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Review article

Aerobic exercise effects on neuroprotection and brain repair following stroke: A systematic review and perspective

Mark W. Austin[a], Michelle Ploughman[a,*], Lindsay Glynn[b], Dale Corbett[c]

[a] Recovery and Performance Laboratory, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada
[b] Health Sciences Library, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada
[c] Canadian Partnership for Stroke Recovery and Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada

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ABSTRACT

Aerobic exercise (AE) enhances neuroplasticity and improves functional outcome in animal models of stroke, however the optimal parameters (days post-stroke, intensity, mode, and duration) to influence brain repair processes are not known. We searched PubMed, CINAHL, PsychInfo, the Cochrane Library, and the Central Register of Controlled Clinical Trials, using predefined criteria, including all years up to July 2013 (English language only). Clinical studies were included if participants had experienced an ischemic or hemorrhagic stroke. We included animal studies that utilized any method of global or focal ischemic stroke or intracerebral hemorrhage. Any intervention utilizing AE-based activity with the intention of improving cardiorespiratory fitness was included. Of the 4250 titles returned, 47 studies (all in animal models) met criteria and measured the effects of exercise on brain repair parameters (lesion volume, oxidative damage, inflammation and cell death, neurogenesis, angiogenesis and markers of stress). Our synthesized findings show that early-initiated (24–48 h post-stroke) moderate forced exercise (10 m/min, 5–7 days per week for about 30 min) reduced lesion volume and protected perilesional tissue against oxidative damage and inflammation at least for the short term (4 weeks). The applicability and translation of experimental exercise paradigms to clinical trials are discussed.

Contents

* Corresponding author at: Recovery and Performance Laboratory, L.A. Miller Centre, 100 Forest Road St. John's, NL, Canada A1A 1E5. Tel.: +1 709 777 2099; fax: +1 709 777 2082.
E-mail address: michelle.ploughman@med.mun.ca (M. Ploughman).

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1. Introduction

Stroke is a leading cause of disability among adults, with only 65% of survivors returning to full functional independence one year after the event (Murray et al., 2012; Wolfe, 2000). Approved treatments to reverse stroke-induced damage are limited, with intravenous fibrinolytic therapy and endovascular clot disruption being two of the only treatments with proven benefit (Ciccone et al., 2013; Jauch et al., 2013). Research examining the results of rehabilitative efforts in physiotherapy, occupational therapy, and speech and language therapy are promising, but the interventions rarely lead to full recovery of function (Langhorne et al., 2011). There is an urgent need for effective stroke treatments supported by high quality clinical research.

In recent years, researchers have begun to investigate the effects of aerobic exercise (AE) as a means of enhancing neuroplastic change and functional outcomes after stroke (Kreisel et al., 2007; Mang et al., 2013). There is emerging evidence suggesting that AE is neuroprotective, preventing age-related brain atrophy and enhancing performance in healthy populations (Cotman and Berchtold, 2002; Kramer et al., 2006) and in populations with neurodegenerative diseases (Ahlskog et al., 2011), however the optimal parameters (days post-stroke, intensity, mode, duration) to influence brain repair processes are not known (Schmidt et al., 2013). Animal studies suggest that early intervention is more effective than delayed intervention (Biernaskie et al., 2004) however intensive treatments given too early (e.g. 1–3 days post-stroke) may exacerbate injury (Risedal et al., 1999). Accordingly, clinical guidelines for stroke now suggest that treatment interventions begin as early as possible, although how intense or how early the intervention should be has not yet been established (Jauch et al., 2013). Large scale trials of very early mobilization and exercise after stroke, such as the AVERT trial, are underway (Bernhardt et al., 2006), and preliminary findings suggest that mobilization within 24 h of stroke is safe (Bernhardt et al., 2008), is associated with better functional recovery (Cumming et al., 2011), and is cost-effective (Tay-Teo et al., 2008). That said, early mobilization is not the same as AE and others have reported that mobilization beginning within 24 h after stroke is associated with poorer outcomes, increased dependency, and higher rates of death when compared to mobilization between 24 and 48 h (Sundseth et al., 2012). If AE were to be implemented as part of early post-stroke care, clinicians would have to be assured (through both animal models and randomized controlled trials) that AE could safely be applied (Bernhardt et al., 2007). In clinical trials, AE interventions have taken place during the sub-acute and chronic stages of stroke. Literature reviews (Brogardh and Lexell, 2012) and meta-analysis (Stoller et al., 2012) report that AE in sub-acute and chronic stroke leads to improved gait and aerobic capacity; however, the evidence that AE influences brain repair, neuroplasticity and cognitive function is less compelling (Stoller et al., 2012).

