Journal of Science and Medicine in Sport 22 (2019) 1090–1096

Contents lists available at ScienceDirect

Journal of Science and Medicine in Sport

journal homepage: www.elsevier.com/locate/jsams

Review

Why exercise may be beneficial in concussion rehabilitation: A cellular perspective

Ryan T. Dech, Scott A. Bishop, J. Patrick Neary*

Faculty of Kinesiology & Health Studies, University of Regina, Canada

ARTICLE INFO

Article history:
Received 10 September 2018
Received in revised form 20 May 2019
Accepted 21 June 2019
Available online 2 July 2019

Keywords:
Trauma
Nervous system
Mild head injury
Acute exercise
Physical activity
Cellular physiology

ABSTRACT

Introduction: Concussion diagnosis and rehabilitation management has become a prevalent area of research, and yet much is still unknown about these complex injuries. Historically, exercise prescription post-concussion was conservatively used for rehabilitation due to the suspected harmful effects that exercise can have on damaged neurons, and increase in symptoms. However, there has been a shift to implement exercise earlier into recovery as several studies have demonstrated positive outcomes.
Objective: The objective of this literature review is to update the reader about new advances in concussion research related to the beneficial effects of physical activity from both a neurometabolic and a broader physiological perspective, using gene expression as a vehicle to demonstrate why and how physical activity has the capacity to optimize recovery from a cellular perspective. To further this clinical guideline, the evidence must continue to support these positive outcomes from an inductive and deductive physiologic approach (i.e., the clinical evidence aligned from a micro- to macroscopic approach and vice versa).
Design: Narrative review.
Methods: Pubmed and Medline were used with the following key words: concussion and, physical activity, neurometabolic, gene regulation, trauma, nervous system, mild head injury, acute exercise, cellular physiology and pathophysiology.
Conclusion: It is our contention that understanding the cellular perspective will help guide clinical management, and promote research into post-concussion exercise.

1. Practical implications

- Exercise can be beneficial for recovering from sport concussion as exercise can amplify cellular healing.
- Exercise can be harmful for recovering from sport concussion if exercise is too intense.
- Understanding the physiology of concussion recovery and why exercise can be both “good” or “bad” may lead to improvements in recovery protocols.

2. Introduction

As per the most recent consensus statement on concussion in sport, the use of exercise as a potential rehabilitation tool is underscored following concussive injury.[1] Furthermore, classifying sport concussion is an unresolved issue as it can be viewed as part of a traumatic brain injury spectrum or as a physiologically reversible injury.[1] Nonetheless, sport-related-concussion (SRC) is typically defined within the following parameters: (1) an injury that is sustained by a direct blow or impulsive force that is transmitted to the head, (2) symptom onset and impairment that is short lived and resolves spontaneously, (3) functional changes (but not structural changes) are typically observed, and (4) a range of signs and symptoms that typically resolves in a sequential course and may involve loss of consciousness.[1] Unfortunately, less emphasis has been placed using physically active recovery as part of the rehabilitation process primary related to limited knowledge in this area as it pertains to the intensity, duration, frequency and volume of exercise that is safe to perform, and the unknown consequences (if any) of exercise on the recovering brain. Furthermore, the literature is limited related to the cellular processes involved in exercise rehabilitation following concussion.

Concussion management differences can also stem from inter-patient variation that may be influenced by several factors including: age, gender, fitness, time since last exercise bout, pharmaceutical agents taken, lifestyle choices prior to a diagnostic assessment (e.g. caffeine, alcohol, and tobacco intake), anxiety, and even time of day.[2–4] Ironically, most of these variables can

* Corresponding author.
E-mail address: Patrick.neary@uregina.ca (J.P. Neary).

https://doi.org/10.1016/j.jsams.2019.06.007
1440-2440/

also influence the response to exercise. Thus, managing and/or controlling these factors is critical for both developing a true understanding of severity and treatment, as well as for avoiding environmental and psychologic factors that confound clinical and physiologic assessments. These potential confounds require nuanced interpretation of the data, such that the modality of exercise and the expected physiologic response can be known (and includes considering the above patient variation factors). Only after this degree of nuanced interpretation is mastered, can one finally consider the differences in how the injured brain is responding or how it might respond during recovery when an exercise intervention is applied.

Furthermore, the above factors make it difficult to set a recovery timeline trajectory, and predict how exercise will impact this timeline.[5–7] Generally, health practitioners have acted conservatively for safety's sake as one patient may be capable of much more stimulation, physical activity, and cognitive loading than another for a given set of presenting symptoms.[2,7,8] Additionally, symptoms are very difficult to compare between individuals because of their relative nature. Thus, an individualized exercise rehabilitation program is paramount to ensure safe recovery.[9,10]

The underlying exercise-induced physiologic mechanisms were not detailed in the new consensus guidelines, as these documents were systematic reviews that were intended to be used for guiding concussion management and future research.[1,7,11–15] Hence, more physiologically-focused studies on the impact of exercise during the early stages of concussion recovery are warranted, as this will help build future consensus statements that may be more tailored to the pathophysiological changes that occur throughout concussion recovery[16,17,18] To better tailor exercise prescription post-concussion, it will be critical to demonstrate at a cellular level how exercise-induced changes in key cellular pathways enhance the recovery process.[1,19]

Therefore, the purpose of this paper is to review how exercise (when introduced early post-injury) may be beneficial for concussion management. The focus herein will largely be on cellular physiology, and will include the following topics: concussion pathophysiology and healthy gene and second messenger systems, and their relation to exercise and brain injury.

