

$\alpha 7$ 烟碱型乙酰胆碱受体在调控动物炎症反应中的作用

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摘 要: $\alpha 7$ 烟碱型乙酰胆碱受体 ($\alpha 7$ nAChR) 属于配体门控离子通道蛋白, 由 5 个相同的亚单位组成, 除在神经细胞表达外, 在多种免疫细胞中也有表达。 $\alpha 7$ nAChR 活化后主要通过核转录因子- κ B (NF- κ B) 和双面神激酶 2-信号传导与转录激活子 3 (JAK2-STAT3) 等信号途径调控细胞因子的基因表达、蛋白质合成, 进而缓解炎症反应。部分营养物质能通过 $\alpha 7$ nAChR 介导的信号途径调控动物炎症反应。本文主要就 $\alpha 7$ nAChR 介导的抗炎作用机制及其在营养物质调控炎症反应中的作用作一综述。

关键词: $\alpha 7$ 烟碱型乙酰胆碱受体; 营养; 调控; 炎症; 机制

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在动物生产中, 许多炎性疾病如猪的肠炎、奶牛的乳房炎等, 会削弱动物健康状况和生产力^[1-2]。因此, 缓解炎症反应对保证动物健康非常重要。研究发现, 胆碱能神经系统在调控炎症反应中发挥重要作用^[3]。在败血症猪上, 刺激传出迷走神经降低了活化单核细胞数量, 缓解了多器官功能障碍^[4]; 仔猪腹泻则伴随着回肠黏膜迷走神经递质乙酰胆碱含量的降低^[5]。 $\alpha 7$ 烟碱型乙酰胆碱受体 ($\alpha 7$ -nicotinic acetylcholine receptor, $\alpha 7$ nAChR) 是烟碱型乙酰胆碱受体的一种亚型, 是介导突触间快速信号传递的配体门控离子通道蛋白, 在巨噬细胞、淋巴细胞等免疫细胞中均有表达^[3]。研究发现, 青年母猪发生子宫内膜炎时, 子宫内膜和肌层 $\alpha 7$ nAChR 蛋白表达降低^[6]; 抑制 $\alpha 7$ nAChR 表达后提高了脂多糖 (lipopolysaccharide, LPS) 诱导的牡蛎血细胞中肿瘤坏死因子 (tumor necrosis factor, TNF) 表达^[7]; 与野生型小鼠相比, $\alpha 7$ nAChR 缺失提高了 LPS 诱导的小鼠血清中炎症细胞因子含量, 同时电刺激迷走神经不

能降低 LPS 诱导的 $\alpha 7$ nAChR 缺失小鼠血清中炎症细胞因子含量^[8]。以上结果说明, $\alpha 7$ nAChR 在胆碱能神经系统介导的抗炎途径中是必需的。本文拟就 $\alpha 7$ nAChR 介导的抗炎作用与作用机制作一综述。

1 $\alpha 7$ nAChR 简述

1.1 $\alpha 7$ nAChR 蛋白结构

$\alpha 7$ nAChR 属于神经递质门控离子通道超家族, 是由 5 个独立 $\alpha 7$ 亚基组装成的一个同型五聚体^[3]。鸡、大鼠和人 $\alpha 7$ 亚基均含有 502 个氨基酸残基, 包括由 23 个氨基酸残基组成的信号肽^[9-11], 斑马鱼 $\alpha 7$ 亚基则含 509 个氨基酸残基^[12]。鸡 $\alpha 7$ 成熟亚基有 479 个氨基酸, 与大鼠、斑马鱼和人 $\alpha 7$ 亚基同源性分别为 79%、76% 和 88%^[11-12]; 其 N 末端胞外区含有 3 个糖基化位点、5 个半胱氨酸 (Cys) 残基, 并含有 4 个 α 螺旋结构的跨膜区^[11]。N 末端胞外的 3 个糖基化位点和其中 4 个 Cys 残基及胞内区第 365 位丝氨酸 (Ser³⁶⁵)

