doi: 10.13241/j.cnki.pmb.2020.10.008

青年和老年小鼠脑糖原及其代谢的差异 *

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摘要 目的:比较青年小鼠和老年小鼠不同脑区糖原及其代谢的差异,为后续相关研究奠定基础。**方法:**分别取雄性 C57BL/6J 青年小鼠(8 周龄)和老年小鼠(18 月龄)皮层、海马、纹状体三个脑区脑组织,通过糖原定量试剂盒检测糖原含量,通过 Western Blot 检测糖原代谢相关酶(包括糖原合成、糖原分解、葡萄糖转运、乳酸转运相关酶类)的表达水平。**结果:**与青年小鼠相比,老年小鼠皮层、纹状体糖原含量明显上升,但海马的糖原含量无明显变化。在糖原合成代谢的关键酶中,糖原合成酶在老年小鼠皮层、纹状体的表达水平明显升高,而海马区则无明显差异;糖原分支酶在老年小鼠皮层的表达水平有所下降,在海马和纹状体则无明显变化。在糖原分解代谢的关键酶中,老年小鼠的糖原磷酸化酶在皮层、海马和纹状体均明显升高,而糖原脱支酶在上述脑区则无明显变化。葡萄糖转运体 1 的表达水平在老年小鼠与青年小鼠各脑区无显著差异。在单羧酸转运体中,老年小鼠单羧酸转运体 1 在各脑区均明显上升,单羧酸转运体 4 在皮层明显升高,其余脑区则无明显差异。**结论:**老年小鼠脑内糖原含量总体上较青年小鼠高,老年小鼠脑糖原代谢通路相关酶的表达与青年小鼠存在明显差异,且不同脑区之间存在异质性。

关键词:脑糖原;糖原代谢;青年小鼠;老年小鼠

中图分类号:R-33;Q593.2;Q591.8 **文献标识码:**A **文章编号:**1673-6273(2020)10-1835-05

Differences of Brain Glycogen and Its Metabolism between Young and Old Mice*

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ABSTRACT Objective: To compare the differences of glycogen metabolism in different brain regions between young mice and old mice, and lay the foundation for further studies. **Methods:** The tissues of cortex, hippocampus and striatum of male C57BL/6J young mice (8 weeks old) and old mice (18 months old) were separately collected. The glycogen levels in these tissues were analyzed with a glycogen assay kit. Western blot was used to detect the expression levels of glycogen metabolism related enzymes. **Results:** Compared to young mice, glycogen levels in the cortex and striatum in old mice were significantly increased, but glycogen level in the hippocampus showed no significant change. Among key enzymes of glycogenesis, the expression of glycogen synthase 1 (GYS1) in the cortex and striatum in old mice was obviously increased, but it didn't show obvious difference in the hippocampus; the expression of glycogen branch enzyme 1 (GBE1) in the cortex was decreased, however, there were no significant changes in the hippocampus and striatum. Among key enzymes of glycogenolysis, the expression of glycogen phosphorylase, brain form (PYGB) in the cortex, hippocampus and striatum was increased, but there were no significant differences in the expression of glycogen debranch enzyme (AGL) in these regions. The expression of glucose transporter 1 in these regions was not significantly changed between young mice and old mice. In addition, among monocarboxylic acid transporters, the levels of monocarboxylic acid transporter 1 (MCT1) in these brain regions in old mice were significantly increased. The levels of monocarboxylic acid transporter 4 (MCT4) in the cortex were obviously increased, but there were no significant differences in other brain regions. **Conclusions:** Generally, brain glycogen levels in old mice were higher than that in young mice. The expressions of enzymes in the pathway of brain glycogen metabolism in old mice were significantly different from that in young mice, and the glycogen metabolism differences were highly heterogeneous among various brain regions.