3. Overview of concussion pathophysiology

Forces applied to the head or body can cause shearing and stretching of neuronal cell bodies and axons, which alter the membrane and receptor structure at the site of injury.[20] A compromised membrane promotes the ability of ions to move down their concentration gradients more freely (e.g., potassium (K^+) efflux and both sodium (Na^+) and calcium (Ca^{2+}) influx). This change in ion flow and regulation results in both altered neuronal metabolism at the site of injury, and at secondary neurons. Moreover, mitochondrial dysfunction at the site of injury and at secondary neurons leads to immediate and delayed glucose metabolism processes.[21,22] The above changes to mitochondria and glucose metabolism can also influence cerebral blood flow processes at the site of injury and at secondary neuroanatomical locations.[16,21,23] The reader is encouraged to review Figs. 1 and 2 to further understand the processes associated with concussion pathophysiology.

Ion dysregulation. One of the mechanisms which connects the site of injury to secondary neurons is the indiscriminate release of glutamate, a neurotransmitter that results in increased *N*-methyl-D-aspartate (NMDA) receptor activity. These receptors allow calcium to move into the intracellular side of a neuron. The en masse rise of intracellular calcium as a result of NMDA receptor activity uncouples glucose metabolism and neurovascular coupling (discussed below).[21,24] Furthermore, the binding of glutamate to NMDA receptors results in the opening of potassium and intracellular voltage-gated channels found on the sarcoplasmic reticulum. Both of these actions only further compromise the regulation of intracellular ion concentrations.[21] Again, this indiscriminate release of glutamate at secondary injury sites is mirrored at the primary site of injury by increased membrane permeability to all ions.[21]

Energy dysregulation. Decreased intracellular ion regulation at primary and secondary neuronal sites can also affect a mitochondria's ability to maintain the proton gradient required for adenosine triphosphate (ATP) synthesis. This may shift glucose metabolism towards anaerobic glycolysis, and further strains the energy requirements needed to restore these large ionic shifts.[25] When mitochondria can no longer function as intended, the excitotoxic effect of the ions can lead to cellular apoptosis.[21] Moreover, the ability to restore ion balances across the neuronal membrane (and reverse the excitotoxic status of the neuron) may be a key factor for stratifying the brain injury into either a TBI (non-reversible cytotoxic damage and neuronal cell death), or a concussion.[10,24] While the mechanism ultimately has a large impact on outcome (concussion vs. TBI), the above-discussed physiology regarding the

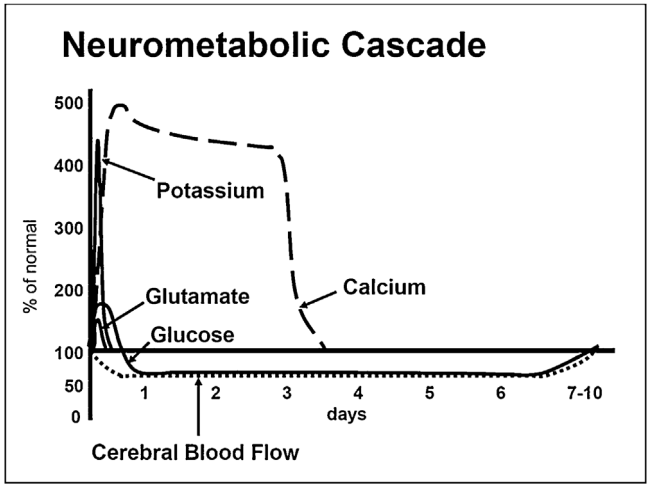

Fig. 1. Changes in ionic, metabolic, and cerebral blood flow changes that occur post-concussion.
Adapted from Reference 21.

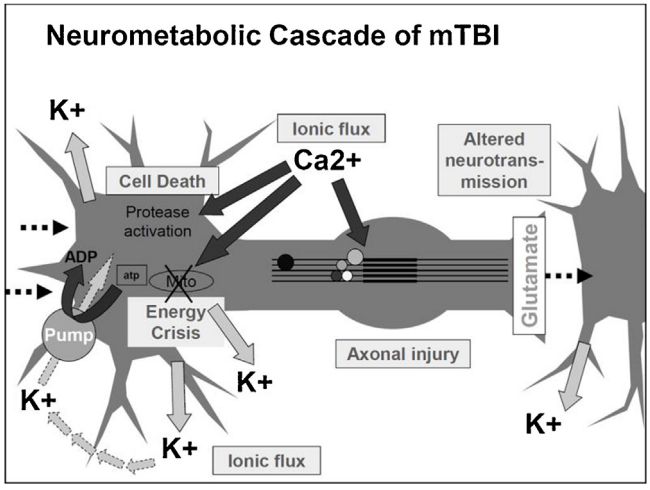

Fig. 2. Model of the cellular processes that affect primary and secondary injury sites following concussion.
Adapted from Reference 21.

neurometabolic changes suggests that there may be a cellular "tipping point". This reduced oxidative capacity can also be reflected through changes in gene expression and transcription, (discussed in a later section).[22]

Structural dysregulation. At the site of injury, microtubules and membrane receptors are being recycled and reorganized with the intent to restore function, and thus promote ion regulation.[14,26] This is crucial as active transport proteins in the plasma membrane such as Ca^{2+}-ATP pump, and the Na^{+}/K^{+} ionic pump, will be saturated, and their efficacy will be limited by: (1) membrane integrity, and (2) the amount of ATP energy stores available. Moreover, assuming that the level of excitotoxicity is reversible (i.e. concussion rather than TBI), the recovering neuron (be it at the site of injury or at a secondary location) is also exposed to decreased regulation of neurovascular coupling, which can also hinder ATP synthesis through decreased nutrient delivery.[27]

Blood flow dysregulation. Neurovascular coupling (NVC) matches oxygen delivery to active tissues from a cellular to regional level via adjustments to capillary bed and pial artery smooth muscle tone.[28,29] NVC is driven by fine-tuned regulation of numerous ions and molecules, including: calcium, potassium, ATP, guanosine triphosphate (GTP — similar to ATP), and nitric oxide (NO).[21,30] Some of these molecules and ions have been discussed above, and the reader should now be familiar with how the post-concussion ion dysregulation can conceivably influence blood flow at primary and secondary locations.[17]