We undertook this systematic review in order to consolidate potentially important findings of post-stroke AE in animal models and clinical trials; specifically, we aimed to ask, (1) at what point after stroke can AE be safely implemented to gain maximum benefit?; (2) What is the relationship, if any, between post-stroke AE and brain repair processes? and (3) What can be gleaned from preclinical evidence to inform future clinical trials?

2. Search methodology

We aimed to identify all human and animal studies relating to stroke, aerobic exercise, cognition and markers of behavioral recovery and neuroplasticity. Excluding non-English titles and following PRISMA guidelines (Liberati et al., 2009), we searched PubMed, CINAHL, PsychInfo, the Cochrane Library, and the Central Register of Controlled Clinical Trials, including all years up to July 13, 2013. Based on previous research, we created the keyword search list (Table 1) and search strategies were designed and performed by a librarian specializing in systematic reviews (LG) with input on keyword selection provided from two other authors (MA, MP). Reference lists of included articles were hand-searched for other studies with potential relevance.

Table 1
Search keywords.

Population	Intervention	Outcome
Stroke hemorrhage	Exercise	Executive function
Ischemia	Motor activity	Cognition
Infarct	Exercise	Plasticity
Cerebral artery occlusion	Physical activity	Recovery
Vascular accident	Aerobic	Memory
Human	Physical conditioning	Brain-derived neurotrophic factor
Animal	Treadmill	Mental process
Mice	Running	Performance
Rat	Fitness	Neurotrophic

Human studies were included if participants were over the age of 18 and had experienced an ischemic or hemorrhagic stroke. No criteria were set for time since stroke occurrence. We included animal studies that utilized any method of global (two vessel occlusion) or focal ischemic stroke (transient or permanent middle cerebral artery occlusion, photothrombosis, endothelin-1-induced occlusion) or intracerebral hemorrhage (collagenase injection).

In human studies, any intervention utilizing AE-based activity (ergometry, swimming, treadmill walking/running) with the intention of improving cardiorespiratory fitness was accepted for this review. Exercise must have been implemented for more than 2 min, following stroke, to meet the threshold for aerobic metabolism (Medbo et al., 1988) and at least one component of AE fitness (perceived exertion, heart rate, etc.) must have been measured. Activities undertaken as task-specific training (i.e. gait practice to improve walking speed) were not included. In animal studies, post-stroke AE included both voluntary exercise (VE), which is placement in a cage with access to a voluntary running wheel, and forced exercise (FE), which included forced motorized treadmill running, placement in a motorized running wheel, swimming, or placement on a rotating rod.

Title results across search databases were merged into a single database and inclusion status independently evaluated by two authors (MA, MP). If the authors disagreed, the title was included. Abstracts of accepted titles were evaluated in the same manner resulting in a final file containing accepted manuscripts. We extracted and categorized the data from the included studies and described methods and data quality using an article summary form. Consistency of findings and methodology across laboratories and stroke models was noted. In order to compare results across studies, we recalculated lesion size by expressing average lesion size in exercising animals as a percentage of the volume of the average lesion size in sedentary controls at the first point of measurement after stroke.

3. Review results

Of the 4250 titles returned in the initial search, a total of 264 abstracts were identified for further review (Fig. 1). Of the final 72 manuscripts, 47 studies involved the effects of exercise on brain repair parameters (lesion volume, oxidative damage, inflammation, cell death, neurogenesis, angiogenesis and stress; Table 2) so were included in this review. The effects of AE on other outcomes such

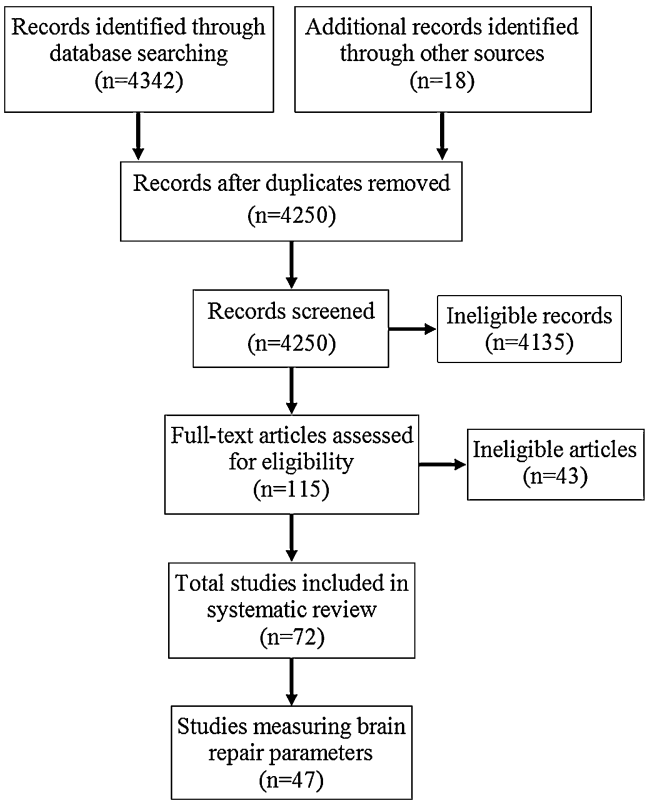

Fig. 1. PRISMA flowchart of search strategy.

