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愤怒大鼠实验模型概述

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【摘要】 愤怒这一负面情绪会对人体产生诸多影响。与愤怒情绪产生有关的脑部区域主要与中央灰质、杏仁核、下丘脑有关。近些年关于愤怒动物模型的研究逐渐增多,愤怒机制的研究也不断深入。关于愤怒模型的研究大部分集中在中缝背核、下丘脑和海马区域,相关的神经递质研究主要与 GABA 的表达和单胺类神经递质含量相关。本文通过检索愤怒有关的动物模型,总结愤怒发生的脑内神经机制,旨在为愤怒情绪的研究提供参考借鉴。

【关键词】 愤怒;动物模型;下丘脑;前额区;海马
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Overview of experimental rat models of anger

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【**Abstract**】 Anger is a negative emotion that can have many effects on the body. The brain regions associated with the production of anger are mainly related to the central gray matter, amygdala, and hypothalamus. There has recently been a gradual increase in research into relevant animal models and the mechanisms of anger. Most studies of anger models have focused on the mid-suture dorsal nucleus, hypothalamus, and hippocampal regions, and related neurotransmitter studies have mainly been related to GABA expression and monoamine neurotransmitter content. This review summarizes the neural mechanisms of anger in the brain based on animal models related to anger, with the aim of providing a reference for the study of angry emotions.

【**Keywords**】 anger; animal model; hypothalamus; prefrontal area; hippocampus
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愤怒是情绪表达的方式之一。情绪是大脑活动与不同社会现实相互作用的产物,由愤怒、厌恶、恐惧、快乐、悲伤和惊讶 6 种离散的基本情绪表现组成,这些情绪可以是单独的,也可以是混合的[1-3]。愤怒是一种非常重要的情绪,与其他负面情绪形成对比,愤怒可以产生正面面对问题的反应[4-5]。任何引起生物反应的内在或外在刺激都被称为压力[6],可引起愤怒的压力就非常普遍。当一个人的目标被阻止时,就会产生愤怒的感觉[7]。极端高温、没有得到预期的奖励、受到不公平的对待、或一个人的目标、计划受到干扰或因某些原因未能实现,这些都可能会引起愤怒[8]。缺乏愤怒控制会对心理健康产生负面影响[9]。通常愤怒情绪可能会导致攻击性行为[10],愤怒控制管理可以减少愤怒,但不能减少攻击性[11],缺乏愤怒控制会导致家庭暴力,甚至会使人产生自杀倾向[12-13]。愤怒的发生与大脑的神经活动有密切关系,深入了解愤怒的神经机制对于愤怒控制的研究具有重要意义。

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愤怒发生的神经机制较为复杂,在已知的与愤怒发生的相关区域,包括杏仁核[8,14-15],下丘脑[16]和导水管周围灰色区域[16],内侧前额叶皮层、腹内侧前额叶、前扣带皮层、后扣带皮层等[17]。愤怒的发生,并不是脑内单独的区域活动产生的,而是单个或多个区域的活动引起的神经反应。动物模型是研究人类疾病的发病机制的重要研究工具[18]。当愤怒应激发生时,大鼠会发生神经内分泌异常并影响其表现。了解愤怒压力的神经内分泌效应对进一步的实验研究和临床应用非常重要。因此,本文旨在对愤怒大鼠模型的神经内分泌方面进行综述,研究与愤怒发生有关的神经内分泌机制。

