Acute and Chronic Effects of Exercise in Health

Blood lactate as a biomarker of depression: a comparative study between runners and sedentary people

Rafaela Pereira[1], Ricardo Marinho de Mello de Picoli[2], Lívia Valenti[3], Gilberto Eiji Shiguemoto[4]

[1]Universidade Federal de São Carlos, Departamento de Psicologia, São Carlos, SP, Brazil [2]Universidade de São Paulo, Instituto de Ciências Matemáticas e Computação, São Carlos, SP, Brazil [3]Universidade de São Paulo, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Ribeirão Preto, SP, Brazil [4]Universidade Federal de São Carlos, Departamento de Ciências Fisiológicas, Programa Interinstitucional em Ciências Fisiológicas, Laboratório de Fisiologia do Exercício, São Carlos, SP, Brazil.

Associate Editor: Álvaro Reischak de Oliveira. Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil. E-mail: alvaro.oliveira@ufrgs.br.

Abstract - Aim: The main objective of this work is to investigate whether recreational running, considered an aerobic exercise, would stimulate blood lactate production, reducing the risk of symptoms of depression. **Methods:** To accomplish this, we compared the depressive symptoms with the Beck Depression Inventory-II, the intensity of physical activity with the International Physical Activity Questionnaire, and blood samples of the D-lactate assay in two groups of participants who practiced and did not practice street running. **Results:** The results showed a negative correlation between blood lactate levels and the severity of symptoms of depression. In addition, running volunteers had significant blood lactate levels and low depression scores compared to non-running volunteers. **Conclusion:** This evidence suggests that street running may reduce symptoms of depression by stimulating blood lactate levels.

Keywords: lactate, exercise, recreational running, depression.

Introduction

The concept of depression arouse in the earlier 17th century[1] and it has been employed to designate both a symptom and a disorder. Several clinical conditions are associated with depressive symptoms, such as post-traumatic stress, dementia, schizophrenia, alcoholism, and other clinical diseases[2]. Specific characteristics classify depressive disorders: sad or depressive mood (i.e., can be an irritable mood in children and adolescents) along with somatic and cognitive alterations that significantly affect the individual's ability to function, with differences between the severity of depression (e.g., mild, moderate or severe) according to the duration, moment and etiology of the symptoms[2].

Depression is multifactorial psychopathology that occurs as a response to stressful situations where different biological, psychosocial, and psychological factors interact. The symptoms refer to alterations in mood (e.g., lack of pleasure), cognition (e.g., diminished attention), and physiology based on the individual's behavior[2]. Among the psychic symptoms are depressed mood, fatigue (e.g., feeling of energy loss), and diminished ability to concentrate, whereas physiological symptoms include alterations in sleep and appetite, besides a reduced sexual interest. In addition, there could be a social retraction, crying crises, suicidal behaviors, psychomotor agitation or retardation, and generalised slowness[2].

Considered the most common psychiatric disorder, affecting 300 million adults worldwide[3], depressive disorders are among the leading causes of the Global Disease Burden and years lived with disability. More than 80% of adults with depression report difficulties at work, home, and social activities[4]. This pathology is the leading cause of health problems and disability globally, resulting in 1 trillion dollars in costs to the global economy. In the Brazilian context, depression affects 11.5 million people (5.8% of the population), being the country in Latin America with the highest prevalence of this disease[3].

Possible procedures suggested for treating depressive symptoms are psychological (e.g., cognitive therapy) and psychiatric (e.g., antidepressant medication) monitoring. However, there is little evidence to support the prescription of antidepressant drugs in general, except for severely depressed patients or when alternative treatments, such as Cognitive Behavioral Therapy (CBT), have not provided desired benefits[5]. In addition, antidepressants are

associated with side effects, such as withdrawal symptoms[6].

Also, despite a large number of studies and advances in the development of antidepressants in the treatment of depression, 30% to 40% of treated patients with medication do not show remission (i.e., reduction of depressive symptoms), mainly because of side effects and a lack of efficient response in all patients[7]. Therefore, since antidepressants target neurotransmitter systems, it is necessary to study further the new cellular pathways that regulate depressive processes. In this case, alternative and preventive forms of treatment are necessary, including the practice of physical exercise, to reduce the risks of chronic diseases such as depression[8].