as behavior and neurotrophins were excluded. No human studies met inclusion/exclusion criteria. Thirty-six of 47 studies employed a model of injury to the middle cerebral artery territory in young adult male rats while two used mice (Gertz et al., 2006; Luo et al., 2007). Only two studies examined the effects of AE in old animals (Ding et al., 2003; Maldonado et al., 2008). Two studies used female animals but did not control for estrous cycle (Maldonado et al., 2008; Wang et al., 2005). Seven studies examined global ischemia in rats (Briones et al., 2004, 2005; Cechetti et al., 2012; Yagita et al., 2006) or gerbils (Lee et al., 2003b; Sim et al., 2004, 2005) and three studied exercise in a hemorrhagic model of stroke (Jin et al., 2010; Lee et al., 2003a, 2005).

Table 2
Included studies.

Outcome	Reference
Lesion volume ($n = 33$)	Chang et al. (2011), Dahlqvist et al. (2003), Ding et al. (2003, 2004), Gertz et al. (2006), Hu et al. (2010), Johansson and Ohlsson (1996), Komitova et al. (2005), Lee et al. (2003a, 2005, 2008, 2009), Luo et al. (2007), Ma et al. (2013a,b), Maldonado et al. (2008), Marin et al. (2003), Matsuda et al. (2011), Quirie et al. (2012), Risedal et al. (2002), Sakakima et al. (2012), Shimada et al. (2013), Wang et al. (2005), Yang et al. (2012, 2003a,b), Zhang et al. (2012a,b,c, 2013a,b,c) and Zheng et al. (2011)
Oxidative damage ($n = 2$), inflammation ($n = 3$) & cell death ($n = 11$)	Cechetti et al. (2012), Lee et al. (2003a,b, 2005), Matsuda et al. (2011), Mizutani et al. (2011), Sakakima et al. (2012), Sim et al. (2004, 2005), Song et al. (2012) and Zhang et al. (2012a,b,d)
Neurogenesis ($n = 14$)	Briones et al. (2004, 2005), Jin et al. (2010), Komitova et al. (2005), Lee et al. (2003b, 2005, 2008), Luo et al. (2007), Shimada et al. (2013), Sim et al. (2004), Song et al. (2012), Yagita et al. (2006) and Zhang et al. (2013a,c)
Angiogenesis ($n = 6$)	Hu et al. (2010), Ma et al. (2013b), Matsuda et al. (2011), Sakakima et al. (2012), Yang et al. (2012) and Zheng et al. (2011)
Stress ($n = 6$)	Dahlqvist et al. (2003), Ke et al. (2011), Mizutani et al. (2011), Ploughman et al. (2005, 2007) and Risedal et al. (2002)

3.1. Aerobic exercise effects on lesion volume

Thirty-three animal studies investigated the effects of AE after stroke on lesion volume. Up to 28 days following stroke, gradual shrinking of the lesion is observed, even in sedentary control animals (Matsuda et al., 2011; Shimada et al., 2013; Yang et al., 2003b; Zhang et al., 2013a). No studies reported an increase in lesion volume following aerobic activity, even when exercise was initiated as early as one day after stroke.

Thirteen studies reported insignificant effects of AE on lesion volume after stroke when compared to sedentary controls. The study methodologies had some common features: (1) exercise was initiated three or more days post-stroke (Ding et al., 2003, 2004; Lee et al., 2005, 2008; Ma et al., 2013a,b; Quirie et al., 2012; Sakakima et al., 2012); (2) the mode of exercise was VE rather than FE (Dahlqvist et al., 2003; Johansson and Ohlsson, 1996; Komitova et al., 2005; Luo et al., 2007; Marin et al., 2003), or the methods included both delayed intervention and VE (Gertz et al., 2006; Maldonado et al., 2008; Risedal et al., 2002).