1 愤怒大鼠模型概述

目前动物的愤怒模型主要以大鼠为主。根据造模方式的不同大致可分为 3 类:(1)夹尾入侵法;(2)社会孤立与居民闯入者;(3)昼夜颠倒环境或慢性心理应激。

(1)夹尾入侵法在国内的应用最早见于须惠仁等[19]的研究,使用纱布包裹尖端的止血钳夹大鼠尾部,令其与其他大鼠打斗,激怒其他大鼠,每天 4 次,每次 30 min。此模型的优势可快速(2 d)建立愤怒模型,但是研究者将同组大鼠饲养在同一笼中,可能造成夹尾鼠无法对笼内大鼠同等的攻击行为,无法控制实验条件的一致性。(2)SHENG 等[20]在夹尾刺激的基础上引入社会隔离,建立社会隔离和居住者入侵的愤怒模型。此模型将大鼠单笼饲养进行社会隔离,这样可解决大鼠同笼饲养可能产生的模型偏差,并且单独的入侵刺激(夹尾大鼠),可保证实验条件的一致性。社会隔离和居住者入侵法是现行最常用的愤怒大鼠模型。(3)许丽等[21]在社会隔离和居住者入侵法的基础上引进昼夜颠倒环境制作大鼠愤怒模型。此模型引入昼夜颠倒环境,类似于 CUMS 抑郁症模型,如长期造模可能引起实验动物出现抑郁情绪或睡眠障碍等其他疾病,应用时应注意时间的控制。愤怒的动物模型与抑郁症的动物模型类似,是以外部的应激刺激为主,使动物产生对抗心理从而引发愤怒的情绪。不同的是,愤怒模型造模时间一般较短且剧烈,延长造模时间可能会造成动物的抑郁情绪,影响模型的效果。

2 与愤怒发生相关的脑区域

杏仁核通常被认为与大脑情感的主要功能有关[22]。愤怒的发生与杏仁核相关区域的活动有密切关系,激活杏仁核可刺激愤怒的增加[23],杏仁核病变会导致控制愤怒的能力下降[24]。激素水平可影响杏仁核的活动,例如睾丸激素水平的增加影响杏仁核活动,诱导产生愤怒[25-26]。杏仁核的内侧和中央核,在情绪表达中发挥重要的作用[27-28],内侧杏仁核可影响竞争性攻击的发生,中央杏仁核可影响掠夺性攻击的发生[29]。杏仁核的基底外侧核,在情绪学习和感知威胁中发挥作用[30],同时基底外侧杏仁核可影响反应性攻击的发生[31]。

杏仁核对中央灰质怒的反应有两条易化和一条抑制途径:杏仁内侧核通过终纹投射到内侧下丘脑,P 物质作用于内侧下丘脑的神经激肽-1 受体,内侧下丘脑投射到中央灰质的谷氨酸能纤维可使中央灰质的 N-甲基-D-天门冬氨酸受体(N-methyl-D-aspartic acid receptor, NMDA)兴奋从而产生防御性愤怒,易化下丘脑对中央灰质的愤怒调制;杏仁基底核以兴奋性氨基酸作为递质,直接作用于中央灰质的 NMDA,增强中央灰质的怒反应。杏仁中央核以脑啡肽为递质,作用于中央灰质的 μ 阿片受体,强力抑制中央灰质的防御性怒反应。此外,杏仁核延伸区域即后侧无名质与愤怒与攻击亦有相关联系[32],直接刺激下丘脑穹隆周围区、腹内侧核及其邻近区域可产生怒的反应。

前额叶皮质是情绪中枢的重要组成部分,参与调节情绪和压力[33],可抑制下丘脑和杏仁体引发的攻击行为[34]。前额叶皮质可分为腹内侧区和背外侧区。背外侧区主要参与认知和执行功能,腹内侧区则主要与积极或消极情感相关[35-37]。腹内侧前额叶皮层(ventromedial prefrontal cortex, vmPFC)是在控制愤怒方面起着关键作用的部位[38]。经颅磁刺激与 vmPFC 有功能连接的内侧前额叶可降低愤怒情绪的表达。较高的 vmPFC 皮层活动与减少愤怒相关[39]。与 vmPMC 相连的左前中额回在控制和减少愤怒方面发挥作用[40]。此外,前扣带和岛叶同样在愤怒的发生中发挥重要作用[41]。

