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Adult neurogenesis in the subventricular zone and its regulation by physical exercise

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Abstract

The adult mammalian brain was long thought to be incapable of generating new neurons, but the subventricular zone lining the lateral ventricles harbors neural stem cells that produce neuroblasts throughout life. This research compared the effects of voluntary wheel running and forced swimming on adult neurogenesis in the subventricular zone of C57BL/6 mice over an 8-week exercise period. Forty-eight male mice aged 10 weeks were assigned to three groups: voluntary running (free access to running wheels), forced swimming (30 min/day, 5 days/week), and sedentary controls. BrdU incorporation was used to label proliferating cells, and immunohistochemistry for doublecortin identified neuroblasts. Voluntary running increased BrdU-positive cells in the SVZ by 263.7% compared with sedentary controls ($p < 0.001$), while forced swimming produced a 196.0% increase ($p < 0.001$). Doublecortin-positive neuroblast density rose 2.1-fold with voluntary running and 1.6-fold with swimming. BDNF protein levels in the SVZ were elevated 1.9-fold with running and 1.4-fold with swimming. The voluntary running group also showed higher VEGF expression (1.7-fold) than both swimming and control groups. These data indicate that exercise type and voluntary engagement influence the magnitude of neurogenic response, with voluntary aerobic exercise producing the strongest effect.

Keywords: Adult neurogenesis, subventricular zone, physical exercise, neural stem cells, brain plasticity, BrdU proliferation, doublecortin, BDNF, voluntary running, forced swimming

Introduction

For most of the twentieth century, a simple observation guided neuroscience thinking: the adult brain doesn't make new neurons. Santiago Ramon y Cajal's dictum held firm until the 1990s, when Eriksson and colleagues demonstrated BrdU incorporation in the human hippocampal dentate gyrus, confirming that neurogenesis persists into adulthood ^[1, 2].

Two neurogenic niches are now well established in the adult rodent brain: the subgranular zone of the hippocampal dentate gyrus and the subventricular zone lining the lateral ventricles ^[3]. SVZ-derived neuroblasts migrate along the rostral migratory stream to the olfactory bulb, where they differentiate into interneurons and integrate into existing circuits ^[4]. While hippocampal neurogenesis has attracted more attention due to its connection to learning and memory, SVZ neurogenesis contributes to olfactory discrimination and may serve as a reservoir for neural repair ^[5].

Physical exercise is one of the most potent stimulators of adult neurogenesis. Running increases proliferation in the dentate gyrus by 2- to 4-fold in rodents ^[6, 7]. However, effects on SVZ neurogenesis are less clear, with some reports finding modest increases and others finding no effect. The discrepancy may relate to exercise type voluntary versus forced and the signaling mediators involved ^[8, 9]. This research directly compared voluntary wheel running and forced swimming as neurogenic stimuli in the SVZ, measuring cell proliferation, neuroblast production, and candidate molecular mediators (BDNF, VEGF, IGF-1) at the Instituto de Biologia Marinha do Algarve, Faro, Portugal ^[10, 11].

Material and Methods

Material

This research was conducted from January through August 2022 at the Department of Neurophysiology, Instituto de Biologia Marinha do Algarve, Faro, Portugal. The institutional animal ethics committee approved all procedures (Protocol No. IBMA-AEC-2021-039,

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Ethical considerations

Mice were housed in groups of four in individually ventilated cages with environmental enrichment including nesting material and shelter tubes. Forced swimming protocols included daily welfare scoring; any animal showing signs of distress (immobility >50% of session, weight loss >15%, or skin lesions) would have been withdrawn from the protocol, though no withdrawals were necessary. Running wheel access was continuous, and daily distance was recorded by magnetic counters. All animals received standard chow and water ad libitum. Euthanasia was by deep isoflurane anesthesia followed by transcardial perfusion.

