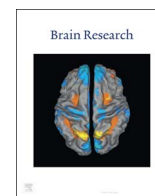




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Research Report

Physical exercise reverses spatial memory deficit and induces hippocampal astrocyte plasticity in diabetic rats

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ABSTRACT

Physical exercise can induce brain plasticity and reduce the cognitive decline observed in type 1 diabetes mellitus (T1DM). We investigated the effects of physical exercise to prevent or reverse spatial memory deficits produced by diabetes and some biochemical and immunohistochemical changes in hippocampal astrocytes of T1DM model. In this study, 56 male Wistar rats were divided in four groups: trained control (TC), non-trained control (NTC), trained diabetic (TD) and non-trained diabetic (NTD). 27 days after streptozotocin-induced (STZ) diabetes, the exercise groups were submitted to 5 weeks of aerobic exercise. All groups were assessed in place recognition (PR) test before and after training. The glial fibrillary acidic protein (GFAP) positive astrocytes were evaluated using planar morphology, optical densitometry and Sholl's concentric circles method. Glucose and glutamate uptake, reduced glutathione (GSH) and glutamine synthetase (GS) levels were measured using biochemical assays. Our main results are: 1-Exercise reverses spatial memory impairments generated by T1DM; 2-Exercise increases GSH and GS in TC but not in TD rats; 3-Exercise increases density of GFAP positive astrocytes in the TC and TD groups and increases astrocytic ramification in TD animals. Our findings indicate that physical exercise reverses the cognitive deficits present in T1DM and induces important biochemical and immunohistochemical astrocytic changes.

1. Introduction

Type 1 diabetes mellitus (T1DM) is clearly associated with an increased risk of mild and moderated cognitive dysfunction related to brain structural abnormalities (Biessels and Reijmer, 2014; Lin et al., 2015; Moheet et al., 2015; Moulton et al., 2015; Musen et al., 2006; Northam et al., 2009; Tonoli et al., 2014). Children with T1DM may present poor performance on visuospatial ability, sustained attention, reading, spelling and writing tests, which are most marked in patients with an early childhood diabetes onset (Biessels et al., 2008; Gaudieri, et al., 2008; Joner et al., 2013a; Nadebaum et al., 2012; Nunley et al., 2015). In adults with T1DM, the cognitive impairments are most evident in the domains of general intelligence, psychomotor speed,

mental flexibility, attention and information processing (Koekkoek et al., 2015; Ryan et al., 2003; Tonoli et al., 2014). Cognitive disorders are also seen in animal models of diabetes (Diegues et al., 2014; Haider et al., 2013; Nagayach et al., 2014).

Astrocytes play many physiological roles in the brain, performing diverse functions such as glycogen synthesis, glutamate uptake and glutathione (GSH) synthesis (Costa et al., 2012; Hansen et al., 2012). In glutamate metabolism, astrocytes are responsible for removing 90% of total glutamate from the synaptic cleft, and its conversion, through glutamine synthetase (GS), into glutamine for replacement in the neurons (Santin et al., 2011; Tanaka et al., 1997). Furthermore, they are able to switch their morphology and proliferation to protect and repair brain damage (Liberto et al., 2004; Pekny et al., 2014).

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GFAP is an intra-cellular intermediate filament protein, essential for the formation of stable astrocytic processes in response to neuronal damage or physiologic demands, and is used as an astrocytic marker (Baydas et al., 2005). In diabetes, the changes described relate to the pattern and level of GFAP expression since it has been shown that GFAP may decrease (Coleman et al., 2004; Guven et al., 2009; Son et al., 2015) or increase (Baydas et al., 2003; Nagayach et al., 2014; Saravia et al., 2002). Changes in astrocyte morphology are seen throughout diabetes. Astrocytes are smaller and less arborized in the earlier stages of T1DM, become hypertrophied with activated phenotype at the 2nd and 4th weeks of diabetes, and dystrophy at the 6th week (Lebed et al., 2008; Son et al., 2015). Astrocyte plasticity is a continuum of changes, thus it is important to study the phenotypic changes in these cells to better understand their response to neurological insult (Liberto et al., 2004; Pekny et al., 2014; Rodnight and Gottfried, 2013; Sofroniew and Vinters, 2010).

Beneficial effects of physical activity have been reported in T1DM cognitive impairment, although it is not so clear if exercise prevents or reverts it (Diegues et al., 2014; Kim et al., 2016; Tuzcu and Baydas, 2006). Exercise can increase the release of neurotrophic factors, induce long term potentiation (LTP), neurogenesis (Cotman et al., 2007; Inoue et al., 2015; Radahmadi et al., 2016; Yang et al., 2015), as well as increase GFAP expression (Biedermann et al., 2016; Li et al., 2005). Physical training enhances astrocyte ramification and the length of their processes, a structural arrangement closely linked to neuronal activity (Fahimi et al., 2016; Saur et al., 2012; Theodosis et al., 2008). In diabetic animals, no study has yet investigated the effects of exercise on astrocytes morphology.

