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Prevention and Rehabilitation

Changes in metabolites level in internet-addicted adolescents through exercise

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ABSTRACT

Background: Internet addiction has been particularly prevalent among adolescents in recent years. This type of addiction, similar to drug addiction, causes dependence and disturbance in brain reward pathways. Physical activity is one way to prevent and treat some types of addiction. Aerobic exercise affects the dopaminergic and serotonergic pathways and improves the side effects of addiction. In this study, we examined the effect of eight weeks of aerobic exercise on the dopamine metabolite including homovanillic acid, L-tryptophan and 5-hydroxy indole acetic acid, which are precursors and the final product of serotonin metabolism in adolescent boys with internet addiction.
Materials and methods: Twenty-nine healthy non-internet addicted and internet-addicted boys were selected and divided into three groups: exercising internet-addicted (G1), internet-addicted (G2), and healthy non-internet addicted (G3) groups. Before and after aerobic exercise, 24-h urine samples were collected, and the target metabolites were analyzed spectrophotometrically.
Results: Results showed that for pre-exercise subjects, there was a significant difference in the homovanillic acid levels in G3 as compared to G1 and G2. For post-exercise cases, the changes were significant in G1 in comparison to G2 and for G2 in comparison G3. For pre-exercise subjects, there was a significant difference in the L-tryptophan level in G3 and G1, as well as G3 and G2.
Conclusion: It can be concluded that Aerobic exercise can improve the dopaminergic system that is disrupted by internet addiction.

1. Introduction

The use of the internet is recognized as a tool for collecting and sending information. It is estimated that users of this powerful tool are about 4.574 billion people equivalent to 58.7 percent of the world's population ("World Internet Users Statistics and 2020 World Population Stats," n.d.). With increasing the internet users, a phenomenon called internet addiction "the tendency to overuse and uncontrolled use of cyberspace and video games" has emerged (Han et al., 2007). Internet addiction is one of the most critical issues for adolescents because they are in a period of vulnerability for experimentation with substances and the acquisition of addictive disorders based on social and neurological factors (Chambers et al., 2003).

As the number of internet users increases, adolescents will become more and more involved in problems related to internet addiction, including depression, anxiety, obsessive-compulsive symptoms, and aggression causing negative outcomes, including problems at school and sleep deprivation. However, quantitative studies have suggested a suitable solution for treating internet addiction. There is little evidence of the effectiveness of available epidemiological and therapeutic methods (Zajac et al., 2017). These methods include pharmacotherapy and non-pharmacotherapy approaches. Non-pharmacotherapy methods include cognitive behavioral therapy (Zhang et al., 2020), motivational interviewing, art therapy, music therapy, and physical training (Huang et al., 2010).

Aerobic exercise can be useful in preventing and treating internet addiction by improving physical and mental conditions (Hong et al., 2020; Zhou et al., 2014). Aerobic exercise can reduce addiction behavior by affecting serotonergic and dopaminergic

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pathways (Rosa et al., 2020; Ussher et al., 2004). On the other hand, internet addiction can cause severe brain damage by affecting these pathways including selective lesion of dopamine terminals, decreased size of dopaminergic cell bodies, and reduction of dopamine active transporter (DAT). That may also lead to neurobiological abnormalities such as other addictive disorders (Hou et al., 2012). Research has shown that these neurobiological abnormalities in dopaminergic and serotonergic systems cause an increase in the extracellular levels of dopamine and serotonin due to a decrease in reabsorption and an increase in the releasing of neurotransmitters as a result of the addiction (Han et al., 2007; Müller et al., 2007).