4. Gene expression & metabolism in concussion: "downstream downregulation"

The concussion-induced ionic dysregulation, energy crisis, and impaired neurovascular coupling, have been discussed above. These previously discussed topics can potentially affect several proteins and second messenger pathways, which can also influence genetic expression. Of significant importance are brain-derived neurotrophic factor (BDNF), cyclic adenosine monophosphate (cAMP) response binding protein (CREB), peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1a), mammalian target of rapamycin (mTOR), and more.[21,31–35] These factors are all essential in facilitating neuropro-

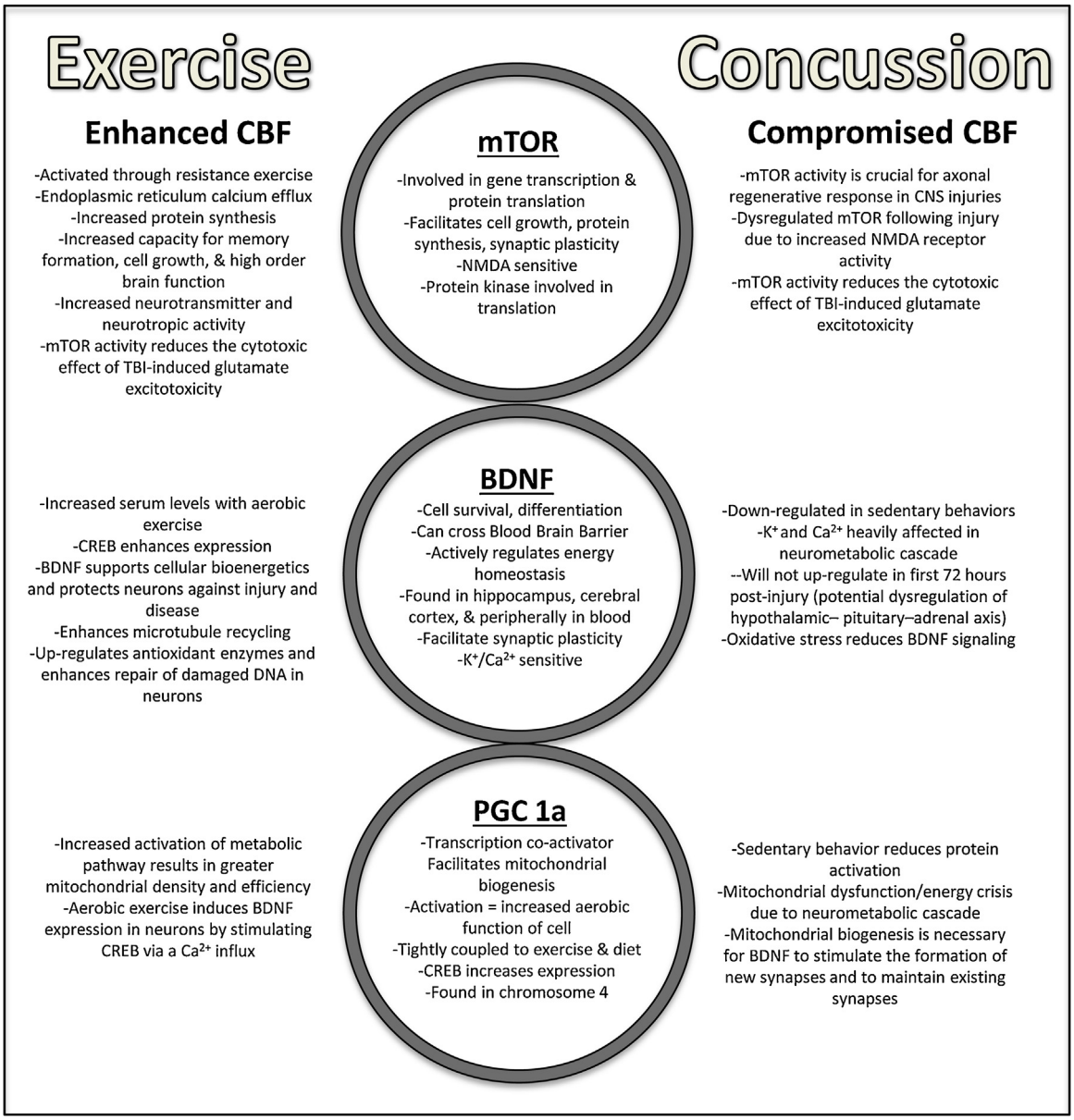

Fig. 3. Key transcription factors which are enhanced with exercise and aide in concussion recovery.

tection and synaptic plasticity in the brain, as well as overall cell efficiency and neuronal homeostasis.[11,12,35–37] The below subsections will focus on the following: the cellular physiology of exercise and neuroplasticity (broadly), how concussion results in changes to select proteins (BDNF, PGC-1a, and mTOR), and how exercise can theoretically reverse concussion pathophysiology. The reader is encouraged to view Fig. 3 below to get an overview of some of the above proteins.