Forced exercise paradigms, whether treadmill FE (Chang et al., 2011; Lee et al., 2005, 2009; Matsuda et al., 2011; Shimada et al., 2013; Wang et al., 2005; Yang et al., 2012, 2003a,b; Zhang et al., 2012a,b,c, 2013a,b,c; Zheng et al., 2011) or running wheel FE (Hu et al., 2010) reduced lesion volumes compared to sedentary controls. However, daily 20 min FE in the form of rota-rod training (4.8 m/min) beginning three days after stroke for two weeks did not result in significant differences (Sakakima et al., 2012). All treadmill training sessions lasted 20–30 min, and took place 5–7 days per week. Despite differences in stroke models, findings were consistent; two studies examined hemorrhagic stroke (Lee et al., 2003a, 2005), the remainder employed models of focal ischemia of various severities.

Further analysis of the effects of FE on lesion volume revealed differential effects of post-stroke exercise onset, duration of exercise, and exercise intensity. All FE protocols that began very early (24 h) after stroke resulted in significant reductions in volume (Chang et al., 2011; Hu et al., 2010; Lee et al., 2005, 2009; Matsuda et al., 2011; Wang et al., 2005; Yang et al., 2012, 2003a,b; Zhang et al., 2012a,b,c; Zheng et al., 2011). Two studies specifically compared timing of FE initiation after stroke and found that early exercise (commencing 24 h post-stroke) reduced lesion volumes significantly more than late exercise (3–7 days post-stroke) (Lee et al., 2005; Yang et al., 2003a).

Volume of the lesion reduces over time even in sedentary stroke control animals but FE appears to augment this effect by protecting tissue that would ordinarily die (Fig. 2). Consistent findings from various studies in different laboratories indicate that longer FE exercise durations (14–28 days) resulted in greater tissue protection than FE for shorter periods (7 days) (Hu et al., 2010; Lee et al., 2009; Matsuda et al., 2011; Wang et al., 2005; Yang et al., 2003b; Zhang et al., 2012a). In one study (Wang et al., 2005), comparing the effect of age (3–4 month old rodents versus 22–24 months) on the timing of FE-induced benefits showed that younger animals gained benefit earlier (i.e. in the first 7 days) compared to the older animals.

In terms of differential effects of exercise intensity (FE) beginning 24 h after stroke, lower intensity exercise (30–40% of rodents' maximum running speed or <10 m/min on a treadmill) (Chang et al., 2011; Lee et al., 2009; Yang et al., 2012; Zhang et al., 2012a,

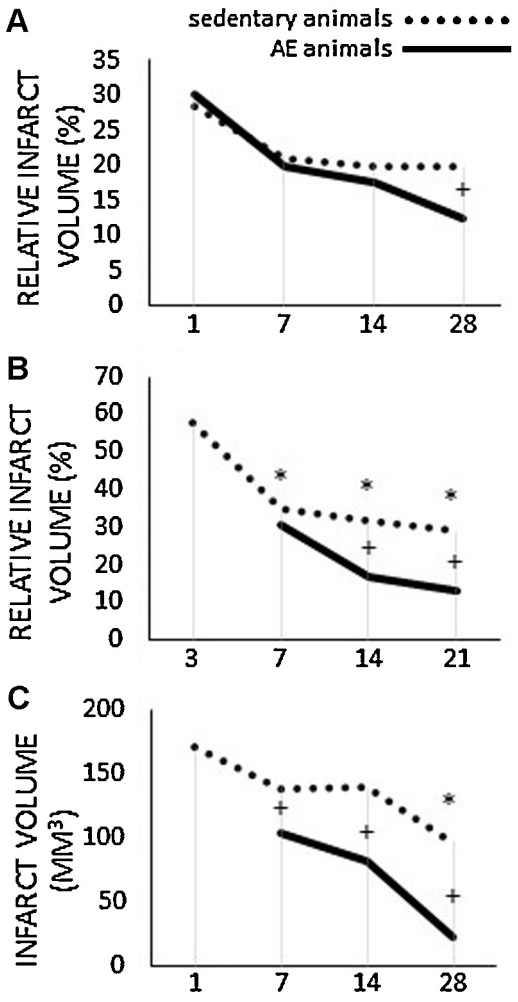

Fig. 2. Data from the three studies, measuring lesion size after FE at similar time points post-stroke are recalculated (A and B only) as a percentage of sedentary stroke control animals. A, Matsuda et al. (2011); B, Zhang et al. (2013c); C, Yang et al. (2003b). *Significantly less than baseline measurement ($p < 0.01$); †Significantly less than control group ($p < 0.05$).