Exercise is a potential alternative low-cost therapy that is relatively safe and has fewer negative side effects than antidepressants[9]. In addition, exercise and sports activity are known to have positive effects on brain physiology[10] being linked to improved mental health[11] and alleviation of anxiety and depression symptoms[12]. Furthermore, recent research indicates benefits from physical activity, including the relief of symptoms of depression[13]. Mainly, physical activity seems to be associated with positive changes in mood states and in the reduction of depressive symptoms, resulting in improvement of individuals' mental health and well-being, and increased quality of life[14,15]. Thus, physical activity is shown as a behavioral mechanism that contributes to mitigating degenerative effects in the physical, social and mental domains, promoting the person's independence and functional autonomy, which results in greater positive mental health[16].

In concern to this assumption, several lines of evidence have shown that aerobic exercise, considered a type of physical activity, acts as a possible therapeutic intervention for complex mood disorders[17]. Recreational running is a current and popular aerobic exercise practice that improves mental health, reduces mortality, and increases physical conditioning[18]. The running practice as exercise and sport rose in the United States in the 70s with the "jogging boom", encouraged mainly by Dr. Kenneth H. Cooper's studies'[19]. Concerning mental health, a study performed by Kruisdijk et al.[9] with human adult patients showed the effectiveness of aerobic exercise therapy (running therapy) in reducing depressive symptoms.

A current hypothesis suggests that physical exercise, like recreational running, stimulates blood lactate production, with this biomarker having antidepressant effects due to psychological processes regulation. This regulation mechanism results from increased intracellular glucose availability to the brain[20]. In this view, low lactate blood levels could be an interesting indicator of depressive symptom development[21,14], leading to alternative pathways to treat depression, such as physical activity, associated with lactate stimulation.

Concerning the lack of studies on the human population, the present study aimed to verify whether recreational running exercise can be related to protective factors for depressive symptoms in young adults and the relationship between blood lactate levels induced by this physical exercise practice on depression symptoms. We hypothesize that lactate blood levels will be higher and more available to the brain in running individuals and could indicate lower depression symptoms, in contrast with non-running individuals or with low physical activity status.

Method

The present study is characterised by a quantitative design investigating the influence of recreational running practice as a protective factor for depression through the correlation between blood lactate levels and depressive symptoms.

Participants

Sixty volunteers (46 females, M = 27.83 years, SD = 7.77) were initially recruited for the study. The participants entering the study met the following specific criteria: 1) were within the target age range (18-45 years); 2) reported no health problems (e.g., anaemia, circulatory or blood clotting problems); 3) were not on anti-depression medication; 4) were not on medical evaluation or treatment for severe or moderate depression before the start of the research. Forty-one participants (33 females, M = 27.17 years, SD = 7.69) were considered after 19 individuals declined to participate in the study. The participants were randomly assigned to a runners group (n = 23) who practice recreational running at least twice a week and a non-runners group (n = 18) who did not practice recreational running. The International Physical Activity Questionnaire (IPAQ) was applied to confirm the physical intensity activity of which group[22]. The runner's group were participants classified in the activity and very activity category. The non-runners were in the irregularly active A, B, and sedentary categories (Figure 1). Tables 1 and 2 show each group's demographic characteristics and data (e.g., age, body mass).

Ethical approval

The present study was conducted in accordance with the national legislation regarding the assessment of human volunteers. Ethical approval for the present study was given by the Human Research Ethics Committee of the Federal University of São Carlos (CEP/UFSCar), under certificate number CAAE 00479218.2.0000.5504.

Materials

Two assessment instruments were used: the Beck Depression Inventory-II[23] (BDI -II) evaluated the depressive symptoms, and the IPAQ[22] measured the type of

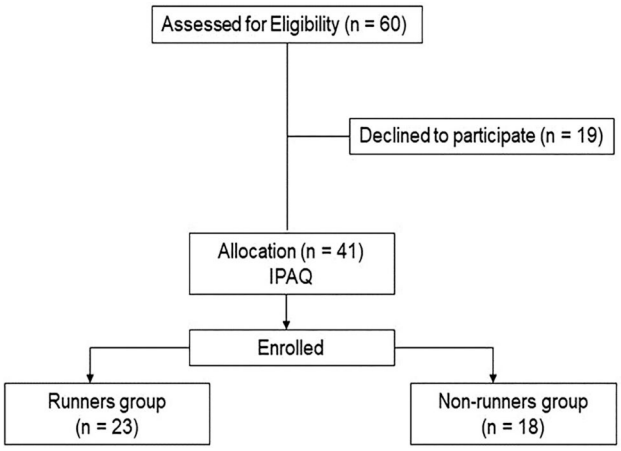

Figure 1 - Flow of participants throughout the study.

Table 1 - Demographic characteristics of participants.