Dopamine does not cross the blood-brain barrier (BBB), so homovanillic acid (HVA), the final product of the dopamine catabolism, can be investigated. These could be measured to evaluate the activity of this pathway. Research shows that the concentration of HVA depends on the interaction with dopaminergic systems (Eric Konicki et al., 1991; Köhnke et al., 2003). Serotonin also does not cross the BBB, so L-tryptophan (Trp) and 5-hydroxy indole acetic acid (5 HIAA), a precursor and the final product of serotonin metabolism, could be considered as markers for the research. These molecules might also be measured to unravel the mechanism of the serotonergic system activity (Filip et al., 2005; Young, 2007). Serotonin and dopamine metabolites do not have complex transport mechanism. This factor helps to better understand the effects of external stimulants on dopaminergic and serotonergic systems (Lin et al., 2019). It is shown that dopamine and serotonin metabolites increase after using addictive stimulants (Haleem et al., 2018; Köhnke et al., 2003).

Internet addiction codifies disorders similar to other types of addiction; additionally, there is no research on the levels of metabolites associated with reward pathways in internet-addicted adolescents, and the effect of exercise on the levels of these metabolites has not been studied. Therefore, the present study addresses, the differences among metabolites related to the reward pathway in internet-healthy adolescent boys. It also examines the effect of aerobic exercise on the levels of these metabolites in internet addicted adolescents.

2. Methods

2.1. Subjects

Subjects included 29 male adolescents 13.41 ± 0.51 years old. The subjects were carried out for an assessment of the third step of their maturation (genital maturation) using an image-based questionnaire according to Tanner classification (Tanner, 1962). In this study, people understood the purpose, and they did not regularly exercise for six months before the study. The research included three groups:

G1: 10 exercising internet-addicted, with a score of 50–60 in internet addiction test (IAT); G2: 8 internet-addicted with an IAT score of 50–60; G3: 11 healthy non-internet addicted with an IAT score of 20–39.

Young (1998) introduced a Diagnostic Questionnaire (YDQ) based on internet addiction (Young, 1998). The Code of Medical Ethics was approved by the Ferdowsi University of Mashhad medical ethics committee, and the written informed consent was obtained from all parents before participation.

2.2. Collection, storage, and preparation of urine samples

For the last 72-h period and during assembly, some foods and the following interfering drugs were avoided ("LabCorp 004069: 5-Hydroxyindoleacetic Acid (HIAA), Quantitative, 24-Hour Urine," n.d., "LabCorp 120253: Homovanillic Acid (HVA), 24-Hour Urine," n.d.). For all three groups' 24-h urine samples were collected in sampling tubes. From 29 boys each 10 mL sampling tube was prefilled with 100 μl of 6 M HCl and was kept in −20 °C in a dark place before analysis (Dairei, Germany) (Miękus et al., 2015). In the first stage, sample extraction was performed. There is a gold standard technique in analytical chemistry called Liquid-liquid Extraction (LLE) that was used here to extract the biogenic amines from the urine samples. The LLE method with diethyl ether was performed to prepare the three groups' urine samples. In this way, 0.2 g NaCl was added to 1 mL of previously acidified urine sample (to maximize the extraction efficiency). To the sample, 1 mL of diethyl ether was added and then vortexed until NaCl dissolution. Nitrogen gas was used to dry the resulting supernatant (Miękus et al., 2015).

2.3. Chemicals and reagents

The following materials were prepared for 24-h urine sample analysis. Homovanillic acid (HVA), L-tryptophan (Trp), and 5-hydroxy indole-3-acetic acid (5-HIAA) were all purchased from Sigma (St. Louis, MO, USA). Hydrochloric acid, diethyl ether, and sodium chloride were purchased from POCh (Gliwice, Poland). Methanol (MeOH) were supplied by Merck (Darmstadt, Germany). All chemicals were of analytical grade and used with no further purification.

2.4. Preparation of stock and working solutions

Stock and working solutions were used to identify the adsorption spectrum of each standard. In order to make stock solutions 1.0 mg of each analyte was added to 1 mL of MeOH. The working solution was diluted with MeOH to prepare concentrate before the analysis. To avoid possible decomposition, the sample was kept in the dark and at low temperatures. The stability of standard stock solutions was checked weekly by recording the UV spectrum.