2013a) tended to reduce lesion volume more than moderate or vigorous intensities whether the duration was 7 days (25–58% of the volume of sedentary control lesions) or 14 days (22–58%). The exception to this trend were the results of three studies (Yang et al., 2012; Zhang et al., 2012a; Zheng et al., 2011) that reported greater lesion reduction (i.e. greater neuroprotective effect), ranging from 21% to 32% of volume of sedentary controls, following moderate intensity exercise (12–20 m/min). All of the rodents in these studies were preconditioned with three days of treadmill training prior to receiving stroke, which in and of itself may have provided some neuroprotective effect. Only Yang et al. (2012) reported that moderate intensity exercise was more effective than low intensity exercise; this study was unique in that rats exercised for five days per week as opposed to seven days, therefore it is possible that less frequent but higher intensity exercise may be of benefit.

In summary, in animal models of stroke, daily FE, but not VE, initiated very early post-stroke and continuing beyond 14 days reduced lesion size by sparing vulnerable tissue. Furthermore, in terms of optimal exercise parameters, in most studies using naïve animals, low to moderate running speeds for greater than 2 weeks post-stroke appeared to be more beneficial than shorter duration or more intensive running protocols.

3.2. Aerobic exercise effects on post-stroke oxidative damage, inflammation and cell death

Following ischemic stroke, excitotoxicity leads to inflammation and oxidative stress in affected tissue, resulting in blood brain barrier dysfunction, microvascular injury, and cell death, that in turn leads to cerebral damage (Lakhan et al., 2009). An increasing body of evidence suggests that progression of ischemic stroke in the acute phase is related to inflammation; however, later inflammatory responses may contribute to repair and recovery (Wang et al., 2007). Thirteen studies included in this review investigated the effects of AE on oxidative damage, inflammation, and/or cell death.

3.2.1. Oxidative damage

Two studies investigated the effects of long term, moderate intensity FE on oxidative damage in models of global (Cechetti et al., 2012) and focal (Song et al., 2012) ischemia. These studies suggest that exercise increases genes and proteins associated with protection from oxidative damage and does not significantly elevate free radical levels. In the global ischemia study, rodents exercised for 12 weeks, three times per week, gradually progressing from 12 to 48 m/min over 12 weeks, resulted in favorable regulation of thiobarbituric acid reactive substances, a marker of oxidative lipid damage, within the hippocampus (but not the cortex or striatum). Superoxide dismutase, an antioxidant defence enzyme, as well as free radical levels were not significantly affected by exercise (Cechetti et al., 2012). Similarly, after focal ischemia of the left parietal lobe, forced swimming exercise, initiated 24 h post-stroke (20 min/day, 5 days/week), suppressed oxidative lipid damage (malondialdehyde) and increased superoxide dismutase activity in the hippocampus of the ischemic hemisphere (Song et al., 2012).

3.2.2. Inflammation

Days after the initial ischemic event, delayed injury and secondary inflammation occurs, especially in regions adjacent to the ischemic lesion (Heiss, 2012). The three studies included in this review report a reduction in inflammation in response to AE after stroke (Mizutani et al., 2011; Sakakima et al., 2012; Zhang et al., 2012d). Two weeks of moderate intensity FE initiated 24 h after stroke in rodents significantly inhibited microglia-mediated release of pro-inflammatory cytokines in perilesional cortex and striatum when assessed after 3, 5, and 7 days of exercise. Furthermore, this protocol also significantly reduced mRNA expression of ICAM-1, which contributes to neuro-inflammation caused by ischemia at the same time points (Zhang et al., 2012d). Two studies examined how delayed exercise, beginning in the sub-acute phase of stroke, might affect more delayed glial responses. Daily 20-min rota-rod training (4.8 m/min), for two weeks beginning 3 days after a focal lesion significantly decreased GFAP (a marker of astroglial cell activity associated with scarring) in areas surrounding the lesion (Sakakima et al., 2012); however, 21 days of mild-to-moderate FE significantly increased GFAP in the cortex (Mizutani et al., 2011).

3.2.3. Cell death

Stroke induces necrosis and a cascade of apoptotic (programmed cell death) events induced by oxygen free radicals, DNA damage, ionic imbalance, and protease activation in the affected tissue (Doyle et al., 2008). Eleven studies investigated the effects of AE after stroke on apoptosis assessed 5–28 days after stroke (Lee et al., 2003a,b, 2005; Matsuda et al., 2011; Mizutani et al., 2011; Sakakima et al., 2012; Sim et al., 2004, 2005; Zhang et al., 2012a, 2013b).