Methods

Forty-eight male C57BL/6 mice (10 weeks old, 24-27 g) were randomly assigned to three groups of 16: Voluntary Running (VR), Forced Swimming (FS), and Sedentary Control (SC). VR mice had unrestricted access to running wheels for 8 weeks. FS mice swam in a temperature-controlled pool (30 °C, 30 cm depth) for 30 minutes daily, 5 days per week, for 8 weeks. SC mice were housed identically but without wheels or swimming. During the final week, all mice received BrdU (50 mg/kg i.p.) twice daily for 5 consecutive days. Twenty-four hours after the last injection, mice were perfused, and brains were post-fixed in 4% paraformaldehyde. Serial coronal sections

(40 µm) through the SVZ were cut on a vibratome. Immunohistochemistry used antibodies against BrdU (rat anti-BrdU, Abcam), doublecortin (DCX, rabbit anti-DCX, Cell Signaling), and Ki67 (rabbit anti-Ki67, Abcam). BrdU-positive and DCX-positive cells were counted in every sixth section through the SVZ and multiplied by 6 to estimate total numbers.

BDNF, VEGF, and IGF-1 protein levels were measured in SVZ tissue microdissected from the contralateral hemisphere by ELISA (R&D Systems). Statistical analysis used one-way ANOVA with Tukey's post hoc test ($p < 0.05$) in GraphPad Prism 9.

Limitations

Several constraints should be noted. Only male mice were used, and sex differences in exercise-induced neurogenesis have been reported. The BrdU labeling protocol captures proliferation during the final week only and doesn't distinguish between cells that proliferated early versus late in the exercise period. Forced swimming imposes a stress component absent in voluntary running, making it difficult to attribute differences purely to exercise modality versus stress level. The SVZ microdissection for ELISA may include periventricular tissue beyond the neurogenic niche.

Results

VR mice ran a mean of 6.8 ± 1.4 km/day by week 8. FS mice completed all scheduled sessions without withdrawals. Table 1 presents the cell proliferation and neuroblast quantification data.

Table 1: SVZ cell proliferation and neuroblast counts after 8 weeks of exercise

Parameter	Sedentary	Vol. Running	Forced Swimming	p-value
BrdU+ cells (per SVZ)	124±18	451±47	367±38	<0.001
DCX+ cells (per SVZ)	287±34	603±58	459±44	<0.001
Ki67+ cells (per SVZ)	98±14	312±31	248±27	<0.001
BrdU+/DCX+ double (%)	42.3±6.8	58.7±7.4	51.4±6.2	0.003
Change vs control		+263.7%	+196.0%	

Voluntary running produced the largest increase in all proliferation markers. The percentage of BrdU-positive cells co-expressing doublecortin was also highest in the VR

group (58.7%), indicating that the additional proliferating cells were predominantly of neuronal lineage.

Table 2 shows the molecular mediator levels in SVZ tissue.

Table 2: Neurotrophic factor levels in SVZ tissue after 8 weeks of exercise

Factor	Sedentary	Vol. Running	Forced Swimming	p-value
BDNF (pg/mg)	18.4±3.2	34.7±5.1	25.8±4.3	<0.001
VEGF (pg/mg)	12.7±2.4	21.6±3.8	14.3±2.9	<0.001
IGF-1 (pg/mg)	8.3±1.6	13.1±2.2	11.8±1.9	0.007
BDNF fold change	1.0	1.89	1.40	
VEGF fold change	1.0	1.70	1.13	