2.5. Exercise training method

The exercise was performed three sessions per week: warm-up (10 min), 12 Stations (V step, Inchworm, Jump rope, Shadowboxing, Step touch, Shatters, Plank-to- knee tap, Footwork switch, Burpees, Step up, Lateral slides, and Jumping jacks) and cool down (10 min). The warm-up protocol consisted of 2 min walking, 3 min jogging, and 5 min static stretching. Subjects held each stretch for 15 s at a point of mild discomfort, and then relaxed for 5 s. The cool-down protocol consisted 2 min of jogging, 3 min walking, and 5 min static stretching. Subjects held each stretch for 15 s at a point of being strong, but not painful, and then relaxed for 5 s. VO2max was estimated using the Queens College Step Test before and after each session. The athlete steps up and down on the platform at 24 steps per minute for males, for 3 min. Then the athlete stops the test, and the heartbeats are measured. Estimation of VO2max can be calculated from the test results, using the following formula (McARDLE et al., 1972):

VO2max (mL/kg/min) = 111.33 - (0.42 x heartbeat rate (bpm)).

The VO2max level was assessed to confirm or reject the effectiveness of aerobic exercise. Exercise intensity was adjusted using the Karvonen formula, in which HR rest and HR max were measured during the VO2max test (Karvonen, 1957). The wireless HR analyzer in Polar E600/Finland was used for the test with a ±5% error. The 8-week exercise training program is shown in Table 1.

Table 1
Aerobic exercise program for eight-weeks.

Week	1	2	3	4	5	6	7	8
Percent intensity (max HR)[a]	65	65	70	70	75	75	80	80
Station activity (min)	1.5	2	2	2.5	2.5	3	3	3.5
Rest time (s)	15	20	20	25	25	30	30	35
Session time (min)	40	48	48	55	55	60	60	69

[a] Maximum heart rate.

2.6. Spectrophotometric analysis

After the extraction of biogenic amines, the absorption of the samples was measured using a spectrophotometer (Photonix Ar 2015) (Kaspar et al., 2019). Fig. 1 shows the absorption spectra of the standards, the addicted samples, and the non-addicted samples, which are deconvoluted by the OriginLab software for each analyte.