Key words: Brain glycogen; Glycogen metabolism; Young mice; Old mice

Chinese Library Classification (CLC): R-33; Q593.2; Q591.8 Document code: A

Article ID: 1673-6273(2020)10-1835-05

* 基金项目:国家自然科学基金重点项目(81730032);国家自然科学基金项目(81671184)

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(收稿日期:2019-12-21 接受日期:2020-01-15)

前言

随着全球人口老龄化的加剧，老龄化已成为癌症、心血管疾病、糖尿病、神经退行性疾病等人类疾病最主要的危险因素之一[1,2]。其中，神经退行性疾病（如阿尔兹海默病等）由于病因和发病机制尚不明确、治疗效果不佳而越来越受到社会的广泛关注[3,4]。近年来，有研究表明，老龄化大脑的能量代谢缺陷与神经退行性变引起的认知障碍密切相关[5-7]，提示我们能量代谢相关的分子有可能成为治疗神经退行性疾病的关键靶点。

脑糖原作为脑内最大的能量储存物质之一，主要储存于星形胶质细胞而非神经元中[8,9]。当神经元能量需求增加时，星形胶质细胞内的糖原可以迅速分解为葡萄糖或者生成乳酸，为神经元活动提供能量支持[10,11]。近年来，越来越多的证据表明，糖原供能可对禽类和哺乳动物的认知和长期记忆的形成产生积极的影响[12,13]。本研究旨在通过比较青年小鼠和老年小鼠脑糖原含量和代谢的差异，为临床诊断和治疗老龄化相关神经退行性疾病提供新的思路。

1 材料和方法

1.1 实验动物和试剂

雄性 C57BL/6J 青年（8 周龄）和老年（18 月龄）小鼠由北京维通利华实验动物技术有限公司提供。微波固定系统（ORW1.5S-Focus）购自南京 Orient Microwave 公司。凝胶成像系统（Bio-Rad）购自美国 La Jolla 公司。酶标仪（infinite M200）购自瑞士 TECAN 公司。糖原定量试剂盒（K648）购自美国 BioVision 公司。BCA 蛋白质定量试剂盒（23225）购自美国 Thermo Scientific 公司。GYS1（ab40867），PYGB（ab154969），GBE1（ab180596），AGL（ab133720），MCT1（ab90582），MCT4（ab180699），GLUT1（ab115730），β-actin（ab119716）等抗体及山羊抗兔二抗（ab6721）购自英国 Abcam 公司。Western blot 化学发光液购自美国 Millipore 公司。

1.2 方法

1.2.1 微波固定及糖原定量 为使糖原定量更加精确，通常采用微波固定的方法[14]。微波固定的原理为：微波产生的高热可迅速失活糖原代谢相关酶类，从而使糖原含量保持在处理时间点的状态。首先，将青年或老年小鼠放置在一个特制的管状空间里，通过活塞将小鼠头部固定于管的顶端。然后将放置小鼠的管子置于微波固定系统，用 1 kW 的高能微波聚焦照射小鼠头部 5 s，使小鼠安乐死。待聚焦照射处死小鼠后，立即开颅取出脑组织，并在显微镜下将皮层、海马、纹状体等脑区分离出来。各脑区糖原的含量按照糖原定量试剂盒的方法进行检测。

1.2.2 免疫印迹分析 青年或老年小鼠给予 5 %水合氯醛（0.6 mL/100 g）腹腔麻醉后开胸，经心脏灌注 0.9 %生理盐水 20 mL，然后断头取脑。冰上取皮层、海马、纹状体等组织后加入适量蛋白裂解液（RIPA 和蛋白酶抑制剂混合）并进行超声震碎。冰上裂解 30 min 后，以 13000 rpm，4 ℃离心 15 min 后取上清。通过 BCA 蛋白质定量试剂盒检测蛋白质的浓度。在 SDS 凝胶上分离不同分子质量的蛋白质，并转移到 0.22 μm 的 PVDF 膜上，然后用 5 %脱脂牛奶封闭液封闭 1 h。接着将条带置于稀释好的一抗：包括 GYS1、PYGB、GBE1、AGL、MCT1、MCT4、GLUT1 或者 β-actin 中（1:1000），在 4 ℃冰箱中孵育过夜。TBST 溶液清洗三次后，将条带置于稀释好的山羊抗兔二抗（1:10000）中并在室温下孵育 2 h。再次用 TBST 溶液清洗三次后，打开发光仪并设定好发光参数，按照 1:1 的比例配制 HRP 化学发光底物，进行扫描显影并使用 Quantity One 软件 5.0 分析条带强度。

