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糖皮质激素在慢性疼痛中的双重作用机制*

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摘要　糖皮质激素（glucocorticoid，GC）是下丘脑-垂体-肾上腺（hypothalamic-pituitary-adrenal，HPA）轴分泌的最终效应激素，通过与糖皮质激素受体（glucocorticoid receptors，GR）结合行使功能。研究发现，GC在慢性疼痛中表现双重作用，内源性GC作为抗炎类固醇通过募集免疫细胞、抑制激酶通路、调节神经胶质细胞在部分类型的神经病理性疼痛及炎性痛中发挥抑痛作用，但在应激情况下，GC水平异常升高参与中枢神经系统神经元的凋亡、兴奋、记忆等，通过调控不同的信号反应或微环境促进病理性疼痛。本文综述GC在慢性疼痛中的作用，了解其发挥镇痛或致痛的双重作用机制。

关键词　慢性痛，糖皮质激素，受体，镇痛，促痛
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慢性疼痛也称为病理性疼痛，是一种常见的临床神经系统疾病，包括神经病理性疼痛、炎性痛和癌痛[1]等。疼痛伴随疾病出现，原发性疾病治愈后，慢性疼痛可能仍持续存在，临床表现为自发性疼痛、痛觉过敏和痛觉超敏[2]。神经系统是糖皮质激素（glucocorticoid，GC）作用的重要靶区，GC参与神经系统的发育、分化及神经元的损伤、存活、再生，对神经元的突触可塑性具有修复、保护和支持作用[3-4]。根据受神经支配的外周区域、疼痛类型和应激刺激的不同，GC显示出促伤害感受和抗伤害感受两种作用。如损伤和炎症可激活下丘脑-垂体-肾上腺（hypothalamic-pituitary-adrenal，HPA）轴，使GC释放到血液中与GR结合调节神经内分泌系统的功能发挥抑痛作用，而压力导致慢性应激下的HPA轴过度激活分泌GC增多也能通过改变神经免疫微环境，参与促进慢性疼痛的发生过程[5-6]。本文对GC在慢性疼痛中的双重作用及其机制研究进展进行综述，探讨其作为慢性疼痛治疗靶点的可能性。

1　GC及其受体的分布与功能

1950年因发现GC并确定在风湿性疾病治疗效果的药学家Hench与Kendall获得诺贝尔医学奖，至今GC已经应用半个多世纪。GC可被划分为内源性和外源性两大类。内源性GC是HPA轴分泌的内源性抗炎类固醇[7]，HPA轴释放的GC在灵长类动物中为皮质醇，在大多数啮齿类动物中为皮质酮（corticosterone，CORT）[8]。外源性GC是人工合成的，如倍他米松、地塞米松，人工合成GC（地塞米松）在自身免疫性疾病、炎症或严重创伤等危患中已大量应用[9]。GC为脂溶性物质可以穿透细胞膜[10]，主要通过与糖皮质激素受体（glucocorticoid receptors，GR）结合，将特定靶基因的转录增强或抑制[11]。GR在中枢神经系统中广泛表达[12]，主要位于神经细胞体的细胞核内。中枢神经系统的小胶质细胞、单核细胞、少突胶质细胞和星形胶质细胞都分泌GR[13]，大脑皮层和皮层下结构（海马、前额叶皮质或杏仁核）的神经元表达高水平GR。脊髓和外周GR主要局限于外周肽能和非肽能伤害性C神经元和Aδ神经元，仅少量存在于有髓鞘机械感受和本体感受神经元[14]。在脊髓内，GR主要位于传入的突触前伤害性神经元、背角突触前和突触后结构以及小胶质细胞[12, 14]。

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1936年Selye首次观察到慢性应激使胸腺萎缩时，应激反应可能对免疫产生影响，且长时间接触GC，GR功能改变，这种改变可能与应激有关[13]。“急性应激”定义为几个小时的应激，应激源包括反复束缚、嗅球切除等。如果这种压力重复几天，称为“亚急性压力”，如果持续数周至数月，称为“慢性压力”[8]。应激或损伤导致下游促肾上腺皮质激素分泌的GC分泌进入循环，参与代谢、认知和抗应激等重要生物过程[15]。慢性应激导致GC过度分泌严重影响海马体突触的结构、功能和可塑性[2]，导致认知能力下降，加重阿尔茨海默病（AD）的后期发展[16-17]；应激还能诱导神经元、雪旺细胞、小胶质细胞、少突胶质细胞和星形胶质细胞的结构改变，导致神经精神障碍（如焦虑样行为）、神经病理性疼痛等。

2　GC在慢性疼痛中的保护作用

2.1　GC在神经病理性疼痛中的保护作用

中枢或局部给予外源性类固醇（药理学）、内源性（生理性）GC升高或GR上调对疼痛行为的改善可能是由于炎症介质局部释放减少，改变了脊髓层面参与痛觉传递的激酶的表达。鞘内注射地塞米松抑制选择性神经损伤（spared nerve injury，SNI）[18-19]和三叉神经节损伤诱发的痛觉过敏和触诱发痛，地塞米松作用脊髓GR通过降低p38MAPK信号通路和NF-κB转录因子激活抑制IL-6、TNF-α的释放，伤害性痛觉传入中断，抑制神经病理性疼痛的发展[20]。地塞米松刺激巨噬细胞干扰NF-κB的激活，下调TNF-α mRNA表达，且地塞米松能够削弱用IL-1β刺激的A549细胞中NF-κB的释放[21]。单次硬膜外注射GC抑制脑内促炎细胞因子水平，刺激抗炎细胞因子IL-10的表达，共同减弱L5脊神经结扎诱发的痛觉过敏[22]。鞘内注射地塞米松能抑制三叉神经节后延髓背角GFAP和OX42表达增加，从而减弱星形胶质细胞和小胶质细胞持续激活状态，抑制疼痛因子的释放[20]，表明GC抑制脊髓背角巨噬细胞、树突细胞、免疫细胞中MAPK的细胞内信号级联，通过抑制促炎细胞因子的转录、上调抗炎因子的表达等发挥镇痛作用。