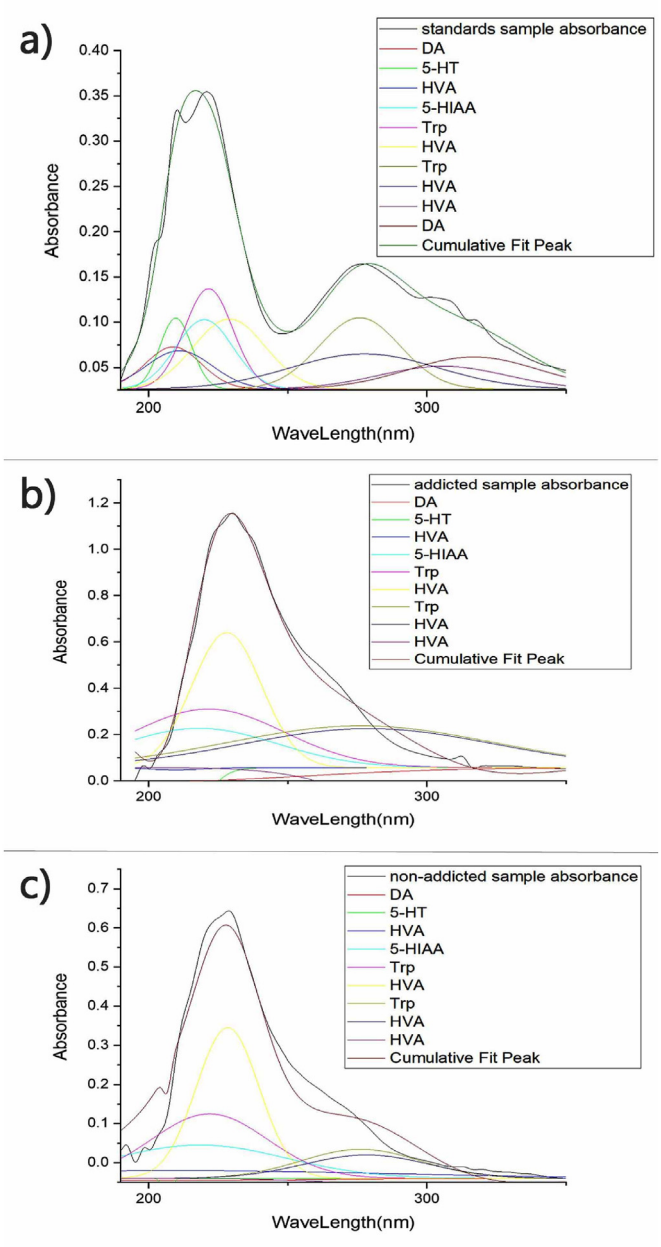

Fig. 1. UV spectra of standards and real samples. Deconvoluted graphs of a) standards with R-Square = 0.944, b) sample addicted deconvolution with R-Square = 0.994, and c) sample non-addicted deconvolution with R-Square = 0.968.

2.7. Statistical analysis

The means and standard deviations of the data were expressed with a statistical significance of $\alpha = 0.05$. The normal distribution of errors was evaluated using Shapiro-Wilk and Kolmogorov-Smirnov tests and the correction of the Lilliefors test and quantile-quantile plot. The variances were determined using the Levene test. Due to the lack of any assumptions in 5 variables, the weighted repeated-measure ANOVA test was used. SPSS software, version 25, was used to perform data analysis (Armonk, NY, USA).

3. Results

The subjects had a mean age of 13.41 ± 0.51 years. The internet addiction scores of the internet addicted groups G1 and G2 were 55.70 ± 5.07 and 58.38 ± 7.30, respectively, and the internet addiction score of the healthy group (G3) was 27.73 ± 7.87.

3.1. Internet addiction and exercise

The results of weighted repeated-measures ANOVA (Table 2) showed that the changes in IAT among the groups (G1, G2, and G3), at the times of pre- and post-intervention were not significant ($F = 2.33$, $p = 0.117$).

3.2. Changes in VO2max

The results of weighted repeated-measures ANOVA (Table 2) showed that the VO2max differences among the groups (G1, G2, and G3) at the times of pre- and post-intervention were significant ($F = 7.86$, $p = 0.002$).

Considering the significance of the changes, we examined the post hoc test, which shows that VO_{2max} was higher in G1 than G2 after aerobic exercise ($p = 0.029$).

3.3. Changes in homovanillic acid due to internet addiction and exercise

The results of weighted repeated-measures ANOVA (Table 3) showed that the changes in urinary HVA levels among the groups (G1, G2, and G3) at the times of pre- and post-intervention were significant ($F = 4.47$, $p = 0.021$).

Considering the significance of the changes, we also examined the post hoc test. The results of pre-exercise show that the changes between groups 2 and 3 ($P = 0.0003$), as well as groups 1 and 3 ($p = 0.0001$), were significant. In the post-exercise, the changes in groups 1 and 2 ($P = 0.038$), as well as groups 2 and 3 ($P = 0.0002$), were significant.

3.4. Changes in L-tryptophan and 5-hydroxy indole acetic acid

The results of weighted repeated-measures ANOVA (Table 3) showed that the changes in urinary Trp level between the groups (G1, G2, and G3) at the times of pre- and post-intervention were significant ($F = 4.93$, $p = 0.015$) but there was no significant difference in 5 HIAA ($F = 0.57$, $p = 0.57$).

Considering the significance of Trp changes, we examined the post hoc test. The results of pre-exercise show that the changes in Trp level between group 3 and 1 ($p = 0.007$), as well as group 3 and 2 ($p = 0.002$), were significant.