Exercise-induced neuronal changes — ion regulation. An acute bout of aerobic exercise will challenge the regulatory capacity for intracellular ion concentrations, as numerous post-synaptic NMDA receptors will be stimulated at an increased frequency and intensity. The exercise-induced increase in flow of extracellular calcium across the neuronal membrane (into the cytosol) will be met with increased intracellular fluxes of calcium from the endoplasmic reticulum.[13,14,26,38] A simplified model which explains this from an exercise perspective is the concomitant presence of norepinephrine and glutamate. More specifically, the binding of norepinephrine to an adrenergic receptor activates membrane-bound G-proteins, which in turn activates phospholipase-C (PLC), and creates diacyl glycerol and inositol triphosphate (IP3).[38–40] The influx of extracellular calcium from the NMDA receptor, in conjunction with inositol triphosphate generated from the adrenergic receptor, will enhance the release of calcium from the endoplasmic reticulum through both endoplasmic reticulum-bound voltage-gated calcium receptors, and the endoplasmic reticulum-bound inositol triphosphate receptors. This regional enhancement of calcium influx from the endoplasmic reticulum will stimulate other nearby endoplasmic reticulum-bound voltage gated calcium receptors and create a retrograde calcium wave back to the soma where calcium-dependent transcription factors and second messengers can be activated (e.g. calmodulin, mitogen associated protein kinase (MAPK), etc.).[38] Many of these transcription factors reinforce the capacity for ion regulation through enhanced genetic expression, which is what is impaired when a concussion is sustained.[3,20,21]

Exercise-induced neuronal changes — energy regulation. The enhancement in postsynaptic NMDA, adrenergic, and endoplasmic reticulum receptor stimulation, will require enhanced glucose metabolism and ATP utilization. Once again, norepinephrine can be used as a simplified model for demonstrating energy regulation during exercise. The G-proteins activated when an adrenergic receptor is stimulated will then activate trans-membranous adenylyl cyclase.[39] The trans-membranous adenylyl cyclase would also be enhanced by soluble adenylyl cyclase enzymes, both of which generate cAMP (an influential second messenger system molecule). The changing levels of cytosolic cAMP influence the activity protein kinase A, which is well known to augment glycolysis and promote micro-domain neurovascular coupling (amongst other second messenger pathways).[39,41] Moreover, cAMP can act through several transcription factors (such as CREB) to enhance the genetic expression of those proteins associated with the regulation of glycolysis.

Exercise can also induce mitochondrial biosynthesis via increases in the protein PGC-1a, which is also associated with CREB, and can play a large role in energy regulation.[42] Hence, exercise can help restore the capacity to monitor metabolism and ATP synthesis post-concussion.

Exercise-induced neuronal changes — structural regulation. The exercise-induced regulation of intracellular ions will also create structural changes at the synapse. Indeed, the increase in intracellular calcium is paired with the activation of cAMP-associated protein kinases and transcription factors, so that cytoarchitecture and organelle distribution is reinforced. More specifically, calcium and calcium-calmodulin dependent proteins (e.g. type II microtubule associated proteins and tau protein) reinforce the localization and structure of the postsynapse.[43,44] This calcium-dependent regulation of post-synapse structure occurs in conjunction with other molecules such as brain derived neurotrophic factor (BDNF; a cAMP product via CREB), which also enhances microtubule recycling.[11,12] The mechanism by which BDNF best enhances cytoarchitecture postsynaptically is still debated. From one perspective, BDNF can bind to its membrane bound receptor, and as the receptor undergoes endocytosis, an increase in tau protein expression can occur via second-messenger systems (i.e. activation of MAPK, phospholipase-C, phosphatidyl inositol triphosphate binding to its cytosolic receptor, and the activation of CREB).[11,12] From another perspective, the same molecule of BDNF can undergo exocytosis back across the synapse, and enhance the pre-synaptic release of glutamate-containing vesicles. The ability of BDNF to modify pre-synaptic release of glutamate, will increase both the rate of NMDA receptor stimulation and amount of calcium influx from the extracellular space; which, will reinforce the relationship between tau protein and calcium.[11,12,45,46]

Another aspect of exercise and structural regulation is organelle redistribution, although the mechanisms are also not fully understood. What is known is that ATP and calcium can influence mitochondrial and endoplasmic reticulum density to areas of activation (which facilitates regional glucose metabolism); and thus includes golgi body arboring (which facilitates regional receptor recycling and peroxisome availability).[13–15,26]

Exercise-induced neuronal changes — other important proteins. As noted above, BDNF is critically important for neuronal function as it helps to mediate ionic, metabolic, and structural processes.[12] The reader is reminded that the above subsections were simplified, and that a more thorough review of the literature can be found with these references.[11,12,44,47]

Another important metabolic pathway stream that is targeted by exercise is the mammalian target of rapamyacin (mTOR). The mTOR pathway is heavily involved in cell growth, synaptic plasticity, and is connected to higher order brain function.[48–50] Several second messengers discussed above interact with mTOR, including: phospholipase-C, phosphatidyl inositol triphosphate, and CREB. Furthermore, mTOR has interactions with eIF-4E binding protein (4E-BP1) and p70 ribosomal S6 protein kinase (p70s6k) where it phosphorylates these protein translation regulators.[51] Ergo, mTOR (in conjunction with BDNF activity) plays a central role in merging extracellular signals such as NMDA receptor activity[49] with metabolic resources for catabolic and anabolic processes, and also facilitates gene transcription and protein translation.[52]

It is also important to note that the PGC1a and mTOR pathways compete for control during exercise and are dependent on the type of stress. When one of these pathways is activated, the other pathway becomes blunted. To simplify, the inverse relationship between mTOR and PGC1a can somewhat be explained as resistance-exercise pathway activation (mTOR — protein synthesis) and aerobic exercise pathway activation (PGC1a — mitochondrial biogenesis). However, though mTOR and PGC1a are in competition it is clear that they both have strong connections to healthy gene expression in neurons.

It should now be clear that both mTOR and BDNF can contribute to ionic, metabolic, and structural regulation through protein synthesis (mTOR) or through other second messenger systems (BDNF). Moreover, the mechanisms by which exercise enhances these processes should now be clear, and thus how exercise can help concussion recovery.

Exercise-induced neuronal changes — neurovascular coupling. As a last note in this section, NVC relies on potassium, calcium, GTP and nitric oxide (NO) signalling. Exercise enhances the regulation of these ions, and thus the regulation of NVC is also enhanced. Nitric oxide is also influenced by cAMP, which again has implications for delivering oxygen to a neuron that will have enhanced metabolic activity and protein synthesis. Thus, exercising for con-

cussion recovery will also help with regulating the match between cellular energy demands and nutrient delivery.