3 愤怒相关神经递质调制

3.1 前额区 5-羟色胺(5-hydroxytryptamine, 5-HT)水平及中缝背核 5-HT、GABA 表达

脑组织中 5-HT 可参与愤怒的调控,并对愤怒导致的攻击有明显抑制作用[42-43]。5-HT 是一种能产生愉悦情绪的单胺类神经递质,可参与情绪、认

知与行为的调节[44-45]，主要储存在中缝背核的突触囊泡内参与调节应激内分泌和行为反应[46-47]。中缝背核的功能与动物的攻击、防御行为等情绪行为密切相关[48-50]。γ-氨基丁酸（γ-aminobutyric acid，GABA）是中枢神经系统中最重要的抑制性神经递质[51]，可影响前额叶皮质的功能，参与调节情绪[52-53]。GABA 浓度升高可致前额叶皮质锥形神经元活动、兴奋性传递减少[54]。5-HT 与 GABA 之间具有相互调节作用，5-HT 可抑制谷氨酸和 GABA 释放[55]。王海娟[56]在愤怒大鼠模型中观察到，中缝背核 5-HT 能神经元释放的 5-HT 显著减少、5-HT 浓度降低，经纤维投射至前额区的 5-HT 水平亦显著降低、前额区 5-HT 浓度降低，中缝背核 GABA 含量显著升高，中缝背核 GABA B 型受体 1 抗体（GABA type B receptor subunit 1，GABABR1）表达显著升高。刘小菊[57]在愤怒大鼠模型中观察到相同的结果，并且还观察到大鼠前额区 5-HT 含量显著低于正常大鼠；使用免疫荧光法观察中缝背核 5-HT 能神经元与 GABABR1 的共表达，观察到 GABABR1 颗粒位于含 5-HT 颗粒的突触膜上，激活中缝背核 GABABR1 特异性受体，前额区 5-HT 含量显著性降低；抑制中缝背核 GABABR1 特异性受体，前额区 5-HT 含量则显著性升高。

3.2　愤怒相关神经递质与下丘脑

下丘脑是愤怒情绪从杏仁核到中央灰质传递的中间部分，下丘脑的活动影响愤怒情绪的传递。愤怒大鼠的中枢调制主要与下丘脑、额叶、海马中 5-羟色胺 2C（5-hydroxytryptamine 2C，5-HT2C）、5-羟色胺 3B（5-hydroxytryptamine 3B，5-HT3B）、GABAB 型受体 2（GABA B receptor 2，GABABR2）表达异常有关[58]。神经递质 5-HT 与 5-HT3 受体的结合导致神经元中的兴奋性反应[59]。突触前 5-HT3 受体介导或调节释放 GABA 和多巴胺（dopamine，DA）[60-61]。李红华[62]建立的郁怒大鼠模型，下丘脑、海马、顶区皮质、额区皮质中 5-HTR3B mRNA 及受体蛋白表达明显升高，高效液相-荧光检测法检测 5-HT 含量明显下降。葛庆芳等[63]同样观察到愤怒大鼠模型下丘脑中 5-HT3BR mRNA 和受体蛋白表达都明显下降。

5-HTR2C 是 5-HT 受体的一个亚型，主要分布在中枢神经系统，在下丘脑、纹状体、额叶皮质、海马、杏仁核等调节 DA 释放[64]。这种受体可显著调节情绪、焦虑和摄食[65]。有研究观察到愤怒大鼠模型中观察到，下丘脑中 5-HTR2C mRNA 及其受体蛋白表达显著降低[66-67]。柳新等[68]在愤怒大鼠模型中发现，顶区皮质和额区皮质中 5-HTR2C mRNA 及其受体蛋白表达呈现显著升高。崔维刚[69]的研究结果与这些结果相同，并且观察到顶区皮质、额区皮质、海马脑区 5-HTR2C mRNA 及其受体蛋白表达显著上升，但在下丘脑中显著降低。此外关于愤怒大鼠模型还有研究者观察到，下丘脑中 GABABR2 mRNA 及其受体蛋白表达下降[70]，胃泌素 mRNA 及其受体蛋白表达显著上升[67]。

关于下丘脑内单胺类神经递质的变化，许丽等[21]观察到 NE 和 DA 含量上升，5-HT 和肾上腺素（E）无明显改变；单胺类神经递质产物 3，4-二羟基苯乙酸（3，4-dihydroxyphenyl，DOPAC）、5-羟吲哚乙酸的含量明显升高，3-甲氧基-4-羟基苯二醇和高香草酸的含量无明显改变。宗绍波等[71]在愤怒大鼠模型下丘脑中观察到 NE 含量明显下降，额叶皮质、顶区皮质，下丘脑 DA 含量上升，下丘脑 5-HT 含量降低。余霞等[72]在愤怒大鼠模型中，观察到下丘脑 DA、NE 含量上升，5-HT 含量下降。薛刚[73]观察到愤怒大鼠模型下丘脑 NE、5-HT 含量下降；额叶皮质、顶区皮质、海马 DA 含量下降，而下丘脑 DA 含量则显著上升。对于在下丘脑区神经递质的含量会出现相反的结果，对比几种造模方法，推测不同的结果可能与造模的方法和大鼠的性别有关。