Table 2
Changes in (VO_{2max}) and (IAT) among the groups and the times (mean ± SD).

		(mean ± SD)			Time × group				
VO_{2max}	group	1(n = 10)	2(n = 8)	3(n = 11)	Sum of Squares	df	mean squares	F	p
	baseline	34.47 ± 7.05	36.36 ± 7.34	40.31 ± 9.94	381.66	2	190.83	7.86	0.002[a]
	after training	45.55 ± 8.26	35.73 ± 5.55	41.45 ± 7.73					
IAT[b]	baseline	55.70 ± 5.07	58.38 ± 7.30	27.73 ± 7.87	180.66	2	90.33	2.33	0.117
	after training	46.80 ± 6.51	49.88 ± 16.83	26.27 ± 7.68					

[a] P < 0.05.
[b] Internet Addiction Test.

Table 3
Changes in (5HIAA, HVA, Trp) among the groups and the times (mean ± SD).

		(mean ± SD)			Time × group				
5HIAA[b]	group	1(n = 10)	2(n = 8)	3(n = 11)	Sum of Squares	df	mean squares	F	p
	baseline	10.47 ± 3.26	12.49 ± 6.71	5.66 ± 2.86	24.34	2	12.17	0.57	0.57
	after training	6.96 ± 4.11	10.29 ± 7.49	5.18 ± 2.67					
HVA[c]	baseline	33.70 ± 8.78	34.03 ± 14.60	13.82 ± 3.91	476.93	2	238.46	4.47	0.021[a]
	after training	21.30 ± 6.50	31.01 ± 10.82	14.67 ± 5.59					
Trp[d]	baseline	14.57 ± 5.19	16.39 ± 7.19	7.04 ± 2.59	126.62	2	63.31	4.93	0.015*
	after training	9.62 ± 4.83	10.52 ± 6.53	7.72 ± 3.08					

[a] P < 0.05.
[b] 5-hydroxyindole acetic acid.
[c] homovanillic acid.
[d] L-tryptophan.

4. Discussion

Given the significant changes in VO2max after exercise training in G1, we believe that aerobic exercise has been effective. This increase in aerobic capacity can be due to the effect of exercise on increasing the maximum cardiac output and increasing the oxidative capacity of muscles and fats (Alves et al., 2016; Baek et al., 2018; Lambert and Evans, 2005). Regular and long-term aerobic exercise, in addition to improving oxidative capacity, can affect the central nervous system and consequently addictive behaviors, including self-regulation (Oaten and Cheng, 2006). In this regard, research shows the preventive role of long-term aerobic exercise in relation to internet addiction and also reduces the internet addiction scores of internet addicted subjects (Lin et al., 2020).

The dopaminergic pathway is one of the pathways associated with addiction that can be affected by exercise. In this study the HVA, metabolite of this pathway, was significantly different before the intervention in healthy group and internet-addicted groups. In this way, the healthy group showed a lower level of HVA as compared to the internet-addicted groups. We believe that internet addiction causes the dopaminergic system disorders by increasing phosphorylation of DAT (Wu et al., 2019), and inhibiting vesicular monoamine transporters (VMAT2) in dopaminergic neurons. VMAT2 is responsible for absorbing cytosolic dopamine into synaptic vesicles (Wimalasena, 2011), which releases the non-vesicular dopamine in the synaptic cleft (Wu et al., 2019). On the other hand, by increasing dopamine in the synaptic cleft, D1 receptor are activated. D1 activates the addiction signaling, which leads to the accumulation of addiction factor FosB (Greenwood, 2019; Wu et al., 2019). Finally, dopamine is converted to HVA in glial cells by monoamine oxidase (MAO) enzyme (Winner et al., 2017) and excreted in the urine (Amin et al., 1992).

