the hypothalamyc pathway) and peripheral (muscle contraction inducible protein) energy metabolism, exercise emerges as a

coadjuvant to the treatment of various metabolic and neuro-psychiatric diseases, via the BDNF-actions.

By increasing the amount of this citoprotective molecule and dopamine in certain regions of the brain, exercise can exert a number of health benefits that may counter negative mental states (Figure 3). Exercise-induced euphoria, neurotransmitters, endocannabinoids, may pave the way for pathways competing with those implicated in sugar-addiction disorders. Obviously, a multitude of interacting factors may conduct an individual toward an increased risk for eating disorders and obesity. Depending on this and because of a paucity of human data in this area, the mere sugar addiction cannot seize the complexity of these conditions.

Also, recent studies show that different types of exercise may be equally crucial for facilitating neuroplasticity (Petzinger et al., 2015). In detail, skilled exercise seem to affect more frontal cerebral circuits compared to pure aerobic exercise. Putative mechanisms may comprise the coupling of an increasing neuronal metabolic demand with a corresponding inflated blood flow.

Further controlled studies should be encouraged to elucidate the relative contribution of different types of exercise on neuroplasticity and the extent by which exercise may challenge compulsive habits, like those leading to addictive behaviors.

## **5. Conclusion**

In the future perspective, the fascinating challenge would be to understand how large is the therapeutical window for the beneficial exercise-effects in this cluster of psychiatric and metabolic disturbances involving addictions. Further studies are needed to mimic and investigate the potency of exercise on these addictive behaviors. Specifically, dose-response studies in which exercise will be administered *ad*

*personam*, that is at individually-tailored levels of intensity, to determine the optimal regimen of physical exercise having clear-cut therapeutic effects. A better understanding of the impact of exercise on eating addictive behaviors will be of assistance in designing improved treatments for patients with sugar attractiveness (liking, wanting, craving) in the clinical arena.

### **Contribution statement**

All authors were responsible for drafting the manuscript and revising it critically for valuable intellectual content. All authors approved the version to be published.

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**Figure 1.** *Flow diagram for progressive identification and selection of studies.*

**Figure 2.** *Biochemical pathways by which brain-derived neurotrophic factors (BDNF) modulate energetics in neurons.* In response to energetic challenges, like exercise, BDNF activate different signalling cascades. Through its receptor tyrosine receptor kinase B (TrkB), BDNF trigger typical constituents of the insulin signalling: PI3k and Akt kinases. In turn, Akt can activate mammalian target of rapamycin (mTOR) and increase dendritic protein synthesis. TrkB activation by BDNF enhances

synaptic plasticity (learning, memory) via multiple mechanisms including PI3-kinase-Akt pathway and other extra cellular signal regulated kinases (ERKs 1 and 2).

Moreover, BDNF can induce  $Ca^{2+}$  influx through transient receptor potential C, like glutamate.  $Ca^{2+}$  serves as a second messenger and may initiate several transduction cascades such as calmodulin-dependent kinase (CaMK) and the transcription factor cyclic AMP response element binding protein (CREB). CREB induces the expression of multiple nuclear genes and encodes the expression of peroxisome proliferator receptor  $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ). PGC-1 $\alpha$  is a master regulator of mitochondrial biogenesis.

**Figure 3. Exercise stimulates neuroplasticity against addictive eating behaviors, like sugar dependence.** The golden card played by exercise in diverting one's addictive behavior: neuroplasticity. By increasing the dopaminergic function and the hippocampus volume via BDNF levels, exercise may deflect sugar addiction from its legitimate reward pathways.