		Runners		Non-Runners	
	Variable	**n = 23**	**%**	**n = 18**	**%**
Gender	Female	16	69.56	17	94.5
	Male	7	30.43	1	5.5
Occupation	Student	10	43.47	15	83.33
	Professor	4	17.39	0	0
	Health professional	3	13.04	0	0
	Others	6	26.08	3	16.66

Table 2 - Characteristics of participants.

	Runners	**Non-Runners**
Age (years)	30 ± 7.54	21 ± 4.93
Height (m)	166 ± 0.09	164 ± 0.07
Body mass (kg)	63.5 ± 10.33	55.5 ± 14.24
Body mass index (kg.m^2)	23.09 ± 2.79	21.16 ± 3.43
IPAQ	Very active	Irregularly active

Note. Values are expressed as mean ± standard deviation.

intensity of physical activity. In addition, a blood sample was collected for biochemical analysis of the L-lactate assay.

BDI-II

According to the diagnosis criteria of DSM-IV, this self-report inventory measures the severity of depressive symptoms[23]. It consists of 21 categories (items) of depression symptoms, and each item is rated for symptom intensity from 0 (little or no distress) to 3 (severe distress). The total inventory score is obtained by summing the 21 items, yielding a total score ranging from 0 to 63. Thus, the score range indicates a: minimal depression (0-13), a mild depression (14-19), a moderate depression (20-28), and a severe depression (29-63).

IPAQ

The IPAQ is an instrument that enables internationally comparable physical activity measures. The short version of the questionnaire was applied for the present study, consisting of eight questions related to physical activities performed in a normal week. The questions measure different dimensions of physical activity (walking and physical efforts of moderate and vigorous intensities) and physical inactivity (seated position), with a minimum duration of 10 continuous minutes[22]. The analysis of physical activity levels was based on the distribution of the questionnaire's answers according to the activity's frequency and duration. The participants were classified into the following categories: (a) very active: score ≥ 150 min/week vigorous activity or score ≥ 60 min/week vigorous activity + ≥ 150 min/week moderate activity and/or walking; (b) active: score 60 min/week vigorous activity or ≥ 150 min/week moderate activity and/or walking or ≥ 150 min/week any added activity (walking + moderate + vigorous); (c) irregularly active: A - ≥ 150 min/week activity and/or five days/week frequency, B - participants who didn't meet any criteria; and (d) sedentary: score < 10 min/week.

Blood sample collection and L-lactate assay

Blood samples were collected in an anticoagulant-free vacuum container (4.5 mL) and centrifuged (3000 g) for 10 min at 4 °C. Supernatants were kept at -80 °C until analysis. The analyses were performed in duplicate to ensure better accuracy and results presented in mg/dL. We used an enzymatic-spectrophotometric method, according to Marti et al.[24]. The method is based on the oxidation of d-lactate to pyruvate by NAD^+ in the presence of bacterial D-LD (EC 1.1.1.28, from Lactobacillus leichmannii). Pyruvate is transformed in a subsequent reaction catalysed by alanine aminotransferase (ALT; EC 2.6.1.2) in the presence of l-glutamate. All reagents of the lactate kit were purchased from LaborLab (Guarulhos, São Paulo, Brazil).

Procedures

The runner's and non-runners groups signed the ethical terms, volunteering to participate in the study, followed by IPAQ and BDI-II instruments application. Then a blood sample was collected for further analysis of blood lactate levels. The described procedures were repeated after 60 days.

Statistical analysis

Statistics were computed using Statistica 7.0 software. Normality was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. Lactate levels, depression scores (BDI-II), and physical activity status (IPAQ) between groups were analysed by one-way ANOVA's (time effect) with repeated measures. Tukey's post hoc test was applied

to examine specific pairwise differences if a significant main effect was observed. Pearson r correlation coefficient was used to detect correlations between lactate levels, depression scale, and physical activity status. $p < 0.05$ was considered statistically significant. Data are reported as means ± standard deviation (*SD*).

Results

Blood lactate level, depression symptoms, and physical activity level

Our primary outcome was the presence of depressive symptoms measured by the BDI scores in runners and non-runners subjects (Figure 2A). Runners' subjects presented a significative low BDI-II scores ($M = 6.63$) compared to non-runners ($M = 12.41$, $p = 0.00145$). The second important outcome was the blood lactate level at rest (Figure 2B). Blood lactate levels presented a significant difference between groups of runners and non-runners ($p = 0.018$). The runners group presented higher blood lactate levels ($M = 2.46$ mmol/L) compared to the non-runners group ($M = 2.03$ mmol/L). Finally, physical activity level was measured by the IPAQ and showed, as expected, that the runner's group presented a significative high level of physical activity ($M = 4.71$) compared to the non-runners group ($M = 2.59$, $p = 0.00011$).