The HVA was significantly different among the exercising internet-addicted group and the internet-addicted group after the intervention. In this way, the exercising internet-addicted group showed a lower level of HVA as compared to the internet-addicted group. We believe that aerobic exercise reduces dopamine release to the synaptic cleft by reducing DAT phosphorylation and VMAT2 activation (Palasz et al., 2019). The result is that the D2 receptor is more active than the D1 receptor because the D2 receptor is more sensitive and is activated at lower concentrations. Finally, unlike the D1 receptor, the D2 receptor inhibits the addiction signaling, which leads to the decrease accumulation of addiction factor FosB (Greenwood, 2019; Wu et al., 2019). On the other hand, by activating VMAT2, more dopamine is stored in the vesicles (Wimalasena, 2011). By dopamine decreasing in the cytosol and synaptic cleft, less HVA is produced and excreted. The possible signaling link between internet addiction and exercise on the HVA rate is shown in Fig. 2.

The serotonergic pathway is one of the pathways associated with addiction that can be affected by exercise. In this study Trp, the precursor to this pathway, was significantly different before the intervention in healthy group and internet-addicted groups. Therefore, the healthy group showed a lower level of Trp than the internet-addicted groups. We believe that internet addiction causes the serotonergic system disorders. Accordingly, Trp competes with amino acids such as tyrosine for active transport across the BBB (Wedekind et al., 2010). Because the level of HVA in addicted groups is higher and tyrosine is the precursor of dopamine, the passage of Trp through the BBB has probably decreased (Müller and Homberg, 2015), and as a result, urinary Trp has increased. On the other hand, changes in 5 HIAA, which is a metabolite of this pathway, was not significant in this study. Serotonin is catabolized in some addicted to methylserotonin, this position may be the reason for the lack of significant changes in 5 HIAA (Patkar et al., 2009).

Based on the non-significance changes of 5 HIAA and Trp after the intervention, we believe more than eight weeks of aerobic exercise is needed to make significant changes in 5 HIAA (Valim et al., 2013). Moreover, aerobic exercise with a maximum aerobic capacity of ≥150% can significantly reduce Trp, and this will happen after activation of the kynurenine synthesis pathway by indoleamine 2,3-dioxygenase enzyme, which has been activated by expressing the proinflammatory factors (Strasser et al., 2016). Accordingly, more research should be done to investigate changes in these metabolites in aerobic exercise with different intensities and periods.

