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妊娠合并糖尿病诱发胚胎先天性神经管缺陷动物模型的MAP 激酶信号传导机制MAP Kinase Signal Pathway in Hyperglycemia-induced Congenital Neural tube defects

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摘要

为了揭示妊娠合并糖尿病诱发胚胎先天性神经管缺陷的分子机制，并探讨其有效的防治方法。 实验选用6个实验组的 Sprague-Dawley 大鼠：第1组为常规饲养的正常对照组；第2组尾静脉注射65mg/kg Streptozotocin (STZ)构建妊娠合并糖尿病、且诱发先天性神经管缺陷的实验组大鼠；第3组为STZ构建的糖尿病、但胚胎不伴有先天性神经管缺陷的大鼠模型；第4、5、6 组为 STZ 构建的糖尿病治疗组大鼠,每日分别给予80mg/mL花生四烯酸(arachidonic acid,AA)、400mg 维生素E、抗氧化剂(维生素 E) 和不饱和脂肪酸 (saflower oil) 混合物 cocktail 治疗。于妊娠第12天取出各组胚胎，解剖显微镜下进行形态学分析；提取卵黄囊细胞蛋白质，应用特异性抗磷酸化抗体进行免疫共沉淀及 Western 印迹，对MAP 激酶 信号途径上各蛋白激酶ERK1/2、JNK1/2、RAF-1活性进行分析。 与正常对照组相比，妊娠合并糖尿病诱发的先天性神经管缺陷胚胎中(第2组)，ERK1/2蛋白激酶活性显著下降，其上游 RAF-1活性相应降低；与此相反，JNK1/2活性明显升高。在给予花生四烯酸、维生素E 补充物治疗后，通过调节MAP 激酶 信号通路蛋白激酶活性，逆转了胚胎神经管缺陷的发生。妊娠合并糖尿病诱发的胚胎先天性神经管缺陷的发生，与MAP 激酶信号传导机制异常密切相关。不饱和脂肪酸和抗氧化剂补充物的治疗作用通过对MAP 激酶信号途径的调控实现的。 AbstractThe aim of the present study was to determine molecular mechanism in hyperglycemia-induced congenital neural tube defects and the its potential pharmacologic
rescuing agents. In order to explore these questions, six study groups of Sprague-Dawley rats were employed: Group 1 was normal control rats with normal diet; group 2 represented streptozotocin (STZ) -induced diabetic rats with congenital neural tube defects in offspring; group 3 included STZ-induced diabetic rats with normal offspring; groups 4,5 and 6 included rats exposed to the same STZ-induced diabetic condition, but receiving daily oral supplementation of 80mg/mL of the sodium salt of arachidonic acid (AA), 400mg of vitamin E and a cocktail of a polyunsaturated fatty acid (saflower oil) plus an antioxidant (vitamin E) respectively. Yolk sac cells were harvested at gestational day 12 from each rat group. Changes in MAPK signaling pathways were detected by western blot analysis using special antibodies directed against phosphorylated forms of extracellular signal regulated kinase (ERK), Jun N-terminal/stress-activated protein kinase (JNK/SAPK). Furthermore, activity of RAF-1, an upstream kinase in ERK1/2 signaling cascade, was evaluated by immunoprecipitation assay. The results showed that in yolk sac cells in embryopathic offspring from experimentally-induced diabetic rats, activities of ERK1/2 were dramatically decreased (group 2). Consisted with these observation, reduction in RAF-1 kinase activity could be discerned in these diabetic yolk sac cells. In contrast, activities of JNK1/2 were significantly increased in yolk sac cells of group 2. Under rescuing circumstance,activations of ERK1/2 and RAF-1 were increased, and JNK1/2 were decreased. MAP kinase signal pathway plays a very important role in hyperglycemia induced neural tube defects. The supplementation of polyunsaturated fatty acid arachidonic acid, and antioxident vitamin E rescued conceptuses from diabetic embryopathy by triggering a restoration of normal membrane signaling pathways.

关键词 神经管缺陷 糖尿病 MAP 激酶 ERK JNK/SAPK RAF-1 动物模型Key words neural tube defect diabetes MAP kinase ERK JNK/SAPK RAF

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