Therefore, this study aimed to evaluate the effects of physical exercise on astrocytic biochemical parameters, such as glucose and glutamate uptake, glutathione content and glutamine synthetase activity in the hippocampus, and density of GFAP positive astrocytes and morphology in the hippocampal CA1 area, as well as investigate whether it prevents or reverses the spatial memory decline observed in streptozotocin-induced (STZ) diabetes T1DM in Wistar rats.

2. Results

2.1. Blood glucose levels and body weight

Blood glucose concentrations were significantly higher in diabetic groups compared to control groups ($P < 0.001$) 48 h after diabetes induction. Diabetic rats also showed significant weight loss when compared to the NTC and TC groups ($P < 0.001$). No differences between the NTD and TD groups were observed in relation to glycemia or body weight during the experiment ($P > 0.05$; Table 1).

2.2. Spatial memory analysis

Analyzing the behavioral effects as shown by the use of the place recognition test, it can be seen that, before the animals were submitted

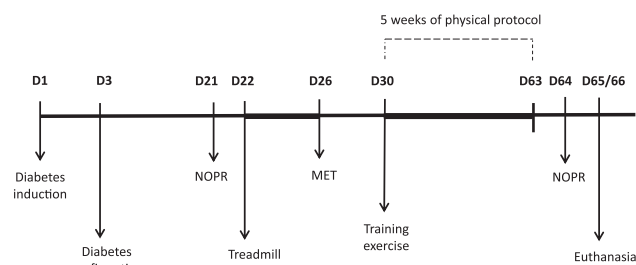


Fig. 1. Time line of the experimental design. D = day; PR Test = place recognition test; MET = maximal exercise test.

to the training protocol, both diabetic groups explored the relocated object for significantly less time than the control groups ($P < 0.05$), which explored the relocated object for similar amounts of time (Fig. 2a). After physical training, the analysis of the exploration behavior showed that NTD rats spent less time exploring the relocated object than all the other groups ($P < 0.05$), this reduction was reverted by physical training in the TD group (Fig. 2b).

2.3. Biochemical assays

2.3.1. Glucose uptake, glutamate uptake, GSH content and GS activity

Glucose and glutamate uptake were not significantly affected in the hippocampus in all groups ($P > 0.05$; Fig. 3a and b).

Physical exercise induced a significant increase in GSH and GS content in the hippocampus of the TC group, when compared to the others groups ($P < 0.05$; Fig. 3c and d).

2.4. Density of GFAP immunoreactive astrocytes

A significantly increased number of GFAP positive astrocytes/mm² was seen in the *stratum radiatum* of CA1 area in TC and TD groups as compared to NTC and NTD animals ($P < 0.01$), showing that exercise was able to increase the density of GFAP immunoreactive astrocytes (Fig. 4a,b). No significant differences were observed between the NTC and NTD groups (Fig. 4a,b).

2.5. Analysis of astrocytic morphology

2.5.1. Analysis of astrocytic ramification

A significant increase in the number of total ramifications was observed in TD rats ($P < 0.05$; Fig. 5Aa). This increase was seen in both the central and lateral orientations in TD animals, indicating that exercise in diabetic rats was able to induce astrocytic ramification in all directions ($P < 0.05$; Fig. 5Ab,c).

2.5.2. Analysis of primary processes

Primary process counting revealed that neither the total number nor the number of centrally located primary processes were affected in

Table 1

Glycemia and body weight values obtained pre, post and following 9 weeks after STZ induction.

Experimental Groups	Pre-STZ		Post- STZ		After Training Protocol	
	Glycemia	Body Weight	Glycemia	Body Weight	Glycemia	Body Weight
	(mg/dl)	(g)	(mg/dl)	(g)	(mg/dl)	(g)
NTC	97 ± 2.1	346 ± 9.5	96 ± 9.4	388 ± 10	106 ± 10.8	415 ± 11
TC	98 ± 2.0	326 ± 8.8	92 ± 10.8	370 ± 9.6	113 ± 12.3	389 ± 10
NTD	99 ± 2.0	362 ± 8.8	375 ± 10.8***	281 ± 9.6***	534 ± 12.3***	270 ± 10***
TD	100 ± 2.0	338 ± 9.1	388 ± 10.2***	272 ± 9.9***	556 ± 12.3***	288 ± 11***

Legends: NTC = non-trained control; TC = trained control; NTD = non-trained diabetic; TD = trained diabetic.

*** $P < 0.001$ comparing diabetic groups (NTD, TD) with controls groups (NTC, TC; mean ± SE).

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