3.3　愤怒相关神经递质在海马区的表达

海马是学习和记忆的关键大脑区域，也与情绪功能和某些精神疾病有关[74]。有研究发现，在愤怒和攻击诱发条件下，左海马和左海马旁回表现出活动增加[75]。血管内皮生长因子（vascular endothelial growth factor，VEGF）诱导的神经刺激在应激反应中起重要作用[76]。SUN 等[77]在愤怒应激大鼠模型中发现，海马体和 CA3 区域中的 VEGFR2 阳性细胞数量减少，在海马体中 VEGF mRNA 表达量下降。

中枢神经递质为大脑的活动提供传递信号，在愤怒的发生和信号的传递中有重要意义。单胺类神经递质往往与精神和情绪变化有关，宗绍波等[71]在愤怒大鼠模型中观察到海马区 DA 的含量下降。杨军平等[78]发现愤怒大鼠模型海马区 5-HT 的代谢产物 DOPAC 含量亦存在上升，同时脑干组织中 NE、5-HT、DA、DOPAC 含量上升。王杰琼等[79]观察到愤怒反应大鼠海马中 5-HTR2C mRNA 和蛋白表达均增高。

GABA 为氨基酸类神经递质,参与调节情绪[53]。杨军平等[78]建立的愤怒大鼠模型中观察到,海马区 GABAA 型受体 α2 mRNA 表达下降。蔡洪信等[80]观察到愤怒情绪模型大鼠海马 GABABR1、GABABR2 和腺苷酸环化酶表达水平降低。GABA 在脑部广泛分布,当愤怒发生时,GABA 可能同时在多个脑区出现异常。耿燕楠[81]发现,在愤怒大鼠模型的顶区皮层、额区皮层、海马和下丘脑中 GABABR2 mRNA 及受体蛋白表达下降。

当愤怒发生时,海马的局部会发生异常。许莉莉等[82]在愤怒大鼠模型中观察到,在海马 CA1 区中 GABABR1、GABABR2 和内向整流型钾通道(KIR)表达水平降低,在海马 CA3 区中 GABABR2 和 KIR 表达水平降低。殷慧敏[83]在愤怒模型大鼠海马 CA3 区锥体细胞间隙变大,部分细胞缺失,排列不够整齐,额叶皮质细胞分布均变稀疏,多为椭圆形,与空白组相比,模型大鼠海马和额叶皮质的 VEGF 的表达和含量、VEGFR2 mRNA 和蛋白表达显著降低。

4 结语

本文通过检索动物的愤怒模型,综述了愤怒情绪的脑内神经机制。愤怒的发生与脑内多个区域有关,在愤怒模型的研究中,大部分研究集中在中缝背核、下丘脑和海马区域,影响情绪的杏仁核区域较少。在现阶段的研究中,愤怒相关的神经机制研究主要与 5-HT 受体和 GABA 受体的表达及单胺类神经递质的含量相关。在前额区 5-HT 含量和 GABABR1 受体表达影响愤怒的发生,在下丘脑中单胺类神经递质及 5-HTR3B、5-HTR2C 和 GABABR2 受体的表达在愤怒中发挥重要作用,在海马区单胺类神经递质和 GABABR1、GABABR2 受体的表达与愤怒的发生亦密切相关。但是愤怒的发生并不是脑部单一区域的活动,在愤怒的研究中应关注不同区域之间的相互影响,并且愤怒情绪也可能会引发或加重其他疾病的症状。免疫机制亦在愤怒的发生中发挥重要作用,在愤怒发生时,免疫与神经之间的相互作用和影响,也是将来需要探索的重要方向。愤怒情绪的研究有助于帮助了解情绪发生的机制和影响,希望本综述可以对愤怒情绪的机制研究提供有益信息。

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