外源性GC通过多种方式影响内源性血浆皮质醇和脊髓GR表达，在中枢和外周的镇痛机制存在差异，可能与GC的暴露或激活时间以及激酶信号通路有关。在脊髓中GC参与脂calin型前列腺素D合酶（lipocalin type prostaglandin D synthase，L-PGDS）合成，蛋白质组学分析带状疱疹疼痛患者鞘内注射GC后，直接影响脉络丛和软脑膜中的基因表达，如L-PGDS表达降低，短期内带状疱疹后神经痛减弱，而对长期神经痛无效[23]。在腰间盘突出大鼠[24]中注射地塞米松恢复L-PGDS/磷脂酰肌醇3激酶/蛋白激酶B/PI3K/Akt信号通路，减轻腰间盘突出诱发的痛觉超敏。脊神经结扎（spinal nerve ligation，SNL）使脊髓GR蛋白水平增加，GR mRNA不变，而鞘内注射GC治疗只有脊髓GR mRNA减少，不会降低机械敏感性。

GC选择性抑制或促进特定细胞分子的分泌参与神经痛的镇痛机制也可能与microRNA有关。三叉神经损伤大鼠的组蛋白甲基化，外周感觉神经元中GR沉默与miR-32-5p启动子的结合，参与转录T型通道表观遗传学机制进而减弱痛超敏[25]，因此microRNA也是理解GR镇痛差异机制的关键。免疫细胞和神经元活化、炎症因子白介素家族、NF-κB信号通路、MAPK激酶家族信号通路的激活以及microRNA等有助于深入了解GC与神经病理性疼痛之间的关系，为选择GC选择性激动剂的研发提供思路（图1）。

2.2　GC在炎性痛中的保护作用

类风湿性关节炎[26]、动物关节内给予缓激肽[27]等引起动物机体产生炎性痛，注射地塞米松可抑制巨噬细胞、滑膜纤维母细胞中IL-6、TNF-α及IL-1β的表达，减轻神经炎症。体外应用地塞米松抑制表皮细胞因子粒细胞诱导一氧化氮（NO）的生成，抑制NF-κB/iNOS信号通路，调节皮肤树突状细胞系中的巨噬细胞集落刺激因子对抗皮肤导致炎症性疾病的机制[28]。体外研究证明，巨噬细胞和滑膜纤维母细胞受到GC的影响，抑制炎症介质释放及伤害性信号通路激活。

GC减弱炎症痛的作用与脊髓和外周GR的表达有关。完全弗氏佐剂（complete Freund’s adjuvant，CFA）诱发关节炎性痛，应用地塞米松引起动物后足和背根神经节（dosal root ganglion，DRG）周围GR上调[29]，DRG中NGF和IL-1β上调被抑制[30]，脊髓中GR下调，前强啡肽原（preprodynorphin，PPD）mRNA表达也被抑制[31]，疼痛过敏减轻，提示GC减弱炎症痛的作用可能归因于脊髓和外周GR的表达差异，而这种差异与神经生长因子家族、炎症因子和PPD局部分泌差异有关。而Li等[29]研究发现，CFA导致脊髓和DRG

伤害性神经元、星形胶质细胞和小胶质细胞中IL-6R和GR共定位增加，机械敏感性增强。注射地塞米松通过抑制GR/IL-6/JAK2/STAT3信号通路，下调伤害感受神经元中降钙素基因相关肽（calcitonin generated peptide，CGRP）及抑制免疫胶质细胞活化，抑制CFA炎性痛[32]。这些暗示GC减弱炎症痛的作用可能与感觉神经元、星形胶质细胞和小胶质细胞痛介质释放、反式信号通路表达受到抑制相关。

地塞米松和环丙沙星联合应用治疗脑肿胀时，GC/GR水平上调，增加过氧化氢酶、精氨酸酶促进小胶质细胞由M1型向M2型转化，有效减少细菌负荷和炎症反应[33]，同时也可通过阻断细菌进入血脑屏障并抑制胶质细胞活化减轻炎性痛。在腰痛炎症[34]或福尔马林炎性痛模型中[35]GR下调，硬膜外注射地塞米松诱导神经元以及包括卫星胶质细胞在内的非神经元细胞中GR免疫反应性得到恢复，进而抑制脊髓I-II层胞浆磷脂酶A2（cPLA2）的表达，逆转炎性痛。此外地塞米松还下调脊髓背角神经递质胆囊收缩素、P物质和降钙素基因相关肽的释放，降低炎症诱导的早期疼痛[36]（图1）。