1.3 统计学分析

采用 GraphPad Prism software version 7.0 进行统计，实验数据采用均数± 标准误（$\bar{x}$± SEM）表示，两两比较采用 t 检验，$P<0.05$ 表示两组数据间有统计学差异。

2 结果

2.1 青年和老年小鼠各脑区糖原含量的比较

将青年小鼠和老年小鼠进行微波辐照处理，并取皮层、海马、纹状体等脑区进行糖原定量。结果发现，与青年小鼠相比，老年小鼠皮层（Young: 1.004 ± 0.09412 vs Old: 1.665 ± 0.2161; P=0.0488）和纹状体（Young: 0.5831 ± 0.167 vs Old: 1.539 ± 0.1179; P=0.0095）糖原水平明显增高，而海马区糖原水平无明显变化（Young: 1.324 ± 0.08217 vs Old: 1.407 ± 0.122; P=0.6063），见图 1。

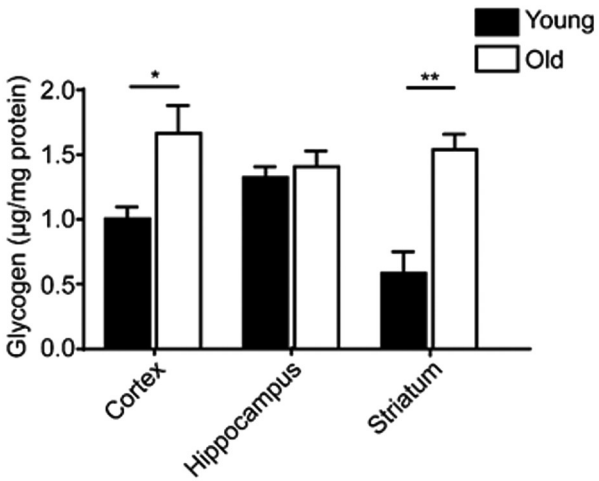

图 1 青年和老年小鼠各脑区脑糖原含量的比较

Fig.1 Comparison of glycogen content in various brain regions between young and old mice

2.2 青年和老年小鼠各脑区糖原合成相关酶类表达水平的比较

脑糖原合成的代谢酶主要为糖原合成酶（GYS1）和糖原分支酶（GBE1）[15]。Western Blot 检测发现，与青年小鼠相比，老年小鼠皮层（Young: 1± 0.0000 vs Old: 1.38± 0.09594; P=0.0167）和纹状体（Young: 0.5944± 0.09572 vs Old: 1.302± 0.2069; P=0.0361）GYS1 表达水平明显升高，而海马区则无明显变化（Young: 1.114± 0.085 vs Old: 1.217± 0.1165; P=0.5145），见图 2A。皮层 GBE1 表达水平有所下降（Young: 1± 0.0000 vs Old: 0.8113 ± 0.06634; P=0.0466），海马（Young: 0.6156± 0.04866 vs Old: 0.5572 ± 0.09013; P=0.5986）和纹状体（Young: 1.041± 0.3234 vs Old: 1.11 ± 0.171; P=0.8590）则无明显差异，见图 2B。