5. Application of exercise to neuronal damage

By this juncture, it is hoped that the reader can understand that in order to have neuroplasticity, there must be a matching of blood flow (i.e., nutrient delivery) to neuronal metabolism. What is critical to note is that several human studies which have demonstrated that NVC is compromised during concussion.[3,53,54] However, performing exercise has been shown to promote recovery.[7,17,22] Thus, the notion that exercise may have a direct application to enhancing recovery from concussion is gaining acceptance.[1,5,7] And yet the question remains - how can exercise promote neurovascular recoupling, and help resolve a concussion-induced metabolic crisis? After all, it has been commonly noted throughout several concussion consensus statements that exercise can cause symptom exacerbation.[17]

The crux of this question has been repeatedly mentioned from a management standpoint – the use of exercise and/or physical activity that does not elicit symptoms.[17] Unfortunately, the physiology that elicits these symptoms has not been well studied from a human "cellular mechanism" point of view. A plausible hypothesis can be drawn by recalling that there remains a large cytosolic and mitochondrial concentration of calcium being sequestered that need to be corrected.[5,7,21] What remains elusive is how much capacity for intracellular ion regulation is restored 72 h post-injury, as this level of restoration can be applied to exercise, which further promotes more ion regulation.

This margin for intracellular ion regulation (and the associated energy reserve) will likely occur under conditions of mild exercise, as recent research suggests that low intensity exercise can be performed safely. If one exerts beyond the exacerbation-threshold, symptoms such as headache or pressure in head (amongst other symptoms — physiological and psychological alike) may manifest for an undetermined period of time. At a cellular level, if exercise intensity is increased beyond this exacerbation-threshold, then there will be an increased oxidative stress within the cell, and may ultimately lead to the activation of apoptotic pathways.[5,20,31,55,56] Thus, mild exercise is important and that increased intensity can be deleterious for recovery.

To further connect the above sections to exercising at intensities below symptom exacerbation, recall that epinephrine is a neurotransmitter strongly associated with exercise, and that it will increase cAMP and CREB concentration levels via transmembrane and soluble adenyl cyclase. cAMP will also promote the synthesis of nitric oxide.[11,12,35,39,47,57] The presence of nitric oxide will aide in delivery of nutrients so that this heightened energy need for ionic regulation is met for the duration of the exercise bout. Moreover, CREB will increase the expression of BDNF and PGC-1a. Increasing the expression of these proteins will promote mitochondrial biosynthesis, organelle restructuring, and improve membrane integrity via microtubule regulation.[13–15]

While the above is technically a theoretical rationale, there have been some human studies to corroborate this thinking that mild exercise is important for recovery and management.[23,56,58] Most recently, Leddy et al. used the Buffalo Concussion Treadmill Test in patients who were initially assessed at an average of 5 days post-injury and exercised until reaching symptom exacerbation. Patients were then instructed to perform home activity at 80% of the initial assessment intensity, which was found to be more beneficial in time to recovery as compared to a stretching group.[59] Additional research has identified that performing exercise for 10–15 min at 40–50% of heart rate maximum in untrained individuals, and 15–20 min at 60–70% of heart rate maximum in trained individuals are good estimates for prescribing exercise post-initial assessment. It is worth noting that maximal heart rate was estimated using the following formula: $208 - (0.7 \times \text{age})$.[60] These estimates will help avoid the exercise-induced ventilation threshold, which can result in hyperventilation, followed by cerebral vasoconstriction.[60] Though inconclusive, there is evidence to suggest that higher exertion (i.e., moderate and greater) can have a detrimental effect to recovery, and so does long-duration aerobic activity at lower intensity levels (greater than 45 min). This is thought to be due to increased oxidative stress, increased cortisol secretion, and impaired cerebral blood flow regulation, among other cardiovascular factors.[60]

Indeed, it has been found through several studies that concussion results in a decreased oxidative capacity, which consequently leads to a down regulation of BDNF.[24] As an example, a mouse-model study monitored exercise prescription throughout recovery, and it was found that BDNF levels were not changed regardless of exercise intensity in the first 72-h.[32] In this study, the same mice were examined 14–20 days post-injury, where it was found that BDNF was increased with exercise. It is thus possible that there is a parallel and synergistic relationship between PGC-1a and BDNF, which may help safely promote concussion recovery. It should also be mentioned that a similar relationship would likely exist between mTOR and BDNF, once again suggesting that enhancing BDNF expression is an integral component of any exercise related recovery process.

Further still, several studies have demonstrated the effect of exercise on CREB levels post-concussion, suggesting that modulation is inhibited in the acute phase as seen by the lack of up-regulation with the onset of an exercise stimulus. However, once ample recovery time has been observed (14–20 days), an up-regulation of CREB can be seen.[34]

6. Summary

This brief review discussed the changes in cellular signalling that occur as a result of exercise, and demonstrated the importance in regulating the neuronal environment in the days immediately following concussion (i.e., BDNF, CREB, mTOR, and PGC-1a are significant markers in both exercise and pathology).[11,12,35,36,49,61] The acute post-concussion phase is an important time period for rest, but theoretically the activation of the above-discussed pathways should provide an environment for beneficial effects related to cellular regenerative processes if mild exercise or physical activity is implemented properly. Said differently, it can be more broadly stated that the above cellular pathways are influenced by, and regulated by, both branches of the autonomic nervous system. And, with the introduction of a mild sympathetic shift via exercise, the cellular benefits of exercise can be obtained without the risk of oxidative and mitochondrial stress. There are several post-concussion human physiology studies which indicate that autonomic balance is disrupted, and is restored over time. Most of these studies cannot measure human cellular physiology per se, but strive to make inferences about autonomic dysfunction with proxy measures such as cerebral blood flow, heart rate variability, among others.[3,16,27,53]

Further still, there have been human studies that have documented that absolute rest (i.e., parasympathetic dominance) has not resulted in a positive outcome as compared to "usual care" consisting of physician directed rest (24–48 h) with return-to-school thereafter, and progressive physical activity (i.e., introduction of sympathetic influence), as per tolerance to exertion.[62,63] Early introduction of sub-symptom activity (i.e., below a symptom exacerbation threshold where ion regulation can still occur) can help cytoarchitectural stability, mitochondrial biosynthesis and neurovascular recoupling. These cellular processes may act in synergy with several others to reverse the pathophysiological processes of a concussion.