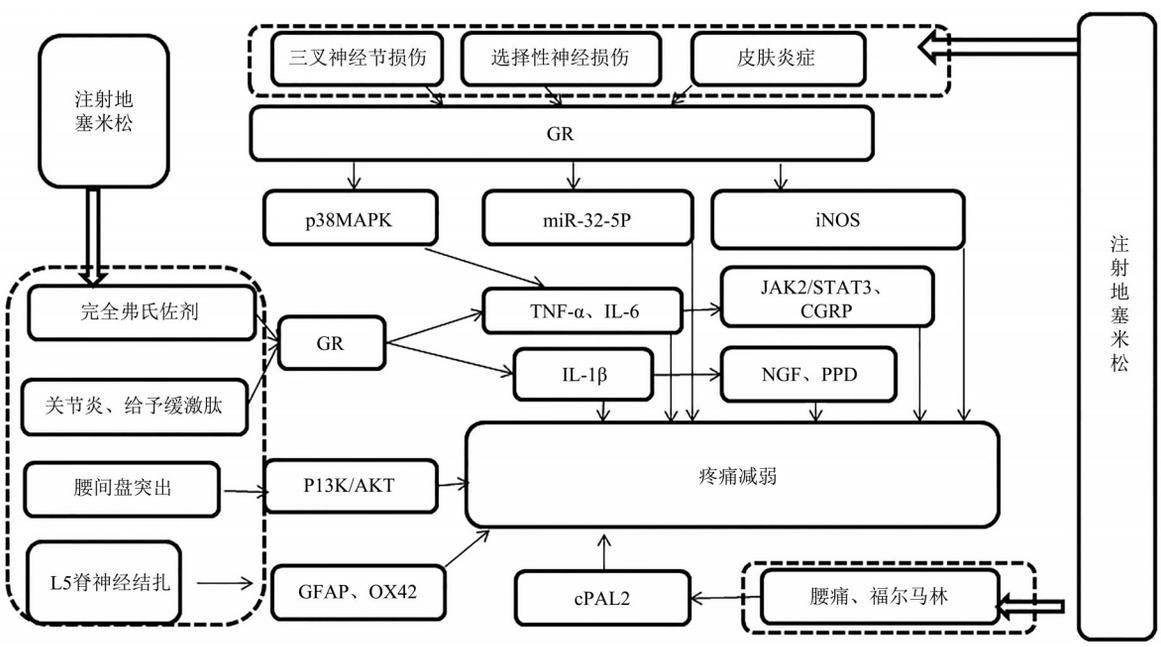

Fig. 1　The mechanism of analgesic effects of GC in chronic pain

图1　GC在慢性疼痛中的镇痛作用机制

3　GC在慢性疼痛中的毒性作用

3.1　GC在神经病理性痛中的毒性作用

应用GR拮抗剂（内源性GC减少）证实了GC/GR参与神经病理性痛的敏化机制。在大鼠坐骨神经慢性压迫性损伤（chronic constriction injury，CCI）疼痛模型[37-39]中，脊髓背角中GR激活，减少兴奋性氨基酸转运体（excitatory aminoacid transporter 3，EAAT3）表达，星形胶质细胞能摄取细胞外过量的谷氨酸并将EAAT3转化为谷氨酰胺供神经元再利用，增强突触间隙N-甲基-D-天冬氨酸受体（N-methy-D-aspartic acid receptor，NMDAR）[39]积聚，引起兴奋毒性造成谷氨酸能传递增强，抑制轴突再生，抑制伤害性刺激敏感性降低。此外CCI大鼠中活化星形胶质细胞能调节大麻素受体1（cannabinoid receptor 1，CB1）[40]、IL-6的释放介导细胞内蛋白激酶C（protein kinase C，PKC）信号刺激GR过度表达加重神经元兴奋性[38]，进一步应用GR拮抗剂RU38486或肾上腺切除抑制GC/GR表达上调可逆转机械性疼痛。表明GC/GR在CCI大鼠星形胶质细胞中表达升高可能是由于谷氨酸能过多积聚，加强伤害性传递信息如大麻素受体、炎症因子和激酶信号通路，诱导GR过表达持续刺激神经元细胞激活所致。

癌症、糖尿病神经病变或带状疱疹后神经痛患

者的自发疼痛强度在日间增强，这在很大程度上取决于肾上腺GC的昼夜变化[41]。CCI小鼠日间GC水平的暂时升高增强脊髓细胞外ATP释放，刺激脊髓背角小胶质细胞中嘌呤能受体表达，降低机械性痛觉超敏阈值[42]。大鼠经单次延长应激或皮下注射CORT诱导血浆皮质酮升高，激活SGK1/ATP信号促进P2X受体（配体门控非选择性阳离子通道超家族）伤害性刺激的感觉传导增强，导致中枢致敏[43]。链脲佐菌素（streptozotocin，STZ）诱导的1型糖尿病大鼠神经病变模型[44]中内源性GC/GR表达慢性升高，下游调节基因2（N-myc downstream-regulated gene 2，NDRG2）是神经分化和突触形成的新型基因家族成员。鞘内注射GR拮抗剂RU486后逆转脊髓星形胶质细胞过度活化释放的NDRG2，恢复星形胶质细胞的形态和细胞骨架F-肌动蛋白的表达减轻疼痛超敏。这些现象表明，GC参与神经病理性疼痛均依赖于GC/GR的高表达诱导的作用机制，可从神经元扩展到小胶质细胞或星形胶质细胞，介导脊髓炎症、激酶、离子通道及基因表达等反应增强导致中枢致敏。

应激会导致痛觉过敏，这取决于压力源的类型强度和持续时间。调节神经病理性疼痛过程的心理社会因素可以加剧损伤诱发的疼痛[45]。嗅球切除术-脊神经结扎（olfactory bulbectomy-spinal nerve ligation，OB-SNL）大鼠模拟抑郁症患者慢性疼痛[46]，鞘内注射地塞米松加重抑郁SNL大鼠的痛觉超敏[47]，脊髓GR表达和核移位速率加快[48]，增强脑源性神经营养因子（brain derived neurotrophic factor，BDNF）介导长时程作用早期兴奋性突触调节，激活突触后BDNF/TrkB信号，诱导NMDAR磷酸化，增加离子通道的开放诱导中枢致敏[49]。束缚应激SNI大鼠CORT增加，通过神经元GR影响中脑导水管周围灰质（periaqueductal gray，PAG）通过其向延髓头端腹内侧区RVM的投射显著增加抑郁样行为表达加剧神经病理性疼痛。此外，SNI大鼠DRG[50]、中脑导水管周围灰质PAG和大脑皮层前扣带回ACC中CREB的靶基因BDNF mRNA随着应激和SNI的结合逐步上调，触发疼痛超敏反应。这些提示在应激后GC表达上调，并参与PAG放大传入的脊髓伤害性信号[51]，间接调节BDNF/CREB等信号通路来促进伤害性信息的传递，加剧心理抑郁和束缚应激下的慢性疼痛。