Correlations between blood lactate levels, depression symptoms, and physical activity status

The comparison between blood lactate levels and depression symptoms (BDI-II scores) showed a strong negative Pearson's correlation coefficient (Figure 3A, $r = -0.88$, $p = 0.000$). It is important to note that the physical activity status (IPAQ scores) presented a moderate positive Pearson's correlation coefficient (Figure 3B, $r = 0.54$, $p = 0.000$). Finally, the comparison between physical activity status and depression scale showed a moderate negative Pearson's correlation coefficient (Figure 3C, $r = 0.56$, $p = 0.000$).

Discussion

There has been an expressive popularisation of recreational running on a national and international level in recent decades. From this perspective, this study was

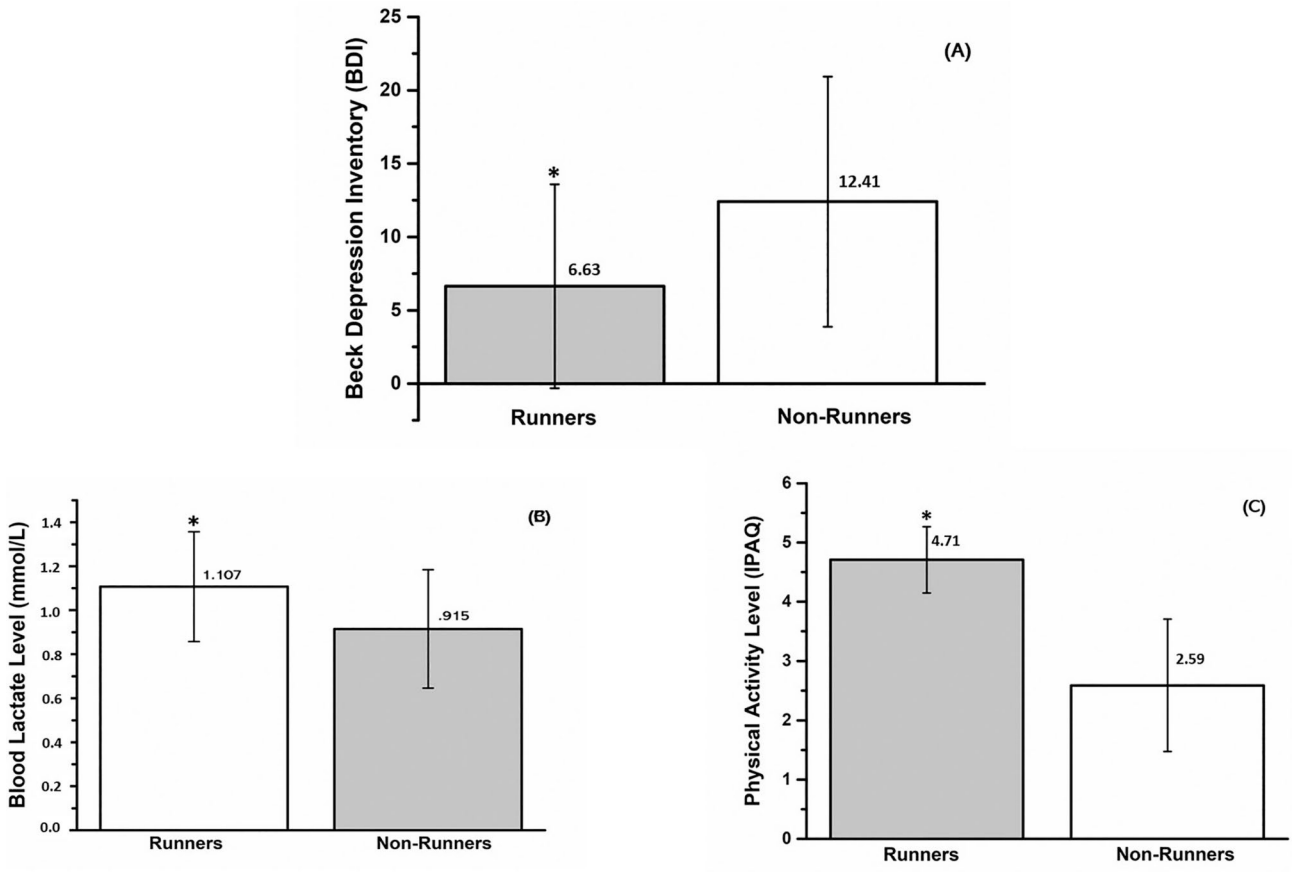

Figure 2 - Depression symptoms, blood lactate levels, and physical activity status between groups. A) Depression Symptoms: BDI-II scores; B) Blood Lactate Levels: mmol/L; C) Physical Activity Level: IPAQ. Runners versus Non-Runners: One-Way ANOVA and posthoc Student t-test, $p < 0.05$.*significant difference for the Non-Runners Group.