Most studies investigating exercise-induced effects on apoptosis after stroke used FE paradigms. Low to moderate intensity (<%60

maximum running intensity or 8–13 m/min, 20–30 min/day) FE exercise initiated 24–48 h after stroke reduced DNA fragmentation (Lee et al., 2005; Zhang et al., 2012a, 2013c) and caspase-3 (Lee et al., 2003a,b; Matsuda et al., 2011; Sim et al., 2004, 2005; Zhang et al., 2013b), all of which are markers and/or facilitators of apoptotic cell death. This regimen also increased bcl-2 (Zhang et al., 2013b) and midkine (Matsuda et al., 2011); known inhibitors of apoptosis.

One of the important considerations in applying exercise post-stroke is identifying the optimal time window for intervention. The studies described above consistently show that exercise is protective when initiated 1–2 days post stroke, at least for the short term (<4 weeks post-stroke). One study, exploring the effects of delayed (3 days) forced rota-rod training (4.8 m/min, 20 min/day, for 14 days) also showed reduced DNA fragmentation and caspase-3 expression in the perilesional region (Sakakima et al., 2012). Only one study examined exercise initiated immediately following stroke (3 h) and found that the protective effect adjacent to the hemorrhagic core was abolished (when tested at 11 days) with this very early intervention (Lee et al., 2005). In contrast to the extensive research in FE, only one study investigated the effects of VE on apoptotic markers. Mizutani et al. (2011) reported that two weeks of 12 h daily running wheel exposure beginning 2 h after middle cerebral artery occlusion significantly reduced pro-apoptotic markers in the ipsilesional cortex seven days after infarction.

In summary, this body of evidence suggests that in animal models, moderate intensity FE beginning 1–2 days after stroke is protective against oxidative damage and ameliorates inflammatory processes early after stroke. Long term protection beyond 28 days has not been studied. Exercise beginning less than 24 h following stroke may not be as beneficial in preventing apoptosis. The role of exercise in glial scar formation in the affected area is less clear.

3.3. Aerobic exercise effects on post-stroke neurogenesis

In adult mammals, adult neurogenesis occurs in the subventricular zone and the subgranular zone of the dentate gyrus of the hippocampus (Wiltrout et al., 2007). Following stroke, these newborn cells tend to migrate toward damaged brain tissue (Wiltrout et al., 2007). In animals, inhibition of neurogenesis is associated with decreases in long term recovery and increases in lesion volume after a focal lesion (Sun et al., 2012).

Fourteen studies examined neurogenesis post-stroke, following both VE (Jin et al., 2010; Komitova et al., 2005; Luo et al., 2007; Yagita et al., 2006); and FE (Briones et al., 2004, 2005; Lee et al., 2003b, 2005, 2008; Shimada et al., 2013; Sim et al., 2004; Song et al., 2012; Zhang et al., 2013a,c). This synthesized data suggests that VE has differential effects depending on exercise duration and housing conditions. Regardless of the model of stroke or timing of AE initiation, long term VE (3–6 weeks) provided rats are not housed in isolation for long periods of time (Komitova et al., 2005; Yagita et al., 2006), enhanced neurogenesis after stroke (Jin et al., 2010; Luo et al., 2007) and may promote migration of surviving newborn cells to the lesion site (Jin et al., 2010).

FE appears to have beneficial effects on neurogenesis as well. Short-term FE (8–14 days) is associated with reduced neurogenesis but also decreased apoptosis (Lee et al., 2003b; Sim et al., 2004; Zhang et al., 2013a) suggesting a possible rescue of neuronal cells. Longer term FE (20–40 min/day) for 2–4 weeks seems to consistently increase neurogenesis (Lee et al., 2008; Shimada et al., 2013; Song et al., 2012; Zhang et al., 2013c) except when exercise is performed for only 5 min a day at low intensities (Briones et al., 2004, 2005).

3.4. Post-stroke aerobic exercise-induced angiogenesis

Induction of angiogenesis, the growth of new blood vessels, not only increases blood flow to the area affected by stroke, but also stimulates recovery mechanisms such as neurogenesis, synaptogenesis, and contributes to synaptic and neuronal plasticity (Ergul et al., 2012; Schmidt et al., 2013). Six studies investigated the effects of AE on angiogenesis after stroke, all of which employed FE paradigms (Hu et al., 2010; Ma et al., 2013b; Matsuda et al., 2011; Sakakima et al., 2012; Yang et al., 2012; Zheng et al., 2011).