高级中枢系统皮层中星形胶质细胞激活，刺激神经元中高迁移率组盒1（high-mobility group box-1，HMGB1）上调，作用于反复应激加剧神经损伤大鼠疼痛的发展。载体皮层扩散抑制（cortical spreading depression，CSD）期间发生应激，皮质中CORT水平显著上升[52]，激活星形胶质细胞，促进神经元释放HMGB1[41]，使三叉神经硬膜肥大并伴随细胞脱颗粒现象发生，致使三叉神经纤维激活引发机体头痛；在培养皮质星形胶质细胞中给予CORT或地塞米松模拟重度抑郁模型[53]中，与CSD载体模型现象一致[53]。此外在前列腺素E2（prostaglandin E2，PGE2）诱导炎症后，反复束缚应激通过GC/GR依赖机制增加DRG感觉轴突生长，上调外周COX2/PGE2/EP4信号，诱导急性疼痛向慢性疼痛倾向过渡[54]。反复应激还能通过上调TRPV1通道表达增加DRG神经元对疼痛刺激敏感性[55]。相同的反复应激刺激皮层和DRG，都导致GC表达增加，诱导星形胶质细胞中和神经元中一系列下游因子的表达和释放。反复应激加剧神经病理性疼痛的关键机制可能是敏化的DRG神经元发出传导至皮层的动作电位，还可激活星形胶质细胞，促进中枢敏化加强神经病理性痛（图2）。

3.2　GC在炎性痛中的毒性作用

GC在不同的应激源下加强炎性痛是复杂机制互动的网络结果，涉及神经系统的各个层面，从脊髓背角的感觉神经元输入到更高级的大脑结构，如额叶皮层、中脑中央灰质杏仁核和海马。预先给予单一或重复的社会失败压力后，大鼠腹腔注射聚肌胞polyI：C[56]或预先急性应激或直接皮下注射CORT后的大鼠用脂多糖（lipopolysaccharide，LPS）刺激[57]，CORT或GC增多激活小胶质细胞，细胞浸润患病或受伤的中枢神经系统，导致脊髓和海马内TLR2/4信号增强[58]可加快腹内侧前额叶皮层（medial prefrontal cortex，mPFC）神经元反应衰减、树突状萎缩和胶质细胞活化使痛觉超敏持续时间延长，影响髓鞘形成神经元发育和生存[59]。表明应激或注射外源性GC增强中枢神经系统海马/脊髓中小胶质细胞释放促炎介质，激活Toll样受体途径后诱导机械痛觉超敏。

中枢神经系统中的海马体分泌的ERK、PKC、Akt激酶信号通路可能是创伤后应激GC表达恢复正常缓解痛觉过敏的机制之一。单一持续应激与CFA模型联合模拟创伤后应激障碍疼痛，组蛋白去乙酰酶4（histone deacetylases 4，HDAC4）调节mPFC中GR上调，mPFC中细胞质GR mRNA、蛋

白质水平增加，激活脊髓小胶质细胞和背角神经元活化，诱导ERK1/2磷酸化参与CREB/c-FOS通路发挥促痛作用[60-61]。此外，GR/ PKC参与创伤后应激诱导mPFC功能性失调机制，可能mPFC是PKC产生与钙离子/钙网蛋白依赖性信号通路受损有关[62]。而海马体中GR蛋白和Akt磷酸化增加但杏仁核没有增加，可能是Akt产生某种未知信号作用于海马体周围神经组织中引起的，同时pAkt对应激介导的焦虑和记忆增强至关重要[63]。此外急性应激诱导内脏超敏反应期间，伤害性DRG神经元中CORT激活GR触发非基因组过程包括PKA、P13K/Akt和PKC蛋白激酶级联反应，导致Pyk2磷酸化促进TRPM8插入膜表面引起内脏超敏反应[64]。上述结果表明慢性应激诱导的内脏痛觉过敏可以在初级和高级中枢不同水平进行选择性治疗。

在生命早期应激也可将神经免疫微环境转变为促炎免疫表型[65]。小鼠产前给予地塞米松GC上调，神经元密度较低，多巴胺能和5-羟色胺能系统失调，诱导有害的长期神经认知效应[66]，且海马少突胶质细胞激活，诱导NOD样受体热蛋白结构域相关蛋白3（NLRP3）/IL-1β信号通路激活，提示少突胶质细胞炎症小体活化可能与早期暴露于高水平GC诱导的脱髓鞘疾病有关[65]。此外怀孕雌鼠进行间歇性应激，GC可能通过[67]海马和DRG神经元中NaV1.7[68]增加感觉神经元的异位放电调控电压门控离子通道依赖性痛觉过敏[69]（图2）。