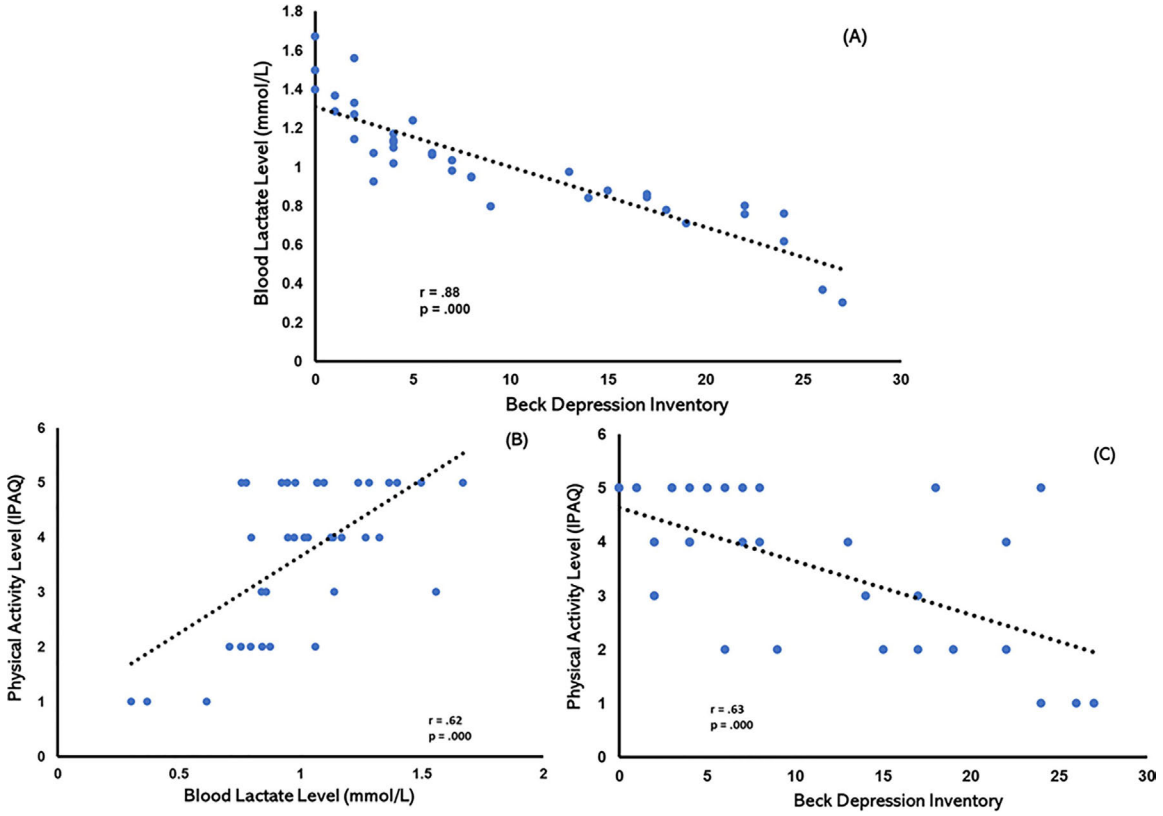

Figure 3 - Pearson's correlation coefficient and p-value between blood lactate levels, depression scale, and physical activity status. Note. A) A scatter plot of Pearson's correlation coefficient between blood lactate levels and depression scores (BDI-II); B) A scatter plot of Pearson's correlation coefficient between physical activity status (IPAQ) and blood lactate levels; C) A scatter plot of Pearson's correlation coefficient between physical activity status (IPAQ) and depression scores (BDI-II).

developed to understand how this aerobic exercise practice is associated with improving mental health in practitioners. The main finding of our study was the relationship between running practice and depression symptoms (BDI-II), corroborating the principal hypothesis addressed in the study that running is an efficient strategy to prevent or oppose depression symptoms. Another important issue in this context is the negative correlation (Pearson's correlation coefficient) between lactate blood levels and the severity of depression symptoms. Runners volunteers presented significative high lactate blood levels and low depression scores compared to non-runners volunteers.