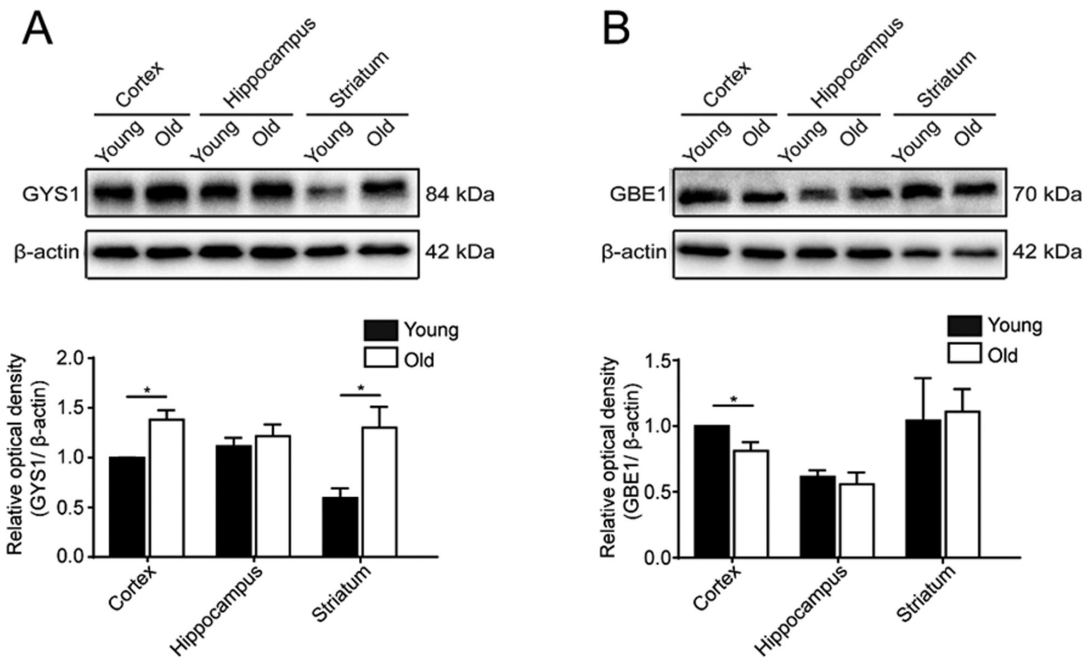

图 2 青年和老年小鼠各脑区糖原合成相关酶类的比较

Fig.2 Comparison of glycogenesis related enzymes in various brain regions between young and old mice

2.3 青年和老年小鼠各脑区糖原分解相关酶类表达水平的比较

脑糖原分解的代谢酶包括脑型糖原磷酸化酶(PYGB)和糖原脱支酶(AGL)[15]。Western Blot 检测发现,与青年小鼠相比,老年小鼠皮层(Young: 1± 0.0000 vs Old: 1.756± 0.06883; *P*=0.0004)、海马(Young: 1.229± 0.04329 vs Old: 1.808± 0.1993; *P*=0.0467)和纹状体(Young: 1.555± 0.295 vs Old: 3.108± 0.4103; *P*=0.0372)PYGB 表达水平均明显升高,见图 3A。AGL 表达水平在皮层(Young: 1± 0.0000 vs Old: 0.8511± 0.07677; *P*=0.1244)、海马(Young: 0.5818± 0.0096 vs Old: 0.4799± 0.1062; *P*=0.3936)及纹状体(Young: 0.718± 0.2013 vs Old: 0.747± 0.1182; *P*=0.9069)均无明显差异,见图 3B。