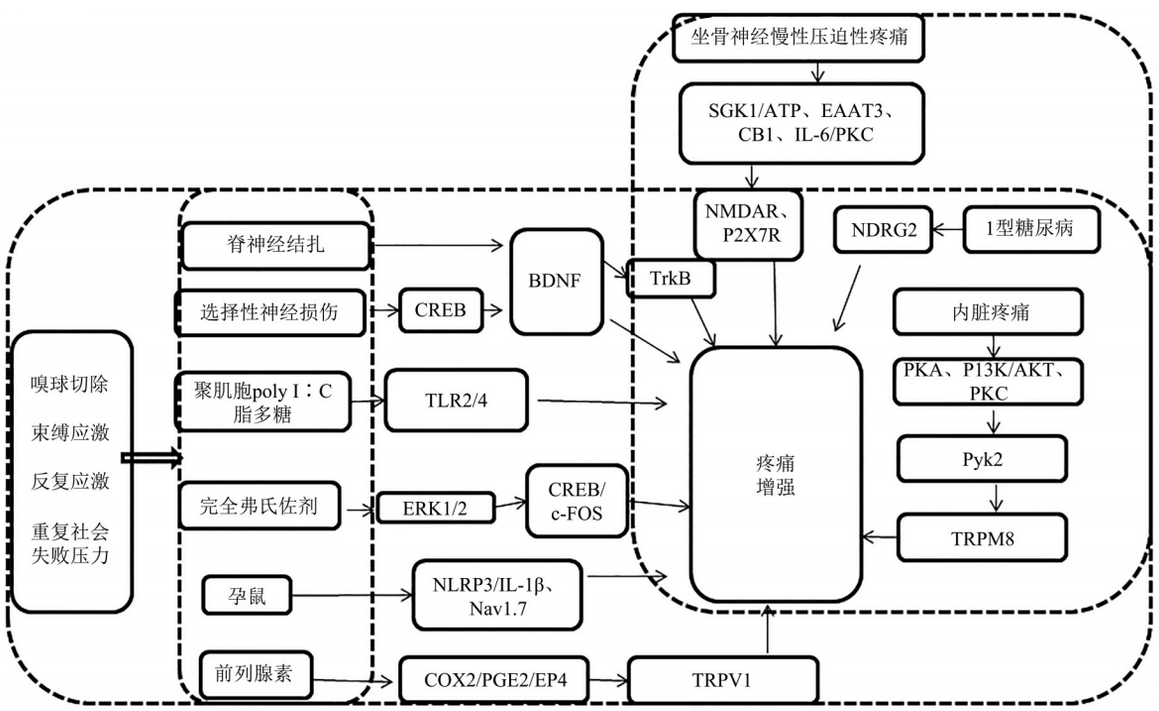

Fig. 2　The mechanism of pain-inducing role of GC in chronic pain

图2　GC在慢性疼痛中的促痛作用机制

4　总　　结

GC是否减轻或加强慢性疼痛取决于GC暴露的区域、剂量、持续时间。在镇痛方面，脊髓和外周组织中的GC在单核细胞、粒细胞、巨噬细胞和神经元中以相对较高或急性升高表达，由于GC在不同的部位和刺激的强度不一样，分泌的基线是不一样的，作用的部位和细胞分泌的因子是不同的，所以不同疼痛模型镇痛的信号通路会有差异，同时也会存在串扰。在致痛方面，GC在应激或非应激情况下诱导或加强神经病理性痛和炎性痛中的信号通路也是不同的。GC主要在中枢部位尤其是海马、皮层、脊髓以相对较高的基线表达，对高级中枢环境会造成损害如突触可塑性改变、胶质细胞结构异常、神经元死亡导致机体出现紊乱，通过不同的信号通路诱导和加强慢性疼痛[70]。慢性疼痛发

生时分泌细胞的GC或GC作用的底物又有差异，如GC在临床中治疗主要作用于2型糖尿病引起的神经病理性痛，而长期使用GC导致胰岛素抵抗又加重神经痛[71]。

目前，广泛用于治疗慢性疼痛的药物都对中枢神经系统有一定的副作用如急性呼吸窘迫综合征、癫痫等[72]。GC已广泛用于治疗慢性疼痛，临床药物有可的松、地塞米松、泼尼松龙等，但长期使用这些GC药物也有一系列的副作用如易患库欣综合征[73]、严重类风湿性关节炎和骨质疏松[74]等。GC前体的过量产生可导致个体的各种疾病，如高血压和高雄激素血症，目前可以通过调节不同组织中游离的GC药物水平改善，微调的GC分子药物的激活机制直接影响GC药物的耐药性和毒性[75]。根据不同慢性疼痛的作用机制，研发靶向性强、毒副作用更小、镇痛效果更明显的GC受体激动剂或抑制剂可能是解决的首要问题。明确GC对慢性疼痛调控的普遍机制，用药理学技术靶向特定细胞类型的GC或GR，可能是开发镇痛剂的研发方向。

参　考　文　献

[1] Odell D W. Epigenetics of pain mediators. Curr Opin Anaesthesiol, 2018, **31**(4): 402-406

[2] Lerch J K, Alexander J K, Madalena K M, *et al*. Stress increases peripheral axon growth and regeneration through glucocorticoid receptor-dependent transcriptional programs. eNeuro, 2017, **4**(4): ENEURO.0246-0217.2017

[3] Wu Q, Xu Z, Song S, *et al*. Gut microbiota modulates stress-induced hypertension through the HPA axis. Brain Res Bull, 2020, **162**: 49-58

[4] Al'absi M, Nakajima M, Bruehl S. Stress and pain: modality-specific opioid mediation of stress-induced analgesia. J Neural Transm (Vienna), 2021, **128**(9): 1397-1407

[5] Takasaki I, Kurihara T, Saegusa H, *et al*. Effects of glucocorticoid receptor antagonists on allodynia and hyperalgesia in mouse model of neuropathic pain. Eur J Pharmacol, 2005, **524**(1-3): 80-83

[6] Amit Z, Galina Z H. Stress-induced analgesia: adaptive pain suppression. Physiol Rev, 1986, **66**(4): 1091-1120

[7] Gjerstad J K, Lightman S L, Spiga F. Role of glucocorticoid negative feedback in the regulation of HPA axis pulsatility. Stress, 2018, **21**(5): 403-416

[8] Sorrells S F, Caso J R, Munhoz C D, *et al*. The stressed CNS: when glucocorticoids aggravate inflammation. Neuron, 2009, **64**(1): 33-39

[9] Podgorny O V, Gulyaeva N V. Glucocorticoid-mediated mechanisms of hippocampal damage: contribution of subgranular neurogenesis. J Neurochem, 2021, **157**(3): 370-392

[10] Ter Heegde F, De Rijk R H, Vinkers C H. The brain mineralocorticoid receptor and stress resilience. Psychoneuroendocrinology, 2015, **52**: 92-110

[11] Liberman A C, Druker J, Perone M J, *et al*. Glucocorticoids in the regulation of transcription factors that control cytokine synthesis. Cytokine Growth Factor Rev, 2007, **18**(1-2): 45-56

[12] Alexander J K, Devries A C, Kigerl K A, *et al*. Stress exacerbates neuropathic pain *via* glucocorticoid and NMDA receptor activation. Brain Behav Immun, 2009, **23**(6): 851-860

[13] Madalena K M, Lerch J K. The effect of glucocorticoid and glucocorticoid receptor interactions on brain, spinal cord, and glial cell plasticity. Neural Plast, 2017, **2017**: 8640970