Corroborating to our results, Lapmanee et al.[25] found that a voluntary moderate-intensity running exercise could be useful in the prevention of the development of mood disorders, such as anxiety- and depression-like behaviours in a rodent model. In addition, other studies have shown beneficial effects of running on depression-like behaviour in rats when promoting hippocampal neurogenesis and stress reduction[26].

In human studies, previous studies have demonstrated that aerobic exercise has reduced depression and anxiety states in clinical populations[27]. According to Cooney et al.[27], the reduction in depression scores represents a moderate effect, equivalent to a difference of approximately five BDI points. A recent study also demonstrated a positive impact of a running exercise program on symptoms of depression in a supportive group setting over three months (e.g., BDI-II) in a sample of youth and adults with complex mood disorders[17]. Our results demonstrated a significant reduction in depression scores in the running group, with a mean difference of 5.78 in BDI scores between runners (6.63) and non-runners (12.41).

Besides being one of the most elementary forms of terrestrial locomotion for humans, recreational running is a physical practice adapted to the urban culture which can be carried out anywhere and without specific equipment requirements and therefore does not have a high cost. Recently, a study organised by the International Association of Athletics Federations (IAAF) and the website Run Repeat.com analysed the results of 70 thousand running events in 193 countries, including Brazil, between the period of 1986 to 2018. The results suggest an increase of 57.8% in the participation of amateur runners in running events in the last 10 years. Specifically, there was a 20% increase in participation in Brazil compared to 2018[28].

Beyond the several health benefits promoted by regular physical exercise practices[29], recreational run-

ning promotes not only cardiovascular and metabolic benefits but also psychological benefits such as improved self-esteem and memory, decreased anxiety, and acting also as a social inclusion tool[15]. Thus, it is possible to observe that runners, especially amateurs, aim at running as a source of promotion of quality of life and social interaction[18]. In fact, physical activity may be considered a particularly important behaviour to target[30], which has been demonstrated to effectively reduce depressive symptoms in those with depression, potentially due to its influence on immunological factors that moderate mood or through promoting cortisol reduction, as well as endorphins and monoamines secretion[31]. In our work, we assessed blood lactate levels as a physiological marker of depressive symptoms related to physical activity, particularly street running. We found that low blood lactate levels at rest presented a strong negative correlation with depressive symptoms, demonstrating that low physical activity status and low blood lactate levels are important factors that can corroborate the development of depressive symptoms. Therefore, running could be a good and efficient physical activity to target depressive subjects.

Growing evidence indicates that lactate is an important energy source for brain metabolism, supporting neuronal function and survival and regulating processing memory[32]. It has been demonstrated that lactate released from astrocytes may be taken up by neurons and metabolised in the tricarboxylic acid cycle[33]. This is the increasing evidence of the metabolic involvement of astrocytes and metabolic coupling in depression[34]. The role of lactate release from astrocytes can be summarised in the involvement to regulate the expression of proteins involved with 5-HT receptor tracking. However, lactate can also downregulate the relative phosphorylation levels of pGSK3a, b, and CREB, which are targets for antidepressant drugs such as lithium[35].

It is important to note that lactate produced peripherally can reach the brain under normal physiological conditions, but the lactate influx from the bloodstream to the brain is fairly limited due to the blood-brain barrier and a small concentration gradient[36]. Using mathematical modelling, Boumezbeur et al.[37] suggested that lactate might contribute ∼10% to the brain metabolism at normal physiologic peripheral levels, but its contribution could increase to∼ 60% with supra-physiologic plasma lactate concentrations. Changes in brain lactate metabolism with exercise are particularly noteworthy[38]. As blood lactate levels rise with increasing exercise intensity, the brain shifts from being a net producer of lactate at rest to being a significant consumer of lactate, importing up to 0.39 mmol/min from the blood during vigorous exercise[39]. Thus, running rise blood lactate levels with increasing intensity and could directly improve learning and memory by maintaining the normal synaptic function[40], and could be an efficient tool in prevention and therapy in different psychological conditions.

In our work, the runner's lactate level at rest is high compared to the non-runners subjects, which could reinforce the good contribution of the running exercise to depressive symptoms. Karnib et al.[14] showed that the rise of lactate levels during exercise acts as an antidepressant and promotes resilience to stress in a CSDS (chronic social defeat stress) mouse model of depression. Carrard et al.[21] proved the lactide antidepressant effect by comparing mice behaviours in the forced swimming test, showing that mice groups with lactate injection had the same behaviours concerning the groups with the injection of antidepressant medication.