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磷酸化位点在鸡、大鼠、斑马鱼和人上是保守的。

1.2 $\alpha 7nAChR$ 蛋白分布

$\alpha 7nAChR$ 在神经系统分布的主要区域为:大脑灰质、海马、基底神经节、丘脑、视叶及视网膜等,其表达分布的细胞主要包括脑区海马星形胶质细胞、成熟树突状细胞、小胶质细胞等^[3];此外, $\alpha 7nAChR$ 在哺乳动物血管内皮细胞、支气管上皮细胞、胸腺上皮细胞、T 淋巴细胞、B 淋巴细胞、血液白细胞、单核细胞、巨噬细胞等均有表达^[3,13],且其结构和功能与神经节上的神经元 $\alpha 7nAChR$ 相似。在斑马鱼上, $\alpha 7nAChR$ 在后脑及其附近区域有表达^[12]。 $\alpha 7nAChR$ 在神经、循环、呼吸、免疫系统中的广泛分布,表明其很可能与多种疾病之间存在联系。

2 $\alpha 7nAChR$ 介导的抗炎作用及其机制

2.1 $\alpha 7nAChR$ 介导的抗炎作用

$\alpha 7nAChR$ 在调控动物炎症反应中具有重要作用。研究发现, $\alpha 7nAChR$ 敲除加剧了肾炎小鼠肾脏损伤和炎性细胞浸润^[14]以及结肠炎小鼠的结肠炎症^[15]。抑制 $\alpha 7nAChR$ 活化则加重了大鼠胰腺炎^[16]、LPS 诱导的大鼠肝脏组织炎性细胞浸润^[17]以及关节炎小鼠软骨变性^[18]。激活 $\alpha 7nAChR$ 则缓解了结肠炎小鼠的结肠组织损伤^[19]、LPS 诱导的大鼠回肠损伤^[20]以及败血症导致的和 LPS 诱导的小鼠肺脏损伤^[21-22],但是加剧了关节炎小鼠关节肿胀^[23]。以上结果说明, $\alpha 7nAChR$ 参与了动物炎症反应的调控,且对不同组织器官炎症的调控存在差异。

细胞因子是炎症反应的主要介质,TNF- α 、白细胞介素(interleukin,IL)-1 等是重要的炎性细胞因子,能调控其他炎症介质的产生。研究发现, $\alpha 7nAChR$ 敲除提高了小鼠血清中 IL-1 β 含量^[24]以及结肠炎小鼠血清中 IL-1 β 、IL-6 和 TNF- α 含量^[15]。抑制 $\alpha 7nAChR$ 活化提高了肺脏损伤兔肺脏组织中 TNF- α 和 IL-6 含量^[25]以及右美托咪啶处理的急性肝脏损伤^[17]和急性胰腺炎^[16]大鼠血清中 TNF- α 和 IL-6 含量,但降低了 LPS 诱导的小鼠骨髓来源的单核/巨噬细胞中 TNF- α 和 IL-10 含量^[26]。激活 $\alpha 7nAChR$ 则降低了结肠炎小鼠结肠组织中 IL-6 和干扰素- γ (interferon- γ ,IFN- γ)含量^[19],烧伤小鼠血清中 IL-6 含量^[27],肺脏损伤大鼠肺脏中 TNF- α 、IL-1 β 和 IL-6 含量^[28],以及 LPS

诱导的小鼠血清^[29]、星形胶质细胞^[30]和单核巨噬细胞^[31]中 TNF- α 和 IL-6 含量。以上结果表明, $\alpha 7nAChR$ 能介导调控炎性细胞因子的产生进而调节炎症反应。

细胞因子的产生受到基因和蛋白质水平的调控。 $\alpha 7nAChR$ 介导的细胞因子含量变化可能与其参与调控细胞因子基因表达、蛋白质合成有关。研究发现, $\alpha 7nAChR$ 敲除提高了肾炎小鼠肾脏^[14]和心肌梗塞小鼠脾脏^[32] TNF- α 、IL-1 β 和 IL-6 等细胞因子基因表达。抑制 $\alpha 7nAChR$ 活化提高了右美托咪啶处理的急性肝损伤大鼠肝脏组织 TNF- α 和 IL-6 的基因表达^[17]。激活 $\alpha 7nAChR$ 则降低了烧伤小鼠胫前肌中 IL-1 β 和 IL-6 基因表达^[27],以及 LPS 诱导的小鼠海马体、前额皮质区^[33]和单核巨噬细胞 J774^[34]中 TNF- α 和 IL-1 β 基因表达。这说明 $\alpha 7nAChR$ 能介导调控细胞因子基因表达。此外,激活 $\alpha 7nAChR$ 降低了 LPS 诱导的小鼠星形胶质细胞^[30]和单核巨噬细胞 J774^[34]中 TNF- α 蛋白表达以及 LPS 诱导的大鼠神经元-小神经胶质细胞共培养中 TNF- α 和 IL-1 β 蛋白表达^[35],说明 $\alpha 7nAChR$ 能介导调控细胞因子蛋白质合成。以上结果说明, $\alpha 7nAChR$ 介导的抗炎作用可能通过调控细胞因子的基因表达、蛋白质合成来实现。