[14] Shaqura M, Li X, Al-Khrasani M, *et al*. Membrane-bound glucocorticoid receptors on distinct nociceptive neurons as potential targets for pain control through rapid non-genomic effects. Neuropharmacology, 2016, **111**: 1-13

[15] Nicolaides N C, Kyratzi E, Lamprokostopoulou A, *et al*. Stress, the stress system and the role of glucocorticoids. Neuroimmunomodulation, 2015, **22**(1-2): 6-19

[16] Canet G, Chevallier N, Zussy C, *et al*. Central role of glucocorticoid receptors in Alzheimer's disease and depression. Front Neurosci, 2018, **12**: 739

[17] Yaniv S P, Lucki A, Klein E, *et al*. Dexamethasone enhances the norepinephrine-induced ERK/MAPK intracellular pathway possibly *via* dysregulation of the alpha2-adrenergic receptor: implications for antidepressant drug mechanism of action. Eur J Cell Biol, 2010, **89**(9): 712-722

[18] Shao J, Xu R, Li M, *et al*. Glucocorticoid receptor inhibit the activity of NF-kappaB through p38 signaling pathway in spinal cord in the spared nerve injury rats. Life Sci, 2018, **208**: 268-275

[19] Wang Q S, Jiang Y H, Wang T D, *et al*. Effects of betamethasone on neuropathic pain in a rat spare nerve injury model. Clin Exp Pharmacol Physiol, 2013, **40**(1): 22-27

[20] Lee M K, Han S R, Park M K, *et al*. Behavioral evidence for the differential regulation of p-p38 MAPK and p-NF-κB in rats with trigeminal neuropathic pain. Mol Pain, 2011, **7**: 57

[21] Bansal A, Mostafa M M, Kooi C, *et al*. Interplay between nuclear factor-kappaB, p38 MAPK, and glucocorticoid receptor signaling synergistically induces functional TLR2 in lung epithelial cells. J Biol Chem, 2022, **298**(4): 101747

[22] Xie W, Liu X, Xuan H, *et al*. Effect of betamethasone on neuropathic pain and cerebral expression of NF-kappaB and cytokines. Neurosci Lett, 2006, **393**(2-3): 255-259

[23] Lu J, Katano T, Nishimura W, *et al*. Proteomic analysis of cerebrospinal fluid before and after intrathecal injection of steroid into patients with postherpetic pain. Proteomics, 2012, **12**(19-20): 3105-3112

[24] Xu W, Ding W, Sheng H, *et al*. Dexamethasone suppresses radicular pain through targeting the L-PGDS/PI3K/Akt pathway in rats with lumbar disc herniation. Pain Pract, 2021, **21**(1): 64-74

[25] Qi R, Cao J, Sun Y, *et al*. Histone methylation-mediated microRNA-32-5p down-regulation in sensory neurons regulates pain behaviors *via* targeting Cav3.2 channels. Proc Natl Acad Sci

USA, 2022, **119**(14): e2117209119

[26] Macfarlane E, Seibel M J, Zhou H. Arthritis and the role of endogenous glucocorticoids. Bone Res, 2020, **8**: 33

[27] Valenti C, Giuliani S, Cialdai C, *et al*. Anti-inflammatory synergy of MEN16132, a kinin B(2) receptor antagonist, and dexamethasone in carrageenan-induced knee joint arthritis in rats. Br J Pharmacol, 2010, **161**(7): 1616-1627

[28] Vital A L, Goncalo M, Cruz M T, *et al*. Dexamethasone prevents granulocyte-macrophage colony-stimulating factor-induced nuclear factor-kappaB activation, inducible nitric oxide synthase expression and nitric oxide production in a skin dendritic cell line. Mediators Inflamm, 2003, **12**(2): 71-78

[29] Li X, Wang W, Chen Q, *et al*. Antinociceptive effects of IL-6R *vs*. glucocorticoid receptors during rat hind paw inflammatory pain. Neurosci Lett, 2020, **738**: 135356

[30] Zhang R X, Lao L, Qiao J T, *et al*. Endogenous and exogenous glucocorticoid suppresses up-regulation of preprodynorphin mRNA and hyperalgesia in rats with peripheral inflammation. Neurosci Lett, 2004, **359**(1-2): 85-88

[31] Ibrahim S I A, Strong J A, Qualls K A, *et al*. Differential regulation of the glucocorticoid receptor in a rat model of inflammatory pain. Anesth Analg, 2020, **131**(1): 298-306

[32] Li X, Shaqura M, Mohamed D, *et al*. Pro-versus antinociceptive nongenomic effects of neuronal mineralocorticoid versus glucocorticoid receptors during rat hind paw inflammation. Anesthesiology, 2018, **128**(4): 796-809

[33] Dey R, Bishayi B. Dexamethasone along with ciprofloxacin modulates *S. aureus* induced microglial inflammation *via* glucocorticoid (GC) -GC receptor-mediated pathway. Microb Pathog, 2020, **145**: 104227

[34] Ibrahim S I A, Xie W, Strong J A, *et al*. Mineralocorticoid antagonist improves glucocorticoid receptor signaling and dexamethasone analgesia in an animal model of low back pain. Front Cell Neurosci, 2018, **12**: 453

[35] Min S H, Soh J S, Park J Y, *et al*. Epidural dexamethasone decreased inflammatory hyperalgesia and spinal cPLA(2) expression in a rat formalin test. Yonsei Med J, 2014, **55**(6): 1631-1639

[36] Beaudry F, Girard C, Vachon P. Early dexamethasone treatment after implantation of a sciatic-nerve cuff decreases the concentration of substance P in the lumbar spinal cord of rats with neuropathic pain. Can J Vet Res, 2007, **71**(2): 90-97

[37] Wang S, Lim G, Mao J, *et al*. Central glucocorticoid receptors regulate the upregulation of spinal cannabinoid-1 receptors after peripheral nerve injury in rats. Pain, 2007, **131**(1-2): 96-105