**Table 1. Studies examining the effects of exercise- or sugar-interventions on neuro-psychiatric and metabolic measures.**

Authors	Design and target	Intervention	Outcomes
(Chen et al., 2016)	Rats, stress, depression	3-wk voluntary wheel running	↓CORT; ↑DA
(Panlilio et al., 2015)	Rats, drug addiction (sucrose, nicotine)	Pressing lever access to sucrose/nicotine, freely available, daily sessions	Nicotine self-administration is continued independently of sucrose, and often more frequently than sucrose
(Avena et al., 2008)	Rats, sugar withdrawn	10% sucrose solution 12hr/d for 28 days; 50% sucrose in solid diet, 2d/wk for 8-9 wks	No effect of sucrose on weight gain

(Cao et al., 2007)	Rats, anxiety	10% sucrose solution <i>ad-libitum</i> for 25 wks	↑body weight; ↑FI, ↑TG, glucose intolerance in suc-fed rats
(Cottone et al., 2008)	Rats, reward processing	50% sucrose in solid diet, 2d/wk for 5 wks	No effect of sucrose on weight gain
(Frazier et al., 2008)	Mice, reward processing	Sucrose pellets <i>ad-libitum</i> for 4-7 wks	↔FBG; ↔glucose tolerance
(Sato et al., 1991)	Rats, reward processing	10% sucrose solution <i>ad-libitum</i> for 3 wks	↑weight gain in suc-fed rats; ↑DA
(Guercio et al., 2015)	Rats, drug addiction (sucrose vs cocaine)	Deep brain stimulation on rats under cocaine/sucrose self administration	↓cue-induced reinstatements of drugs
(Schulte et al., 2015)	Humans, sugar addiction	YFAS to assess addiction to 35 foods in 120 participants	GL and fat associated with addictive-like behaviors
(Steptoe and Bolton, 2007)	Humans, mood	Cycling @ 25W,100W	↑POMS @25W and @100W
(Weinberg et al., 1988)	Humans, mood	Swimmings, running, racquetball, tennis	↑POMS, ↑state anxiety inventory
(Zervas et al., 1993)	Humans, mood	Aerobics (40, 60, 80% HRmax)	↑POMS, ↑ state anxiety inventory
(Coelho et al., 2014)	Humans, elderly, Alzheimer's disease	Acute aerobic exercise	↑BDNF
(Speisman et al., 2013)	Rats, aging, cognition	Running daily for 12 wks	↑Hippocampal neurogenesis, ↑neuromodulation
(Hamani et al., 2012)	Rats, depression	Deep brain stimulation on rats under mild stress with sucrose access	Improved depression, ↑BDNF
(Rojas Vega et al., 2006)	Humans, healthy athletes; neuroplasticity	Acute aerobic exercise	↑BDNF
(Rojas Vega et al., 2008)	Humans, healthy athletes; neuroplasticity	Acute aerobic exercise	↑BDNF; ↑IGF-1
(Seifert et al., 2010)	Humans, obesity	12-wk aerobic training	↑BDNF
(Ströhle et al., 2010)	Humans, healthy and patients with panic disorders	Acute aerobic exercise	↑BDNF; visual analogue scale for arousal and anxiety correlated with BDNF