Two weeks of moderate to high intensity FE beginning 1–3 days following focal ischemia resulted in increased expression of a variety of angiogenesis-promoting proteins, including angiopoietein-1 (Zheng et al., 2011), CD-31 cells (Hu et al., 2010; Matsuda et al., 2011; Sakakima et al., 2012; Yang et al., 2012), MMP2 and VEGF mRNA (Ma et al., 2013b) and TIE-2 receptors (Zheng et al., 2011) in the cortex surrounding the lesion (Hu et al., 2010; Ma et al., 2013b; Matsuda et al., 2011; Sakakima et al., 2012) and striatum (Yang et al., 2012). The same benefits are not seen in lower intensity exercise (8 m/min) (Yang et al., 2012) or when training continues beyond two weeks post-ischemia. Matsuda et al. (2011) reported that mild-to-moderate FE beginning 2 days after middle cerebral artery occlusion significantly increased PECAM-1 expression (a marker of endothelial cells, which are involved in angiogenesis) in a widespread area around the infarct after three days, seven days, and 14 days of exercise. Beneficial effects were lost after four weeks of training.

In summary, in animal models of focal ischemia, two weeks of moderate to high intensity FE induces pro-angiogenic proteins and genes in widespread cortical and subcortical areas. These potentially beneficial effects are not seen with protocols using lower intensity and longer duration bouts of exercise. No studies were identified that investigated the effects of VE on angiogenesis.

3.5. Stress response to post-stroke aerobic exercise

Excessive stress after focal ischemia (i.e. placement of an intruder rodent in a cage with a larger, aggressive rodent) may elevate corticosterone to such an extent that it impairs cognitive function (Sugo et al., 2002). On the other hand, mild stress (i.e. placement of a rodent in a confined tube) with resulting smaller increases in corticosterone, may improve spatial memory (Faraji et al., 2011). AE, depending on dose and intensity, is likely a stressor. Six studies, using animal models of stroke, assessed the effects of post-stroke AE on serum or plasma corticosterone levels (Dahlqvist et al., 2003; Ke et al., 2011; Mizutani et al., 2011; Ploughman et al., 2005, 2007; Risedal et al., 2002).

Although a single bout of either VE or FE following stroke, regardless of intensity, increases corticosterone levels (Ploughman et al., 2005, 2007); the effects appear to be temporary (Ploughman et al., 2007). Importantly, serum corticosterone levels after a single bout of exercise, even when particularly high, do not seem to significantly impact factors associated with brain plasticity (BDNF, IGF-I, synapsin-I), at least in the short term (Ploughman et al., 2005, 2007). That said, the threshold dividing positive from negative effects of exercise-related stress is not known.

Seven days of short term (Ke et al., 2011) or longer term (four weeks) (Dahlqvist et al., 2003) VE does not significantly elevate blood levels of corticosterone. Conversely, two weeks of 12 h daily VE wheel exposure significantly increased heat shock protein 70 (HSP70) and heat shock factor 1 adjacent to the infarct, which are markers of cellular stress (Mizutani et al., 2011), and four weeks of 24 h daily VE wheel exposure significantly increased adrenal gland weight (Risedal et al., 2002).

In summary, single bouts of VE or FE only temporarily elevate corticosterone, and this elevation does not appear to impact

proteins and genes associated with neuroplasticity. However, significant increases in other stress markers (e.g. HSP70, adrenal weight) occur when VE is performed for two or more weeks. The effect of prolonged FE protocols on serum corticosterone and consequent effects in CNS stress proteins (e.g. HSP70) after stroke, either in patients or animals, is not known.

4. Discussion

4.1. Early exercise post-stroke

We aimed to determine the point at which aerobic exercise could be safely implemented after stroke to gain maximum benefit. Contrary to what we expected, none of the included studies showed an expansion of lesion size even when exercise (regardless of mode or intensity) was initiated within 24 h post-stroke. In fact our synthesized findings suggested that early-initiated (24–48 h post-stroke) moderate *forced* exercise (10 m/min, 5–7 days per week for about 30 min) reduced lesion volume more than later onset exercise (>3 days). Furthermore, forced exercise initiated at 24 h protected perilesional tissue against oxidative damage and inflammation.

The therapeutic window to initiate exercise to influence lesion volume, inflammation, oxidative stress and cell death, at least in animal models, seems to be short; with exercise onset before 3 h or beyond 3 days having little benefit. However it is important to consider that the therapeutic window in which neuroplastic processes are optimal in human stroke is much longer than that observed in animal studies. Furthermore, although aerobic exercise seems to suppress innate inflammatory responses, inflammation and removal of dysfunctional neurons may in fact contribute to repair and recovery (Wang et al., 2007).