Conclusion

In summary, our work can conclude first that recreational running exercise is an excellent tool for preventing and treating depressive symptoms. Second, the blood circulating lactate levels could be a good physiological marker to correlate with depressive symptoms.

Acknowledgments

The manuscript received financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)

References

1. Lacerda ALT, Del Porto JA. Depressão ao longo da história. In: Depressão: teoria e clínica. Porto Alegre, Artmed; 2018. p. 19-27.
2. American Psychiatric Association. Transtornos Depressivos. In: DSM-5: Manual diagnóstico e estatístico de transtornos mentais. Ed. Artmed, Porto Alegre; 2014. p. 155-88.
3. World Health Organization. Depression and other common mental disorders: global health estimates. Available from: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf. [Accessed 1st June 2022].
4. Brody DJ, Pratt LA, Hughes J. Prevalence of depression among adults aged 20 and over: United States, 2013-2016. NCHS Data Brief. 2018;(303):1-7.
5. Cohen ZD, DeRubeis RJ. Treatment selection in depression. Ann Rev Clin Psych. 2018;14(1):209-36. doi
6. Ebmeier KP, Donaghey C, Steele JD. Recent developments and current controversies in depression. Lancet. 2006;367 (9505):153-67.
7. De Almeida RN, Galvão ACM, da Silva FS, Silva EAS, Palhano-Fontes F, Maia-de-Oliveira, JP, et al. Modulation of serum brain-derived neurotrophic factor by a single dose of ayahuasca: observation from a randomized controlled trial. Front in Psych. 2019;10:1234.
8. Kandola A, Lewis G, Osborn DPJ, Stubbs B, Hayes JF. Depressive symptoms and objectively measured physical