2.2 $\alpha 7nAChR$ 介导的抗炎作用机制

经典的 $\alpha 7nAChR$ 活化产生的胞内效应由离子通道介导,在一些非神经细胞中,如 T 细胞中, $\alpha 7nAChR$ 活化能提高胞内钙离子(Ca^{2+})浓度^[36]。在神经元和非神经元细胞中, $\alpha 7nAChR$ 活化还能通过活化双面神激酶 2(Janus kinase 2, JAK2)和磷酸肌醇 3 激酶(phosphatidylinositol 3-kinase, PI3K)引起丝氨酸/苏氨酸激酶(Akt)磷酸化^[37]。研究表明, $\alpha 7nAChR$ 介导的抗炎作用可能主要通过核转录因子- κB (nuclear factor-kappa B, NF- κB)信号途径与 JAK2-信号传导与转录激活子 3(signal transducer and activator of transcription 3, STAT3)信号途径实现。

2.2.1 NF- κB 信号途径

NF- κB 信号途径在调控炎症反应中发挥重要作用,参与调节多种细胞因子的表达^[3]。研究发现,激活 $\alpha 7nAChR$ 降低了 LPS 诱导的心肌损伤小鼠心肌组织中 NF- $\kappa B/p65$ 的表达^[38],烧伤小鼠肌肉^[27]和子痫前期病人单核细胞中 NF- κB 活性^[39],LPS 诱导的小鼠单核巨噬细胞中 NF- κB /

p65 磷酸化^[31,34], LPS 诱导的小鼠星形胶质细胞中 NF- κ B 核转位及其活性^[30], 以及小鼠炎性脂肪细胞中 NF- κ B/p60 和 p65 的转录活性^[40]。抑制 $\alpha 7$ nAChR 活化则增加了 LPS 诱导的心肌损伤小鼠心肌组织^[38]和慢性阻塞性肺病大鼠肺脏组织中 NF- κ B 表达^[41], 心搏停止大鼠大脑皮质和海马体中 NF- κ B 磷酸化水平^[42], 右美托咪啶处理的急性肝损伤大鼠肝脏组织中 NF- κ B/p65 磷酸化^[17], 以及 LPS 诱导的人支气管上皮细胞中 NF- κ B/p65 的表达和转录活性^[43]。这说明 $\alpha 7$ nAChR 介导的抗炎作用与 NF- κ B 密切相关。静息状态下, NF- κ B 通常以 p50-p65 异二聚体的形式与 NF- κ B 抑制蛋白 (inhibitor nuclear factor-kappa B, I κ B) 结合而呈非活化状态; 当 I κ B 被 I κ B 激酶 (I κ B kinase, IKK) 磷酸化进而泛素化被降解后, p65 和/或者 p50 亚基进入细胞核调控相关基因表达。同时, NF- κ B 受到上游信号分子 Toll 样受体 4 (Toll-like receptor 4, TLR4) 和髓样分化蛋白 88 (myeloid differential protein 88, MyD88) 的调控。研究发现, 激活 $\alpha 7$ nAChR 抑制了 LPS 诱导的小鼠单核巨噬细胞和星形胶质细胞中 I κ B 磷酸化^[30-31], 并抑制了 LPS 诱导的小鼠单核巨噬细胞中 IKK α/β 磷酸化^[31]以及心肺分流术导致的大鼠海马区 TLR4 和 MyD88 基因和蛋白表达^[44]。抑制 $\alpha 7$ nAChR 活化提高了 LPS 诱导的人支气管上皮细胞^[43]和右美托咪啶处理的急性肝损伤大鼠肝脏组织^[17]中 I κ B 的磷酸化。以上结果说明, $\alpha 7$ nAChR 活化后能抑制 I κ B 的降解, 进而抑制 NF- κ B 核转位, 最终抑制炎性细胞因子表达, 缓解炎症反应。