The challenge in translating findings in animal models to clinical trials include understanding the optimal timing of intervention for people who have more severe stroke or who are challenged by co-morbidities. These patients suffer from paralysis, spasticity and reduced fitness which impacts their ability to exercise. Furthermore, since most experiments studied the effects of exercise in adolescent and young adult animals, exercise effects on the older adult and senescent brain after stroke are not known. Although most people who survive stroke begin to be mobilized after a few days, studies examining the effects of very early mobilization (<24 h) in acute care are conflicting. The AVERT trial, for example, reported superior outcomes (Bernhardt et al., 2006, 2008; Cumming et al., 2011), while others report increased dependency and higher mortality when compared to mobilization within 24 and 48 h (Sundseth et al., 2012). The optimal parameters for early exercise intervention tailored to patient health, age and stroke severity are not known (Bernhardt et al., 2007). In order to advance understanding of aerobic exercise timing, researchers must utilize methods to map brain perfusion, inflammation, and neuronal activity in order to monitor exercise effects during the acute phase of stroke.

4.2. Optimal exercise parameters to promote brain recovery

Our review revealed a preponderance of studies employing FE paradigms compared to VE. Based on the description of aerobic exercise in clinical trials (Mackay-Lyons et al., 2013; Ploughman et al., 2008), the FE protocol, with investigator or therapist-determined speed and duration, may be more similar to the post-stroke clinical condition. There may be little clinical translational value of VE regimes in stroke rehabilitation studies. Furthermore, even though both regimes are stressful to animals (Ploughman et al., 2007), FE but not VE, reduced lesion volume.

In terms of the differential effects of mode of exercise training, only five of 42 included studies employed exercise training without a wheel or treadmill; four used rotating rod (Ding et al., 2003; Lee et al., 2008; Sakakima et al., 2012; Yang et al., 2012) and another examined forced swimming exercise (Luo et al., 2007). The rotating rod activity combines coordination and balance with locomotion and when compared to similar doses of treadmill training (8 m/min), rotating rod exercise did not affect lesion size (Ding et al., 2003; Yang et al., 2012). Only two studies reported enhanced reparative process with rotating rod (angiogenesis (Yang et al., 2012) and neurogenesis (Lee et al., 2008)) compared to the strong body of evidence using treadmill and wheel running. Although studies employing swimming exercise were also included in this review, the one study examining this mode of exercise (Luo et al., 2007) found no benefit, however exercise duration was only 60 s twice per day. Because of safety concerns and the requirement for symmetrical movement of all four limbs, swimming for aerobic training may not be suitable for patients with hemiplegia in the early stages of stroke recovery. In order to translate findings from exercise and rehabilitation studies using animal models of stroke to clinical trials, the mode of exercise is important with (forced) treadmill or wheel running being more applicable to practice.

Understanding the dosage of exercise (intensity and duration) required to impact brain repair after stroke is critical to translation to clinical trials and clinical practice (Schmidt et al., 2013). We found that treadmill or wheel running speeds varied from a low of 8 m/min to a high of 22 m/min. The effect of intensity, particularly in forced exercise, was fairly consistent across stroke models with moderate intensity (30–50% of the running speed capacity or 10–12 m/min) being most effective in reducing lesion volume, decreasing inflammation and promoting neurogenesis. The exception is in the effects of exercise on angiogenesis, where faster running speeds for shorter duration (moderate to high intensity, <2 weeks) result in robust increases in markers of angiogenesis adjacent to the lesion (Hu et al., 2010; Ma et al., 2013b; Matsuda et al., 2011; Sakakima et al., 2012) and in the striatum (Yang et al., 2012). It is likely that all the exercise regimens are stressful, but there appears to a threshold where just the 'right' amount of exercise promotes neuroprotective and brain repair mechanisms and the optimal parameters are challenging to reproduce in VE protocols. Future studies in animal stroke models should carefully implement gradually increasing intensities and durations of exercise in a range of stroke models (hemorrhagic and ischemic), severity (size), and locations (e.g., cortex, striatum).

4.3. Short versus long term benefits

Even when exercise is initiated early, the effects on the damaged brain are both short and long term. Although several studies showed that longer duration FE (28 days) resulted in a more robust reduction in lesion volume, oxidative damage, apoptosis and inflammation, the majority of protocols were 5–16 days. Only one study examined outcome (oxidative stress) beyond 28 days (12 weeks (Cechetti et al., 2012)). This raises the question whether exercise truly provides long term neuroprotection and brain repair. Future studies should examine longer term outcome after cessation of exercise to determine the durability of benefits.

5. Conclusions

Studies employing a range of animal models consistently showed that moderate forced exercise, employed 24 h post-stroke, induced significant beneficial effects on short term outcomes (4 weeks). In order to translate these findings to clinical research, preclinical trials must examine the effects of exercise titration in the

longer term and in various severities of stroke. To assure safety in human studies, researchers must employ precise imaging of brain tissue function during the exercise intervention in order to determine the immediate effects on the brain in the acute phase of stroke.

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