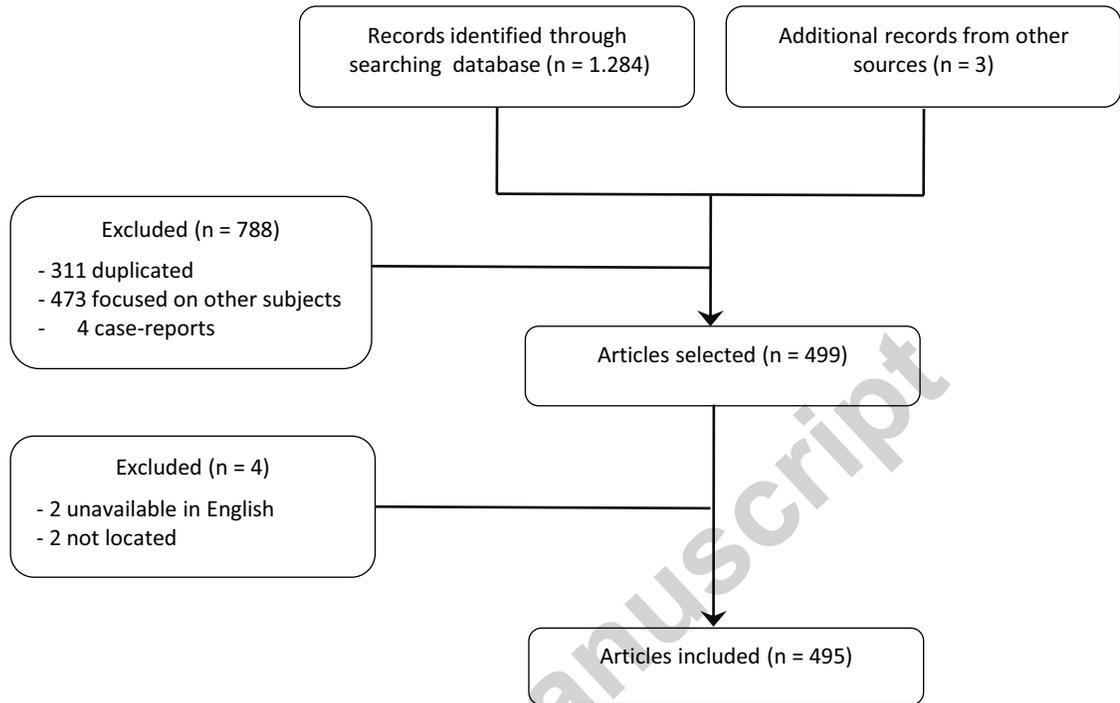
(Winter et al., 2007)	Humans, healthy subjects	Acute aerobic exercise	↑BDNF; ↑DA; ↑NE
(Coelho et al., 2011)	Humans, elderly	Resistance training (75% 1RM), 10-wk, 3 d/wk, 60min	↑BDNF
(Erickson et al., 2011)	Humans, elderly	Aerobic exercise, 50-60% HR reserve for 6 mo	↑BDNF, cognitive function, VO <sub>2</sub> max
(Laske et al., 2010)	Humans, elderly, depression	Acute aerobic exercise	↑BDNF
(Herrera et al., 2016)	Rats, anxiety, depression	Voluntary or forced wheel running, 5 d/wk for 7 wk	↑DA, ↑CREB, ↑tyrosine
(Clark et al., 2015)	Rats, uncontrollable stress, depression	Freely wheel running for 6 wk	↑DA, ↑serotonin
(Thanos et al., 2016)	Mice, Drd <sub>2</sub> transgenic, addiction, rewarding	Locomotor activity assessed bi-monthly in an optical sensor acrylic arena	↑lifespan in Dr <sub>2</sub> <sup>-/-</sup> , lifespan correlated with environment enrichment
(Petzinger et al., 2007)	Mice, MPTP transgenic, Parkinson's disease	Treadmill running, 5 d /wk for 28 d @ 15m/min	↑motor performance (improved balance) modulated by DA-transmission
(Grilo et al., 2012, 2005)	Humans, binge eating behaviors	Fluoxetine, CBT	↑ binge abstinence in CBT + placebo; weight loss ns
(Guerdjikova et al., 2012)	Humans, binge eating behaviors	Duloxetine	Significantly greater rate of binge reduction for drug in longitudinal analysis but not LOCF end-point analyses