2.2.2 JAK2-STAT3 信号途径

JAK2-STAT3 信号途径在调控细胞因子表达、炎症反应中发挥重要作用^[45]。 $\alpha 7$ nAChR 介导的抗炎作用可能与 JAK2-STAT3 信号途径密切相关。研究发现, 激活 $\alpha 7$ nAChR 活化提高了 LPS 活化的小鼠巨噬细胞中 STAT3 磷酸化, 且不能降低 STAT3 活性缺失小鼠巨噬细胞中 TNF- α 表达^[45]; 提高了小鼠炎性脂肪细胞中 STAT3^{S727} 磷酸化^[40]; 但降低了烧伤小鼠肌肉^[27]和小鼠单核巨噬细胞^[34]中 STAT3 磷酸化以及小鼠炎性脂肪细胞中 STAT3^{Y705} 磷酸化^[40]。抑制 $\alpha 7$ nAChR 则阻止了尼古丁诱导的小鼠巨噬细胞和人冠状动脉内皮细胞中 STAT3 磷酸化^[45-46]。STAT3 能被胞质中 JAK2 激活。进一步研究表明, 抑制 $\alpha 7$ nAChR 提高了慢

性阻塞性肺病大鼠肺脏组织中 JAK2 表达^[41], 而抑制 JAK2 磷酸化后抑制了 $\alpha 7$ nAChR 活化诱导的小鼠巨噬细胞中 STAT3 磷酸化^[45]。以上研究结果表明, $\alpha 7$ nAChR 活化能通过 JAK2-STAT3 信号途径发挥抗炎作用, 但在不同组织器官炎症或损伤模式下的作用方式存在差异。

2.2.3 其他途径

除了 NF- κ B 和 JAK/STAT3 途径外, $\alpha 7$ nAChR 介导的抗炎作用还可能与其他信号通路有关, 如胞外信号调节激酶 (ERK)、p38 丝裂原活化蛋白激酶 (p38 MAPK)、环磷酸腺苷 (cAMP) 与蛋白激酶 A (PKA) 等。研究发现, 激活 $\alpha 7$ nAChR 活化抑制了 LPS 诱导的小鼠腹膜巨噬细胞中 ERK、JNK 与 p38 MAPK 磷酸化^[21]。此外, 前列腺素 E2 (prostaglandin E2, PGE2) 能提高 cAMP 含量与 PKA 活性。研究表明, 激活 $\alpha 7$ nAChR 活化提高了 LPS 活化的人单核细胞中 PGE2 含量, 而抑制 $\alpha 7$ nAChR 则降低了 PGE2 含量, 说明 $\alpha 7$ nAChR 活化后可能通过调节内源 PGE2 的产生来发挥抗炎作用^[47]。

3 营养物质通过 $\alpha 7$ nAChR 对炎症反应的调控作用

越来越多的研究发现, 多种营养素, 包括精氨酸 (Arg)、 ω -3 脂肪酸、维生素 D₃、胆碱等能够提高动物免疫功能。研究表明, 一些营养物质可以通过激活迷走神经缓解动物炎症, 调节动物免疫功能。Nijima 等^[48]报道, 静脉注射 Arg 与赖氨酸 (Lys) 提高了大鼠胸腺迷走传出神经活性和胸腺 T 细胞释放, 而对肝脏迷走神经切除大鼠没有影响, 说明 Arg 与 Lys 可以通过迷走神经调节大鼠免疫功能。另外, 高脂饲料能降低出血性休克大鼠血液中 TNF- α 与 IL-6 含量, 而化学阻滞迷走传入神经或切断迷走神经抑制了这一作用^[49-50], 说明高脂饲料能通过迷走神经调节动物炎症。

进一步研究发现, 营养物质能通过 $\alpha 7$ nAChR 调节动物炎症反应。高脂饲料降低了 LPS 诱导的小鼠肺泡巨噬细胞和肺间质巨噬细胞^[51]以及母鼠后代肝脏^[52]中 $\alpha 7$ nAChR 蛋白表达, 但提高了大鼠下丘脑外侧和腹中侧 $\alpha 7$ nAChR 与配体的结合^[53]; 抑制和激活 $\alpha 7$ nAChR 则分别抑制了高脂饲料降低出血性休克大鼠血液中 TNF- α 与 IL-6 含量的作用^[50]和高脂诱导的小鼠肝细胞中 TNF- α