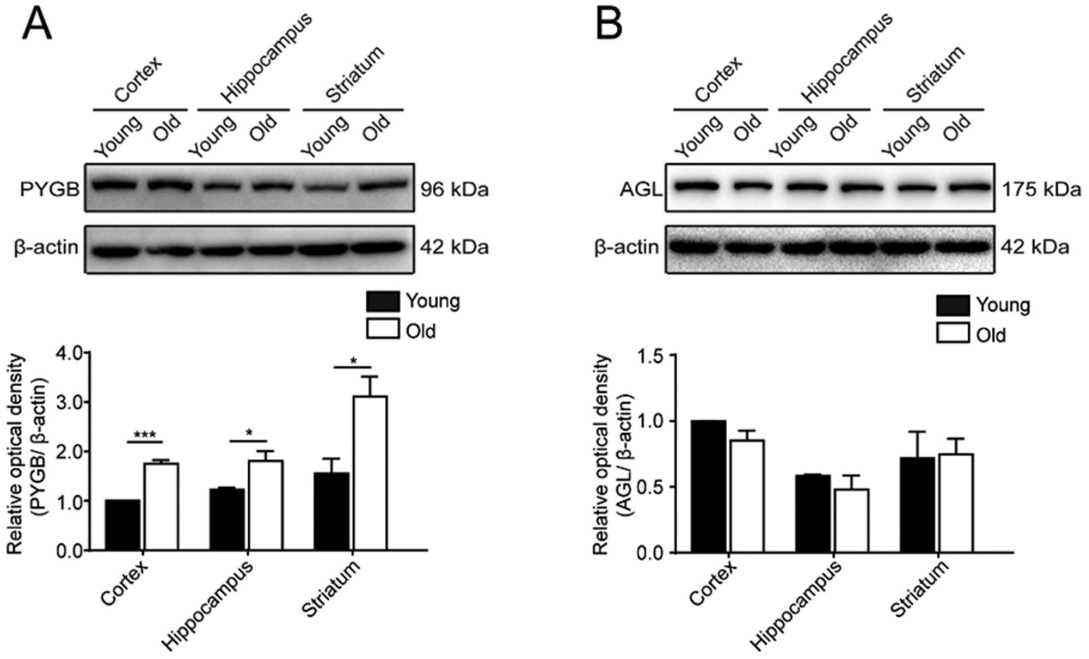

图 3 青年和老年小鼠各脑区糖原分解相关酶类的比较

Fig.3 Comparison of glycogenolysis related enzymes in various brain regions between young and old mice

2.4 青年和老年小鼠各脑区葡萄糖转运体表达水平的比较

星形胶质细胞对葡萄糖的摄取是糖原合成的先决条件,这个过程需要葡萄糖转运体(Glucose Transporters, GLUTs)的参与。在脑内,星形胶质细胞主要表达 GLUT1[16]。Western Blot 结果发现,青年小鼠和老年小鼠 GLUT1 表达水平在皮层(Young: 1± 0.0000 vs Old: 0.8278± 0.08835; *P*=0.1230)、海马(Young: 0.8956± 0.1498 vs Old: 0.6624± 0.09139; *P*=0.2546)及纹状体(Young: 0.9409± 0.1103 vs Old: 1.141± 0.07848; *P*=0.2131)区

域均无明显差异，见图 4。

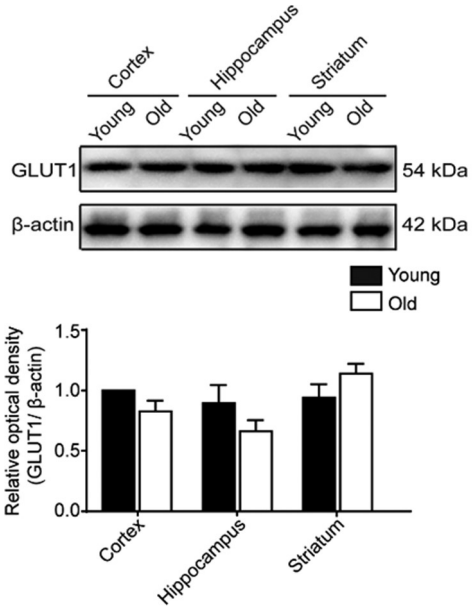

图 4 青年和老年小鼠各脑区葡萄糖转运体的比较

Fig.4 Comparison of glucose transporter in various brain regions between young and old mice