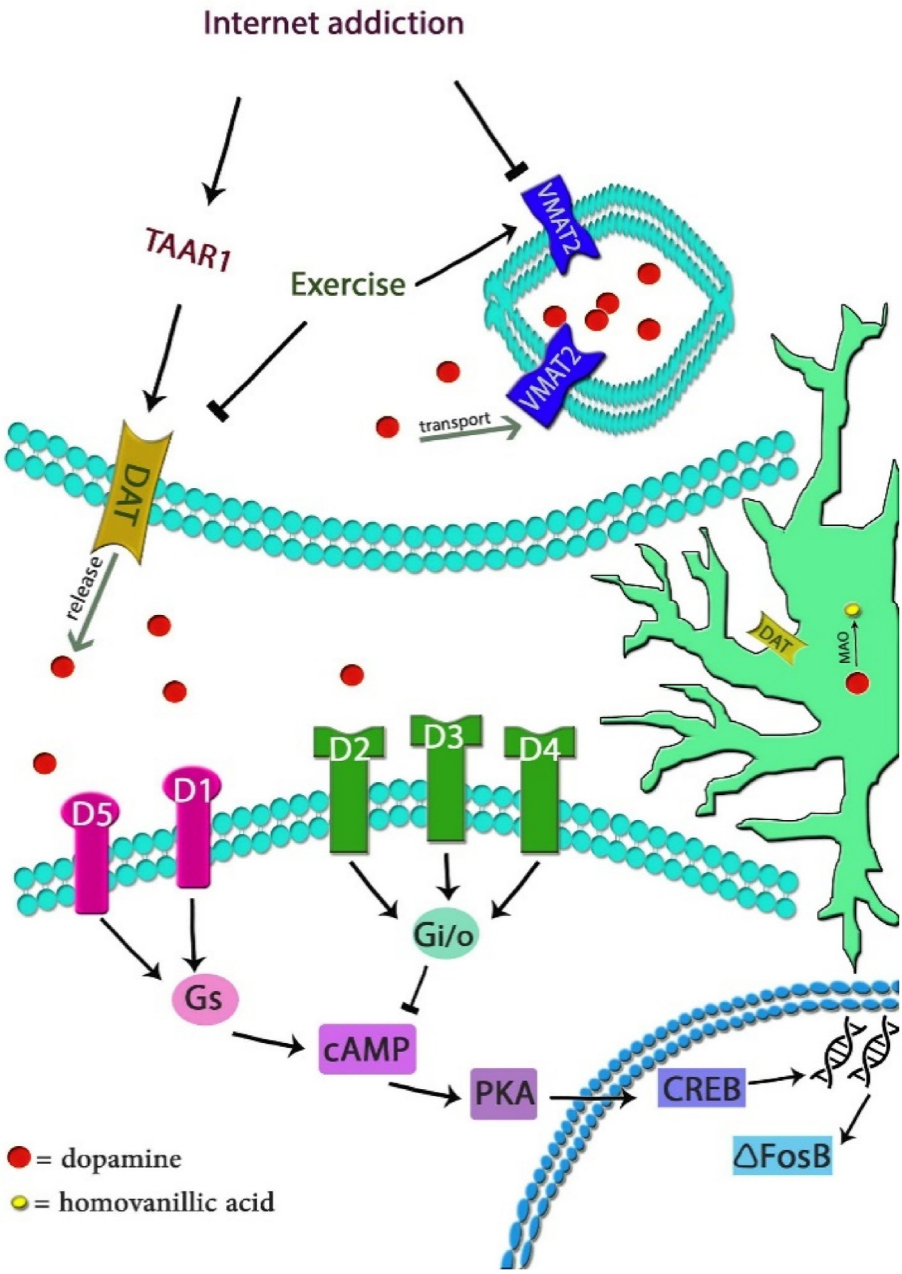

Fig. 2. Dopamine signaling in internet addiction and exercise. Internet addiction increases dopamine in the synaptic cleft by DAT phosphorylation and inhibiting VMAT2, thereby activating D1 and D5 receptors. Exercise activates VMAT2 and reducing DAT phosphorylation, thus reducing dopamine synaptic cleft and activating D2, D3, and D4 receptors.

4.1. Limitations

Due to the effect of diet on dopamine and serotonin activity, diet was controlled 72 h before sample collection but it was not controlled during 8 weeks of exercise. G2 and G3 did not exercise regularly during the study, as a result, daily activity related to lifestyle, in any of the groups was not investigated. Dopamine, serotonin, and their receptors were not measured directly in the brain.

5. Conclusion

Eight weeks of aerobic exercise does not seem to be enough to mitigate internet addiction and changes in the serotonergic system significantly. Internet addiction can disrupt the dopaminergic system, and increasing HVA. This type of addiction also increases the Trp level. On the other hand, aerobic exercise can improve the dopaminergic system and reduce the HVA level. Accordingly, sports activities can be used to improve the function of the dopaminergic system of internet-addicted adolescents. It is suggested that long periods of aerobic exercise to be used in future research and that higher intensities be evaluated to improve the condition. For a more detailed study of the serotonergic system, other metabolites of this pathway can also be examined.

CRediT authorship contribution statement

Fereshteh Korehpaz-Mashhadi: Data curation, Formal analysis, Investigation, Software, Writing – original draft. **Hossein Ahmadzadeh:** Conceptualization, Data curation, Formal analysis, Funding

acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Amir Rashidlamir:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization. **Nahid Saffari:** Investigation, Methodology, Writing – review & editing.

Declaration of competing interest

There are no conflicts to declare.

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