activity and sedentary behaviour throughout adolescence: a prospective cohort study. Lancet Psychi. 2020;7(3):262-71.
9. Kruisdijk FR, Hendriksen IJ, Tak EC, Beekman AT, Hopman-Rock M. Effect of running therapy on depression (EFFORT-D). Design of a randomised controlled trial in adult patients [ISRCTN 1894]. BMC Pub Health. 2012;12 (1):50.
10. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Mayo Clin Proc. 2011;86(9):876-84.
11. Mul JD, Soto M, Cahill ME, Ryan RE, Takahashi H, So K, et al. Voluntary wheel running promotes resilience to chronic social defeat stress in mice: a role for nucleus accumbens ΔFosB. Neuropsychopharm. 2018;43(9):1934-42.
12. Mattson MP. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. Cell Met. 2012;16(6):706-22.
13. Chen L, Zhou C, Tan C, Wang F, Gao Y, Huang C, et al. Stereological study on the positive effect of running exercise on the capillaries in the hippocampus in a depression model. Front Neuroanat. 2017;11:93.
14. Karnib N, El-Ghandour R, El Hayek L, Nasrallah P, Khalifeh M, Barmo N, et al. Lactate is an antidepressant that mediates resilience to stress by modulating the hippocampal levels and activity of histone deacetylases. Neuropsychopharm. 2019;44(6):1152-62.
15. Weinberg RS, Gould D. Foundations of sport and exercise psychology. Champaign, Human Kinetics; 2019.
16. Penseyres I, Martin JL. Improving understanding of the physiological mechanisms of exercise to better treat depression. Rev Med Suisse. 2018;14(605):950-2.
17. Keating LE, Becker S, McCabe K, Whattam J, Garrick L, Sassi RB. Effects of a 12-week running programme in youth and adults with complex mood disorders. BMJ Open Spo Ex Med. 2018;4(1):1-7.
18. Sanfelice R, Souza MK, Neves RVP, Santos RT, Olher RR, Souza LH, et al. Análise qualitativa dos fatores que levam à prática da corrida de rua. Rev Bras Presc Fisio Exerc. 2017;11(64):83-8.
19. Dias C. Corrida de rua no país do futebol. Recorde. 2017;10 (1):1-32.
20. Forsman J, Keltanen T, Liberg B, Sajantila A, Masterman T, Lindroos K. Glucose metabolism in completed suicide: a forensic-pathological pilot study. Croat Med J. 2017;58 (1):34-9.
21. Carrard A, Elsayed M, Margineanu M, Boury-Jamot B, Fragnière L, Meylan E, et al. Peripheral administration of lactate produces antidepressant-like effects. Mol Psych. 2018;23(2):392-9.
22. Benedetti TRB, Antunes PDC, Rodriguez-Añez CR, Mazo GZ, Petroski, ÉL. Reprodutibilidade e validade do Questionário Internacional de Atividade Física (IPAQ) em homens idosos. Rev Bras Med Esp. 2007;13:11-6.
23. Beck AT, Steer, RA, Brown, GK. Beck depression inventory (BDI-II). São Paulo, Pearson Clinical Brasil; 2014.
24. Marti R, Varela E, Segura RM, Alegre J, Surinach JM, Pascual C. Determination of D-lactate by enzymatic methods in biological fluids: study of interferences. Clin Chem. 1997;43(6):1010-15.
25. Lapmanee S, Charoenphandhu J, Teerapornpuntakit J, Krishnamra N, Charoenphandhu N. Agomelatine, venlafaxine, and running exercise effectively prevent anxiety- and depression-like behaviors and memory impairment in restraint stressed rats. PLoS One. 2017;12(11):1-23.
26. Yau S-Y, Lau BW-M, Tong J-B, Wong R, Ching Y.-P, Qiu G, et al. Hippocampal neurogenesis and dendritic plasticity support running-improved spatial learning and depression-like behaviour in stressed rats. PLoS One. 2011;6(9):1-151-15.
27. Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, et al. Exercise for depression. Coch Database Syst Rev. 2013:9;1-129.
28. Andersen JJ. The state of running 2019. Available from: https://runrepeat.com/state-of-running [Accessed1st June 2022].
29. Liu Y, Yan T, Chu JM-T, Chen Y, Dunnett S, Ho Y-S, et al. The beneficial effects of physical exercise in the brain and related pathophysiological mechanisms in neurodegenerative diseases. Lab Invest. 2019;99(7):943-57.
30. Grabovac I, Stefanac S, Smith L, Haider S, Cao C, Jackson SE, et al. Association of depression symptoms with receipt of healthcare provider advice on physical activity among US adults. J Affect Dis. 2020;262:304-9.
31. Schuch FB, Vancampfort D, Richards J, Rosenbaum S, Ward PB, Stubbs B. Exercise as a treatment for depression: a meta-analysis adjusting for publication bias. J Psych Res. 2016;77:42-51.
32. Newman LA, Korol DL, Gold PE. Lactate produced by glycogenolysis in astrocytes regulates memory processing. PLoS One. 2011;6(12):1-11.
33. Bélanger M, Allaman I, Magistretti PJ. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Met. 2011;14(6):724-38.
34. Powell CL, Davidson AR, Brown AM. Universal glia to neuron lactate transfer in the nervous system: physiological functions and pathological consequences. Biosensors. 2020;10(11):183.
35. Ernst J, Hock A, Henning A, Seifritz E, Boeker H, Grimm S. Increased pregenual anterior cingulate glucose and lactate concentrations in major depressive disorder. Mol Psych. 2017;22(1):113-9.
36. Mosienko V, Teschemacher AG, Kasparov S. Is L-lactate a novel signaling molecule in the brain? J Cer Blood Flow Met. 2015;35(7):1069-75.
37. Boumezbeur F, Petersen KF, Cline GW, Mason GF, Behar KL, Shulman GI, et al. The contribution of blood lactate to brain energy metabolism in humans measured by dynamic 13C nuclear magnetic resonance spectroscopy. J Neurosci. 2010;30(42):13983-91.
38. Maddock RJ, Casazza GA, Buonocore MH, Tanase C. Vigorous exercise increases brain lactate and Glx (glutamate +glutamine): a dynamic 1H-MRS study. NeuroImage. 2011:57(4):1324-30.
39. van Hall G, Stømstad M, Rasmussen P, Jans Ø, Zaar M, Gam C, et al. Blood lactate is an important energy source

for the human brain. J Cer Blood Flow Met. 2009;29 (6):1121-9.
40. El Hayek L, Khalifeh M, Zibara V, Abi Assaad R, Emmanuel N, Karnib N, et al. Lactate mediates the effects of exercise on learning and memory through SIRT1-dependent activation of hippocampal brain-derived neurotrophic factor (BDNF). J Neurosci. 2019:1661-718.

Corresponding author

Gilberto Eiji Shiguemoto, Universidade Federal de São Carlos, Departamento de Ciências Fisiológicas, Programa Interinstitucional em Ciências Fisiológicas, Laboratório de Fisiologia do Exercício, São Carlos, SP, Brazil.
E-mail: gileiji@ufscar.br.

Manuscript received on November 30, 2021
Manuscript accepted on April 20, 2022