与 *IL-6* 基因表达^[52]。胆碱是一个内源性 $\alpha 7nAChR$ 激动剂^[54]。研究发现,饲粮胆碱缓解了脑损伤导致的大鼠大脑海马体等区域 $\alpha 7nAChR$ 活性下降及脑部炎症^[55],但降低了 LPS 诱导的大鼠胎盘 $\alpha 7nAChR$ 蛋白表达^[56];注射胆碱则上调了 LPS 处理的小鼠海马区 $\alpha 7nAChR$ 表达及活性^[57],且不能降低 $\alpha 7nAChR$ 敲除小鼠血清中 TNF- α 含量^[58],说明胆碱能通过活化 $\alpha 7nAChR$ 调控动物炎症反应。此外,Arg 提高了大鼠前额皮质和海马体 $\alpha 7nAChR$ 蛋白表达^[59];维生素 D₃ 降低了糖尿病大鼠大脑皮层^[60]和小脑^[61] $\alpha 7nAChR$ 基因表达;而蛋氨酸-胆碱缺乏诱导了 $\alpha 7nAChR$ 敲除小鼠肝脏中 *TNF* 基因表达^[62]。以上结果说明,饲粮脂肪水平、胆碱、维生素 D₃ 等营养因素可能通过 $\alpha 7nAChR$ 调控动物炎症。

肠内信号可以通过活化位于迷走传入神经纤维的化学感受器激活迷走神经^[63]。胆囊收缩素 1 受体 (CCK-1R) 则是位于迷走传入神经纤维上的化学感受器之一^[64]。在大鼠上的研究表明,抑制 CCK-1R 表达能抑制高脂饲粮降低出血性休克大鼠血液中 TNF- α 与 *IL-6* 含量的作用,而抑制 $\alpha 7nAChR$ 表达也有同样的作用,说明高脂饲粮可能通过活化迷走传入神经上的 CCK-1R,刺激迷走神经,活化 $\alpha 7nAChR$ 调节动物炎症^[49-50]。这一结果说明,肠内营养可能通过激活迷走传入神经,进而活化 $\alpha 7nAChR$ 调控动物炎症反应。

4 小结与展望

$\alpha 7nAChR$ 广泛存在于神经细胞与多种免疫细胞中,其活化后可以通过阻止 I κ B 降解和 p65 核转位、调控 NF- κ B 转录活性进而调控细胞因子的产生,缓解炎症;同时还可以通过 JAK2-STAT3 信号途径调控细胞因子表达,产生抗炎作用。近年来, $\alpha 7nAChR$ 介导的抗炎作用越来越受到研究者的关注,并被广泛用于治疗人类多种炎症性疾病。但对于 $\alpha 7nAChR$ 介导的抗炎作用在动物上研究较少,且其活化后胞内信号传递机制,尤其是不同信号通路之间的相互作用研究较少,有待进一步研究。此外, $\alpha 7nAChR$ 在营养物质调控炎症反应中的作用研究非常少,有必要开展相关研究,为动物抗病营养研究提供新的支撑。

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Role of $\alpha 7$ -Nicotinic Acetylcholine Receptor in Regulating Anti-Inflammatory Response of Animals

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Abstract: $\alpha 7$ -nicotinic acetylcholine receptor ($\alpha 7$ nAChR) is a ligand-gated ion channel protein and consists of five $\alpha 7$ subunits. Besides neurocyte, $\alpha 7$ nAChR also expresses in several immune cells. Activating $\alpha 7$ nAChR could attenuate inflammatory response by modulating gene expression, protein synthesis of cytokines mainly through nuclear factor-kappa B (NF- κ B) and Janus kinase 2-signal transducer and activator of transcription 3 (JAK2-STAT3) signalling pathways. Several nutrients could regulate inflammation through $\alpha 7$ nAChR signalling. This review focused on the underlying mechanisms of anti-inflammation effects mediated by $\alpha 7$ nAChR and the role of $\alpha 7$ nAChR in inflammatory regulation of nutrients. [*Chinese Journal of Animal Nutrition*, 2021, 33(11):6001-6008]

Key words: $\alpha 7$ -nicotinic acetylcholine receptor; nutrition; regulation; inflammation; mechanism

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