[38] Wang S, Lim G, Zeng Q, *et al*. Expression of central glucocorticoid receptors after peripheral nerve injury contributes to neuropathic pain behaviors in rats. J Neurosci, 2004, **24**(39): 8595-8605

[39] Le Coz G M, Anton F, Hanesch U. Glucocorticoid-mediated enhancement of glutamatergic transmission may outweigh anti-inflammatory effects under conditions of neuropathic pain. PLoS One, 2014, **9**(3): e91393

[40] Wu N, Tasker J G. Nongenomic glucocorticoid suppression of a postsynaptic potassium current *via* emergent autocrine endocannabinoid signaling in hypothalamic neuroendocrine cells following chronic dehydration. eNeuro, 2017, **4**(5): ENEURO.0216-0217

[41] Karatas H, Erdener S E, Gursoy-Ozdemir Y, *et al*. Spreading depression triggers headache by activating neuronal panx1 channels. Science, 2013, **339**(6123): 1092-1095

[42] Koyanagi S, Kusunose N, Taniguchi M, *et al*. Glucocorticoid regulation of ATP release from spinal astrocytes underlies diurnal exacerbation of neuropathic mechanical allodynia. Nat Commun, 2016, **7**: 13102

[43] Yuan Y, Zhen L, Li Z, *et al*. Trans-resveratrol ameliorates anxiety-like behaviors and neuropathic pain in mouse model of post-traumatic stress disorder. J Psychopharmacol, 2020, **34**(7): 726-736

[44] Zuo Z F, Liao Y H, Ding T, *et al*. Astrocytic NDRG2 is involved in glucocorticoid-mediated diabetic mechanical allodynia. Diabetes Res Clin Pract, 2015, **108**(1): 128-136

[45] Zhang Z, Wu H, Liu Y, *et al*. The GCs-SGK1-ATP signaling pathway in spinal astrocytes underlied presurgical anxiety-induced postsurgical hyperalgesia. Anesth Analg, 2019, **129**(4): 1163-1169

[46] Chen J, Wang Z Z, Zuo W, *et al*. Effects of chronic mild stress on behavioral and neurobiological parameters-role of glucocorticoid. Horm Behav, 2016, **78**: 150-159

[47] Wei X, Sun Y, Luo F. Impaired spinal glucocorticoid receptor signaling contributes to the attenuating effect of depression on mechanical allodynia and thermal hyperalgesia in rats with neuropathic pain. Front Cell Neurosci, 2017, **11**: 145

[48] Schossler Garcia C, Garcia P R, Da Silva Espíndola C N, *et al*. Effect of m-trifluoromethyl-diphenyl diselenide on the pain-depression dyad induced by reserpine: insights on oxidative stress, apoptotic, and glucocorticoid receptor modulation. Mol Neurobiol, 2021, **58**(10): 5078-5089

[49] Peng H Y, Chen G D, Lai C Y, *et al*. Spinal serum-inducible and glucocorticoid-inducible kinase 1 mediates neuropathic pain *via* kalirin and downstream PSD-95-dependent NR2B phosphorylation in rats. J Neurosci, 2013, **33**(12): 5227-5240

[50] Wen J, Xu Y, Yu Z, *et al*. The cAMP response element- binding protein/brain-derived neurotrophic factor pathway in anterior cingulate cortex regulates neuropathic pain and anxiodepression like behaviors in rats. Front Mol Neurosci, 2022, **15**: 831151

[51] Norman G J, Karelina K, Zhang N, *et al*. Stress and IL-1beta contribute to the development of depressive-like behavior following peripheral nerve injury. Mol Psychiatry, 2010, **15**(4): 404-414

[52] Shimba A, Ikuta K. Control of immunity by glucocorticoids in health and disease. Semin Immunopathol, 2020, **42**(6): 669-680

[53] Hisaoka-Nakashima K, Azuma H, Ishikawa F, *et al*. Corticosterone induces HMGB1 release in primary cultured rat cortical astrocytes: involvement of pannexin-1 and P2X7 receptor-

dependent mechanisms. Cells, 2020, **9**(5): 1068

[54] Zhou Y M, Wu L, Wei S, *et al*. Enhancement of acid-sensing ion channel activity by prostaglandin E2 in rat dorsal root ganglion neurons. Brain Res, 2019, **1724**: 146442

[55] Ma W, Li L, Xing S. PGE2/EP4 receptor and TRPV1 channel are involved in repeated restraint stress-induced prolongation of sensitization pain evoked by subsequent PGE2 challenge. Brain Res, 2019, **1721**: 146335

[56] Chijiwa T, Oka T, Lkhagvasuren B, *et al*. Prior chronic stress induces persistent polyI: C-induced allodynia and depressive-like behavior in rats: possible involvement of glucocorticoids and microglia. Physiol Behav, 2015, **147**: 264-273

[57] Frank M G, Thompson B M, Watkins L R, *et al*. Glucocorticoids mediate stress-induced priming of microglial pro-inflammatory responses. Brain Behav Immun, 2012, **26**(2): 337-345

[58] Loram L C, Taylor F R, Strand K A, *et al*. Prior exposure to glucocorticoids potentiates lipopolysaccharide induced mechanical allodynia and spinal neuroinflammation. Brain Behav Immun, 2011, **25**(7): 1408-1415

[59] Nie X, Kitaoka S, Tanaka K, *et al*. The innate immune receptors TLR2/4 mediate repeated social defeat stress-induced social avoidance through prefrontal microglial activation. Neuron, 2018, **99**(3): 464-479.e467

[60] Qi J, Chen C, Meng Q X, *et al*. Crosstalk between activated microglia and neurons in the spinal dorsal horn contributes to stress-induced hyperalgesia. Sci Rep, 2016, **6**: 39442

[61] Zhang L, Chen C, Qi J. Activation of HDAC4 and GR signaling contributes to stress-induced hyperalgesia in the medial prefrontal cortex of rats. Brain Res, 2020, **1747**: 147051