Additionally of note, high variability in symptom presentation post-injury due to stimulation, in combination with behaviour change (e.g., a high performance athlete becoming suddenly sedentary) can cloud clinical understanding of severity. Said differently, reducing or limiting an active individual can prove much more detrimental than originally thought.[22] It must also be noted that the high variability in symptom score and clinical challenges are also resultant of a gross under-and-over self-reporting issue that has been well documented. However, this is not to discount the effect of rapid change from frequent exertion/activity to isolated rest that an athlete may experience.

Ultimately, there are several factors that are associated with neuronal health and synaptic plasticity. In the acute phases of concussion, several pathways are blunted through sedentary behaviour and remain in a down-regulated state while at rest.[32] Conversely, sub-symptom threshold physical activity has been found to be associated with enhanced signalling pathways, that mitigate the effects of a concussion and optimize recovery and resolution.[7,10,12,22] What was not discussed herein, but is an area for future discussion is how sub-symptom activity can be physiologically challenged by modifying different aspects of exercise (i.e. duration, time, modality, intensity etc).

Funding sources

This research review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to report.

Acknowledgements

All authors acknowledge Drs Bjornson, Goodman, Bhambhani, and Asmundson, for their contribution to our lab's critical thinking related to concussion and physiology, and the application to patients. We also thank the Canadian Institutes of Health Research and the Saskatchewan Health Research Foundation for the research funding support that has provided the foundation for our work.