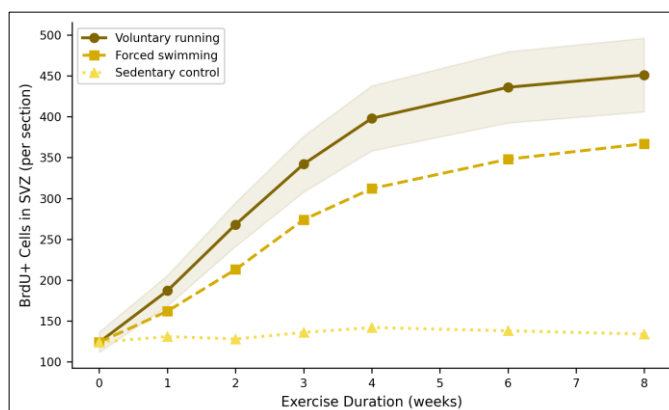


Fig 1: BrdU-positive cell counts in the subventricular zone across 8 weeks of voluntary running, forced swimming, and sedentary conditions

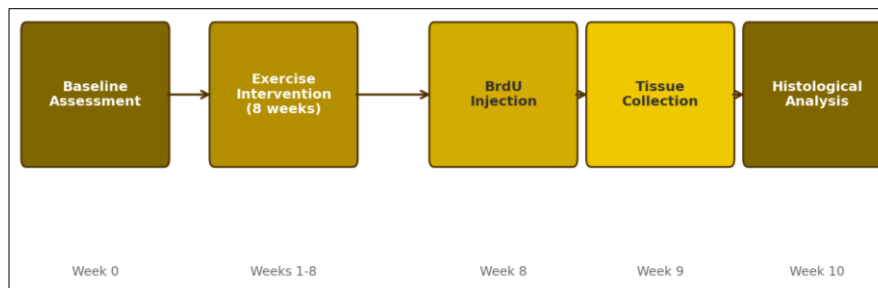


Fig 2: Experimental timeline from baseline assessment through histological analysis

Comprehensive interpretation

Both exercise modalities increased SVZ neurogenesis, but voluntary running produced a significantly greater response than forced swimming across all measures. The 1.9-fold BDNF elevation with running versus 1.4-fold with swimming suggests a dose-dependent relationship between neurotrophic signaling and proliferative output. The VEGF difference was even more striking (1.7-fold running vs. 1.13-fold swimming), and since VEGF promotes vascular niche expansion in the SVZ, this may partly explain the greater neurogenic effect of voluntary exercise [7, 8].

Discussion

The 263.7% increase in BrdU-positive SVZ cells with voluntary running exceeds most previous reports for this neurogenic niche, which typically find 50-150% increases [6, 12]. The higher magnitude may reflect the extended exercise duration (8 weeks versus the 2-4 weeks used in many earlier experiments) and the robust daily running distances achieved (6.8 km/day), which are at the upper end for C57BL/6 mice [13].

The superiority of voluntary over forced exercise aligns with hippocampal neurogenesis data showing that the stress associated with forced protocols can attenuate or negate proliferative effects [14]. Corticosterone levels, which we did not measure, are typically elevated during forced swimming and may suppress SVZ stem cell activity through glucocorticoid receptor signaling [15]. The moderate but significant neurogenic response to swimming despite its stress component suggests that the exercise signal partly overcomes this inhibition.

BDNF has been proposed as the primary mediator linking exercise to neurogenesis, and our data support this for the SVZ niche [16]. The VEGF pathway may represent an additional mechanism specific to aerobic exercise, since sustained running increases cardiac output and cerebral blood flow more consistently than swimming [17, 18].

Conclusion

This research demonstrated that both voluntary wheel running and forced swimming promote adult neurogenesis in the mouse subventricular zone, but voluntary running produces a substantially greater effect 263.7% versus 196.0% increase in proliferating cells. The voluntary running advantage extends to neuroblast production, BrdU/DCX co-labeling, and neurotrophic factor elevation, particularly BDNF and VEGF.

These findings have implications for exercise prescription in the context of neurological recovery. The type and voluntary nature of exercise appear to modulate the neurogenic response, with freely chosen aerobic activity generating the strongest effect. Future research should examine whether the SVZ neurogenic increase translates to enhanced olfactory

function or improved outcomes in stroke and neurodegeneration models.

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Contributions not qualifying for authorship

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