2.5 青年和老年小鼠各脑区单羧酸转运体表达水平的比较

糖原分解产生的乳酸由单羧酸转运体（Monocarboxylic Acid Transporters, MCTs）转移并输送给神经元。在脑内，星形胶质细胞主要表达 MCT1 和 MCT4[17]。Western Blot 结果显示，与青年小鼠相比，老年小鼠 MCT1 表达水平在皮层（Young: 1± 0.0000 vs Old: 1.287± 0.06984; *P*=0.0147）、海马（Young: 1.054± 0.0488 vs Old: 1.463± 0.09692; *P*=0.0197）及纹状体（Young: 1.087± 0.05487 vs Old: 1.548± 0.106; *P*=0.0181）区域均明显上升，见图 5A。MCT4 的表达水平在皮层（Young: 1 ± 0.0000 vs Old: 1.299± 0.09903; *P*=0.0394）明显升高，而在海马（Young: 1.083± 0.1443 vs Old: 1.05± 0.1794; *P*=0.8940）及纹状体（Young: 0.5855 ± 0.06694 vs Old: 0.7418 ± 0.06715; *P*=0.1745）则无明显差异，见图 5B。

3 讨论

目前，全球人口老龄化的趋势日益加重。联合国在 2015 年讨论全球人口老龄化问题的报告中指出：预计到 2050 年，全球 60 岁及以上老年人口的数量将增长一倍以上，接近 21 亿[18]。有研究显示，几乎所有老年人的大脑都表现出与神经退行性变有关的特征性变化，如老年斑，神经纤维缠结等[19-21]，严重者还会

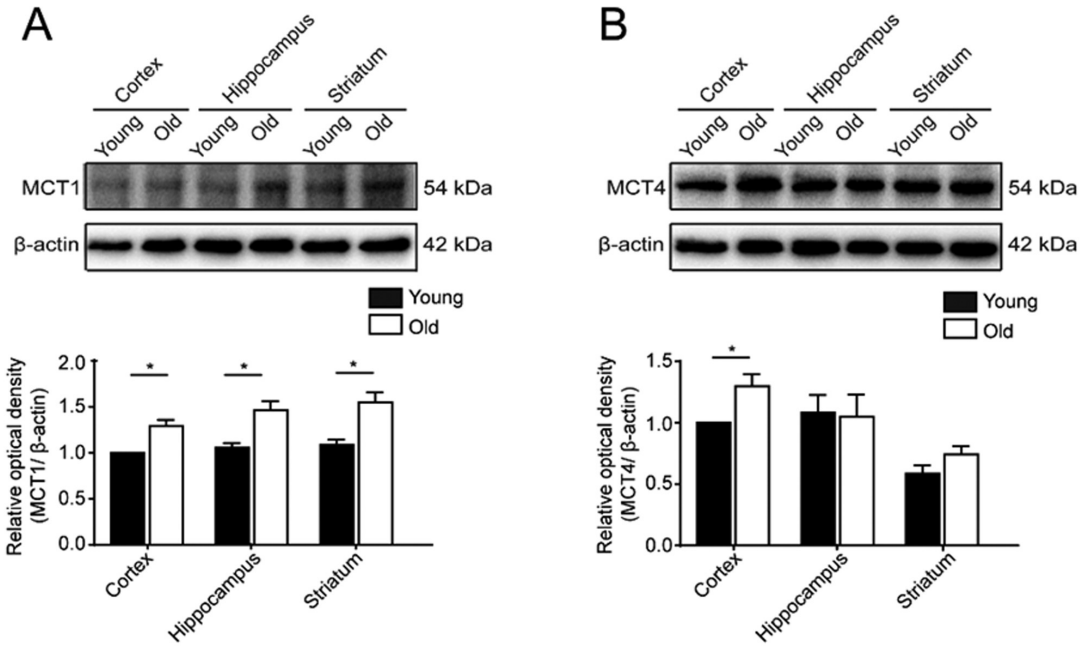

图 5 青年和老年小鼠各脑区单羧酸转运体的比较

Fig.5 Comparison of monocarboxylic acid transporters in various brain regions between young and old mice