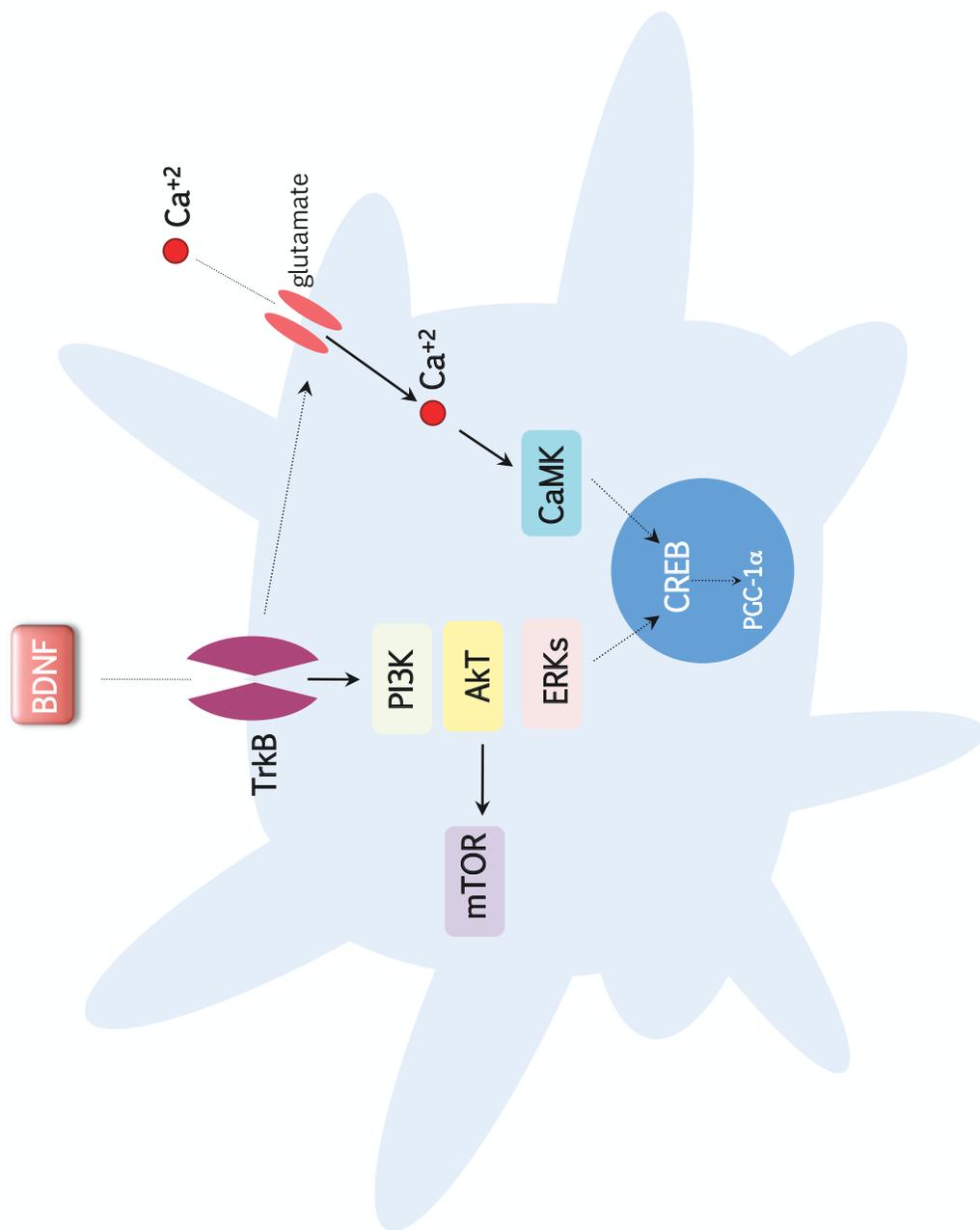
Abbreviations: ↑ = significant increase; ↓ = significant decrease; ↔ = unchanged; BDNF = brain-derived neurotrophic factor; CBT = cognitive-behavior therapy; CREB = cAMP response element-binding protein; CORT = glucocorticoid; d = day; DA = dopamine; FBG = fastig blood glucose; FI = fasting insulin; IGF-1 = insulin-like growth factor 1; GL = glycemic load; HR, heart rate; LOCF = last observation carried forward; m = meters; min = minutes; mo = month; NE, norepinephrine; ns = not significant; POMS = profile of mood states; 1RM = repetition maximum; TG = triglycerides; VEGF, vascular endothelial growth factor; VO<sub>2</sub> = oxygen uptake; YFAS = Yale food addiction scale; wk = week.

**Highlights**

- Sugar over-consumption may alter the reward system like in drug addictions
- Exercise promotes neuroplasticity counteracting competing reward processes
- Personalized exercise may assist the treatment of metabolic and affective disorders

Accepted manuscript





EXERCISE



## NEUROPLASTICITY

neurotransmission

neurogenesis  
synaptogenesis

dopamine

BDNF

dopaminergic  
pathwayshippocampus

- ① mesocortical tract
- ② mesolimbic tract
- ③ nigrostriatal tract