References

1. McCrory P, Meeuwisse W, Dvorak J et al. Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, 2016. *Br J Sports Med* 2017; 51(11):838–847. http://dx.doi.org/10.1136/bjsports-2017-097699, bjsports-2017-097699.
2. Ellis MJ, Leddy J, Willer B. Multi-disciplinary management of athletes with post-concussion syndrome: an evolving pathophysiological approach. *Front Neurol* 2016; 7:1–14. http://dx.doi.org/10.3389/fneur.2016.00136.
3. McCrea M, Meier T, Huber D et al. Role of advanced neuroimaging, fluid biomarkers and genetic testing in the assessment of sport-related concussion: a systematic review. *Br J Sports Med* 2017; 51(12):919–929. http://dx.doi.org/10.1136/bjsports-2016-097447, bjsports-2016-097447.
4. Ryan ML, Ogilvie MP, Pereira BMT et al. Heart rate variability is an independent predictor of morbidity and mortality in hemodynamically stable trauma patients. *J Trauma* 2011; 70(6):1371–1380. http://dx.doi.org/10.1097/TA.0b013e31821858e6.
5. Kamins J, Bigler E, Covassin T et al. What is the physiological time to recovery after concussion? Systematic review. *Br J Sports Med* 2017; 51(12):935–940. http://dx.doi.org/10.1136/bjsports-2016-097464, bjsports-2016-097464.
6. Mccrory P, Feddermann-demont N, Dvořák J et al. What is the definition of sports-related concussion: a systematic review. *Br J Sports Med* 2017; 51:877–887. http://dx.doi.org/10.1136/bjsports-2016-097393.
7. Schneider KJ, Leddy JJ, Guskiewicz KM et al. Rest and treatment/rehabilitation following sport-related concussion: a systematic review. *Br J Sports Med* 2017; 51(12):930–934. http://dx.doi.org/10.1136/bjsports-2016-097475, bjsports-2016-097475.
8. Ellis MJ, Leddy JJ, Willer B. Physiological, vestibulo-ocular and cervicogenic post-concussion disorders: an evidence-based classification system with directions for treatment. *Brain Inj* 2015; 29(2):238–248. http://dx.doi.org/10.3109/02699052.2014.965207.
9. Leddy J, Hinds A, Sirica D, Willer B. The role of controlled exercise in concussion management. *Pm&R* 2016; 8(3):S91–S100. http://dx.doi.org/10.1016/j.pmrj.2015.10.017.
10. Leddy JJ, Willer B. Use of graded exercise testing in concussion and return-to-activity management. *Curr Sports Med Rep* 2013; 12(6):370–376. http://dx.doi.org/10.1249/JSR.0000000000000008.
11. Marosi K, Mattson MP. BDNF mediates adaptive brain and body responses to energetic challenges. *Trends Endocrinol Metab* 2014; 25(2):89–98. http://dx.doi.org/10.1016/j.tem.2013.10.006.
12. Murray PS, Holmes PV. An overview of brain-derived neurotrophic factor and implications for excitotoxic vulnerability in the hippocampus. *Int J Pept* 2011; 2011. http://dx.doi.org/10.1155/2011/654085.
13. Renvoisé B, Blackstone C. Emerging themes of ER organization in the development and maintenance of axons. *Curr Opin Neurobiol* 2010; 20(5):531–537. http://dx.doi.org/10.1016/j.conb.2010.07.001.
14. Ramirez OA, Couve A. The endoplasmic reticulum and protein trafficking in dendrites and axons. *Trends Cell Biol* 2011; 21(4):219–227. http://dx.doi.org/10.1016/j.tcb.2010.12.003.
15. MacAskill AF, Kittler JT. Control of mitochondrial transport and localization in neurons. *Trends Cell Biol* 2010; 20(2):102–112. http://dx.doi.org/10.1016/j.tcb.2009.11.002.
16. Len TK, Neary JP. Cerebrovascular pathophysiology following mild traumatic brain injury. *Clin Physiol Funct Imaging* 2011; 31:85–93. http://dx.doi.org/10.1111/j.1475-097X.2010.00990.x.
17. Leddy JJ, Haider MN, Ellis M, Willer BS. Exercise is medicine for concussion. *Curr Sports Med Rep* 2018; 17(8):262–270. http://dx.doi.org/10.1249/JSR.0000000000000505.
18. Ellis MJ, Leddy J, Cordingley D, Willer B, Ellis MJ. A physiological approach to assessment and rehabilitation of acute concussion in collegiate and professional athletes. *Front Neurol* 2018; 9:1–14. http://dx.doi.org/10.3389/fneur.2018.01115.
19. McCrory P, Meeuwisse WH, Aubry M et al. Consensus statement on concussion in sport—the 4th international conference on concussion in sport held in Zurich, November 2012. *PM R* 2013; 5(4):255–279. http://dx.doi.org/10.1016/j.pmrj.2013.02.012.
20. Barkhoudarian G, Hovda DA, Giza CC. The molecular pathophysiology of concussive brain injury. *Clin Sports Med* 2011; 30(1):33–48. http://dx.doi.org/10.1016/j.csm.2010.09.001.
[21]. Giza CC, Hovda DA. The new metabolic cascade of concussion. *Neurosurgery* 2014; 75(04):S24–S33. http://dx.doi.org/10.1227/NEU.0000000000000505.
22. Mychasiuk R, Hehar H, Ma I, Candy S, Esser M. Reducing the time interval between concussion and voluntary exercise restores motor impairment, short-term memory, and alterations to gene expression. *Eur J Neurosci* 2016; 44(7):2407–2417. http://dx.doi.org/10.1111/ejn.13360.
23. Leddy JJ, Kozlowski K, Donnelly JP, Pendergast DR, Epstein LH, Willer B. A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. *Clin J Sport Med* 2010; 20(1):21–27. http://dx.doi.org/10.1097/JSM.0b013e3181c6c22c.
24. Buckley TA. Acute and lingering impairments in post-concussion postural control. *Concussions Athl Brain Behav* 2014:139–165. http://dx.doi.org/10.1007/978-1-4939-0295-8.
25. Laker SR. Return-to-play decisions. *Phys Med Rehabil Clin N Am* 2011; 22(4):619–634. http://dx.doi.org/10.1016/j.pmr.2011.08.004.
26. Segal M, Korkotian E. Roles of calcium stores and storeoperated channels in plasticity of dendritic spines. *Neurosci* 2016; 22(5):477485. http://dx.doi.org/10.1177/1073858415613277.
27. Bishop S, Dech R, Baker T, Butz M, Aravinthan K, Neary JP. Parasympathetic baroreflexes and heart rate variability during acute stage of sport concussion recovery. *Brain Inj* 2017; 9052:1–13. http://dx.doi.org/10.1080/02699052.2016.1226385.
28. Willie CK, Colino FL, Bailey DM et al. Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function. *J Neurosci Methods* 2011; 196(2):221–237. http://dx.doi.org/10.1016/j.jneumeth.2011.01.011.
29. Venkat P, Chopp M, Chen J. New insights into coupling and uncoupling of cerebral blood flow and metabolism in the brain. *Croat Med J* 2016; 57(3):223–228. http://dx.doi.org/10.3325/cmj.2016.57.223.
30. Peterson EC, Wang Z, Britz G. Regulation of cerebral blood flow. *Int J Vasc Med* 2011; 2011. http://dx.doi.org/10.1155/2011/823525.
31. Griesbach GS. Exercise after traumatic brain injury: is it a double-edged sword? *PM R* 2011; 3(6):S64–S72. http://dx.doi.org/10.1016/j.pmrj.2011.02.008.
32. Griesbach GS, Hovda DA, Molteni R, Wu A, Gomez-Pinilla F. Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. *Neuroscience* 2004; 125(1):129–139. http://dx.doi.org/10.1016/j.neuroscience.2004.01.030.
33. Griesbach GS, Gomez-Pinilla F, Hovda DA. The upregulation of plasticity-related proteins following TBI is disrupted with acute voluntary exercise. *Brain Res* 2004; 1016(2):154–162. http://dx.doi.org/10.1016/j.brainres.2004.04.079.
34. Kreber LA, Griesbach GS. The interplay between neuropathology and activity based rehabilitation after traumatic brain injury. *Brain Res* 2016; 1640:152–163. http://dx.doi.org/10.1016/j.brainres.2016.01.016.
35. Lonze BE, Ginty DD. Function and regulation of CREB family transcription factors in the nervous system. *Neuron* 2002; 35(4):605–623. http://dx.doi.org/10.1016/S0896-6273(02)00828-0.