出现特定脑区突触和神经元的丢失，导致学习记忆受损、认知功能障碍、个性改变及精神行为异常，甚至完全失去自主活动能力[22]。因此，神经退行性疾病也成为最常见、社会负担最重的疾病之一[4,21]。近年来，已有大量证据表明，大脑葡萄糖摄取及代谢能力的降低，以及线粒体功能的丧失与老龄化所引起的学习、记忆及认知障碍相关[6,16,23]，改善衰老过程中的能量代谢紊乱，能有效减少神经元凋亡，提高小鼠认知能力[24]。这些结果提示我们能量代谢相关的分子有可能将成为治疗老龄化相关的神经退行性疾病的靶点。

脑糖原被认为是脑内最大的能量储存物质之一，其主要分布于星形胶质细胞而非神经元中[9,25]。生理状态下，人类大脑糖原含量在 0.5 g 至 1.5 g 之间，约占大脑总重量的 0.1%[15]，在缺血 / 缺氧环境下，脑糖原含量会明显增加，用于应对能量代谢危机[26]。脑糖原的分解与脑内葡萄糖代谢密切相关，Brooks 等提出的 " 乳酸穿梭假说 " 认为：星形胶质细胞的糖原可分解产生乳酸，当神经元能量需求增加时，神经元会优先利用糖原分解产生的乳酸而非葡萄糖，进入神经元细胞的乳酸可经氧化磷酸化产生 ATP，从而为神经元提供能量支持[27,28]。虽然这一假说

目前仍然存在较大争议[29],但 Suzuki 等发现抑制糖原分解将直接影响小鼠记忆以及长时程增强（Long Term Potentiation, LTP)的形成[13],提示糖原代谢可能在阿尔兹海默病等神经退行性疾病中发挥重要作用。然而,关于糖原代谢是否随年龄发生变化这一科学问题尚无系统性报道。

本实验通过比较青年小鼠和老年小鼠脑糖原代谢的差异,旨在揭示糖原代谢随年龄变化的规律。结果显示,随着年龄的增加,小鼠大脑(包括皮层、海马、纹状体)糖原代谢能力明显增强,这与 Dominika 等[30]通过蛋白质组学得到的结果一致。在三个脑区中,老年小鼠皮层和纹状体糖原含量明显上升,糖原合成、糖原分解、乳酸转运的能力也明显增强,但海马区糖原含量无明显变化,仅表现为糖原分解和乳酸转运能力的增加。Yuki 等[14]通过糖原特异性抗体染色证明,虽然老年小鼠海马区的糖原在含量上与青年小鼠无明显差异,但糖原颗粒已明显发生异常改变,表现为大颗粒 " 沉积 " 样改变,提示海马区同样存在年龄相关的糖原代谢改变。此外,有研究报道年龄会引起葡萄糖摄取能力的降低[31,32],这与我们的实验结果不一致,我们的结果显示星形胶质细胞对葡萄糖的摄取能力基本相同。这种差异可能是由于实验对象选择的不同所造成的,先前的研究分别利用大鼠及 APP/PS1 转基因小鼠, 而本研究采用 18 月龄处于生理状态的野生型小鼠。我们推测,老年小鼠神经元代谢能力降低是引起星形胶质细胞糖原含量升高的主要原因,为满足神经元能量需求,星形胶质细胞糖原代谢能力代偿性增加,为神经元输送乳酸等能量物质的能力代偿性增加。

本研究对青年小鼠和老年小鼠脑糖原代谢特征进行了系统性比较。下一步我们仍需要运用药理学手段对糖原代谢进行干预,深入探讨不同年龄状态下糖原代谢模式的不同及其具体机制,为年龄相关神经退行性疾病提供新的治疗策略。

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