36. Wrann CD, White JP, Salogiannnis J et al. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. *Cell Metab* 2013; 18(5):649–659. http://dx.doi.org/10.1016/j.cmet.2013.09.008.
37. O'Leary T, Wyllie DJA. Neuronal homeostasis: time for a change? *J Physiol* 2011; 589(20):4811–4826. http://dx.doi.org/10.1113/jphysiol.2011.210179.
38. Heusner CL, Martin KC. Signaling from synapse to nucleus, in *Structural and Functional Organization of the Synapse*, Hell JW, Ehlers MD, editors, New York, NY, Springer Science+Business Media LLC, 2008, p. 601–620.
39. Steegborn C. Structure, mechanism, and regulation of soluble adenylyl cyclases — similarities and differences to transmembrane adenylyl cyclases. *Biochim Biophys Acta Mol Basis Dis* 2014; 1842(12):2535–2547. http://dx.doi.org/10.1016/j.bbadis.2014.08.012.
40. Meitzen J, Luoma JI, Stern CM, Mermelstein PG. β1-Adrenergic receptors activate two distinct signaling pathways in striatal neurons. *J Neurochem* 2011; 116(6):984–995. http://dx.doi.org/10.1111/j.1471-4159.2010.07137.x.
41. Zippin JH, Chen Y, Straub SG et al. CO_2/HCO_3– and calcium-regulated soluble adenylyl cyclase as a physiological ATP sensor. *J Biol Chem* 2013; 288(46):33283–33291. http://dx.doi.org/10.1074/jbc.M113.510073.
42. Schnyder S, Handschin C. Skeletal muscle as an endocrine organ: PGC-1α, myokines and exercise. *Bone* 2015; 80:115–125. http://dx.doi.org/10.1016/j.bone.2015.02.008.
43. Avila J, Lucas JJ, Perez M, Hernandez F. Role of tau protein in both physiological and pathological conditions. *Physiol Rev* 2004; 84(2):361–384. http://dx.doi.org/10.1152/physrev.00024.2003.
44. Chen Q, Zhou Z, Zhang L et al. Tau protein is involved in morphological plasticity in hippocampal neurons in response to BDNF. *Neurochem Int* 2012; 60(3):233–242. http://dx.doi.org/10.1016/j.neuint.2011.12.013.
45. Sheng Z, Lee A, Catterall WA. Initiation and regulation of synaptic transmission by presynaptic calcium channel signaling complexes 2 calcium currents in excitable cells 3 calcium channel subunit structure. *Struct Funct Organ Synap* 2008;(80):147–172.
46. Turrigiano G. Homeostatic synaptic plasticity. *Struct Funct Organ Synap* 2008:535–552. http://dx.doi.org/10.1007/978-0-387-77232-5_18.
47. Sleiman SF, Henry J, Al-Haddad R et al. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β-hydroxybutyrate. *Elife* 2016; 5:1–21. http://dx.doi.org/10.7554/eLife.15092.
48. Swiatkowski P, Nikolaeva I, Kumar G et al. Role of Akt-independent mTORC1 and GSK3β signaling in sublethal NMDA-induced injury and the recovery of neuronal electrophysiology and survival. *Sci Rep* 2017; 7(1):1539. http://dx.doi.org/10.1038/s41598-017-01826-w.
49. Hoeffer CA, Klann E. mTOR signaling: at the crossroads of plasticity, memory, and disease. *Trends Neurosci* 2011; 33(2):1–17. http://dx.doi.org/10.1016/j.tins.2009.11.003.mTOR.
50. MacInnis MJ, Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity. *J Physiol* 2016; 00:1–16. http://dx.doi.org/10.1113/JP273196.
51. Takei N. Brain-derived neurotrophic factor induces mammalian target of rapamycin-dependent local activation of translation machinery and protein synthesis in neuronal dendrites. *J Neurosci* 2004; 24(44):9760–9769. http://dx.doi.org/10.1523/JNEUROSCI.1427-04.2004.
52. Yoshii A, Constantine-Paton M. Postsynaptic BDNF-TrkB signaling in synapse maturation, plasticity, and disease. *Dev Neurobiol* 2010; 70(5):304–322. http://dx.doi.org/10.1002/dneu.20765.
53. Meier TB, Bellgowan PSF, Singh R, Kuplicki R, Polanski DW, Mayer AR. Recovery of cerebral blood flow following sports-related concussion. *JAMA Neurol* 2015; 87106(5):1–9. http://dx.doi.org/10.1001/jamaneurol.2014.4778.
54. Ellis MJ, Ryner LN, Sobczyk O et al. Neuroimaging assessment of cerebrovascular reactivity in concussion: current concepts, methodological considerations, and review of the literature. *Front Neurol* 2016; 7:1–16. http://dx.doi.org/10.3389/fneur.2016.00061.
55. Baker JG, Freitas MS, Leddy JJ, Kozlowski KF, Willer BS. Return to full functioning after graded exercise assessment and progressive exercise treatment of post-concussion syndrome. *Rehabil Res Pract* 2012; 2012:1–7. http://dx.doi.org/10.1155/2012/705309.
56. Leddy JJ, Baker JG, Willer B. Active rehabilitation of concussion and post-concussion syndrome. *Phys Med Rehabil Clin N Am* 2016; 27(2):437–454. http://dx.doi.org/10.1016/j.pmr.2015.12.003.
57. Potter LR. Guanylyl cyclase structure, function and regulation. *Cell Signal* 2011; 23(12):1921–1926. http://dx.doi.org/10.1016/j.cellsig.2011.09.001.
58. Leddy JJ, Baker JG, Kozlowski K, Bisson L, Willer B. Reliability of a graded exercise test for assessing recovery from concussion. *Clin J Sport Med* 2011; 21(2):89–94. http://dx.doi.org/10.1097/JSM.0b013e3181fdc721.
59. Leddy JJ, Haider MN, Ellis MJ et al. Early subthreshold aerobic exercise for sport-related concussion: a randomized clinical trial. *JAMA Pediatr* 2019:1–8.
60. Worts PR, Burkhart SO, Kim JS. A physiologically based approach to prescribing exercise following a sport — related concussion. *Sport Med* 2019; 49(5):683–706. http://dx.doi.org/10.1007/s40279-019-01065-1.
61. Takei N, Nawa H. mTOR signaling and its roles in normal and abnormal brain development. *Front Mol Neurosci* 2014; 7:1–12. http://dx.doi.org/10.3389/fnmol.2014.00028.
62. Thomas DG, Apps JN, Hoffmann RG, Mccrea M. Benefits of strict rest after acute concussion: a randomized controlled trial. *Pediatrics* 2015; 135(2). http://dx.doi.org/10.1542/peds.2014-0966.
63. Buckley TA, Munkasy BA, Clouse BP. Acute cognitive and physical rest may not improve concussion recovery time. *J Head Trauma Rehabil* 2017; 31(4):233–241. http://dx.doi.org/10.1097/HTR.0000000000000165.