[62] Wen L, Han F, Shi Y. Changes in the glucocorticoid receptor and Ca^{2+}/calreticulin-dependent signalling pathway in the medial prefrontal cortex of rats with post-traumatic stress disorder. J Mol Neurosci, 2015, **56**(1): 24-34

[63] Eagle A L, Knox D, Roberts M M, *et al*. Single prolonged stress enhances hippocampal glucocorticoid receptor and phosphorylated protein kinase B levels. Neurosci Res, 2013, **75**(2): 130-137

[64] Luo Q Q, Wang B, Chen X, *et al*. Acute stress induces visceral hypersensitivity *via* glucocorticoid receptor-mediated membrane insertion of TRPM8: Involvement of a non-receptor tyrosine kinase Pyk2. Neurogastroenterol Motil, 2020, **32**(10): 1514-1528

[65] Maturana C J, Aguirre A, Saez J C. High glucocorticoid levels during gestation activate the inflammasome in hippocampal oligodendrocytes of the offspring. Dev Neurobiol, 2017, **77**(5): 625-642

[66] Van Der Merwe J L, Sacco A, Toelen J, *et al*. Long-term neuropathological and/or neurobehavioral effects of antenatal corticosteroid therapy in animal models: a systematic review. Pediatr Res, 2020, **87**(7): 1157-1170

[67] Lerch J K, Puga D A, Bloom O, *et al*. Glucocorticoids and macrophage migration inhibitory factor (MIF) are neuroendocrine modulators of inflammation and neuropathic pain after spinal cord injury. Semin Immunol, 2014, **26**(5): 409-414

[68] Korner J, Meents J, Machtens J P, *et al*. β1 subunit stabilises sodium channel Nav1.7 against mechanical stress. J Physiol, 2018, **596**(12): 2433-2445

[69] Wang H J, Xu X, Xie R H, *et al*. Prenatal maternal stress induces visceral hypersensitivity of adult rat offspring through activation of cystathionine-beta-synthase signaling in primary sensory neurons. Mol Pain, 2018, **14**: 1744806918777406

[70] Mcewen B S, Kalia M. The role of corticosteroids and stress in chronic pain conditions. Metabolism, 2010, **59**(1): S9-S15

[71] Li J X, Cummins C L. Fresh insights into glucocorticoid-induced diabetes mellitus and new therapeutic directions. Nat Rev Endocrinol, 2022, **18**(9): 540-557

[72] Rivara M, Zuliani V. Novel sodium channel antagonists in the treatment of neuropathic pain. Expert Opin Investig Drugs, 2016, **25**(2): 215-226

[73] Messina O D, Vidal L F, Wilman M V, *et al*. Management of glucocorticoid-induced osteoporosis. Aging Clin Exp Res, 2021, **33**(4): 793-804

[74] Hughes R A, Mehndiratta M M, Rajabally Y A. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev, 2017, **11**(11): CD002062

[75] Jia Z, Zhao G, Wei X, *et al*. Structural optimization of HPMA copolymer-based dexamethasone prodrug for improved treatment of inflammatory arthritis. J Control Release, 2020, **324**: 560-573

The Dual Role of Glucocorticoids in Chronic Pain*

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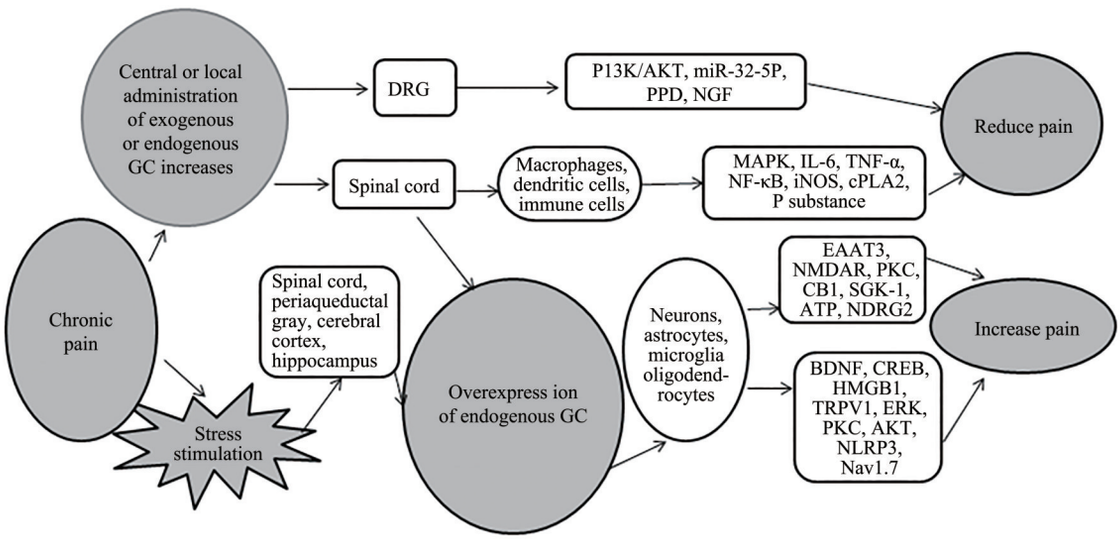
Graphical abstract



Abstract Glucocorticoid (GC) was the final effect hormone in hypothalamic-pituitary adrenal (HPA) axis. Pain, disease, and stress can trigger increased GC expression. Depending on the peripheral area innervated by the nerve, the type of pain, and the stress stimulus, GC has been shown to be both injury-promoting and injury-resisting in chronic pain. In the context of chronic pain, GC induces the structural plasticity of neurons, schwann cells, microglia, oligodendrocytes and astrocytes through its interaction with glucocorticoid receptors (GR), which participate in the apoptosis, excitation and memory of neurons and immune cells of the nervous system, causing pain behavior to decrease or increase. GC is mainly expressed at a relatively high baseline in the central neuronal system, especially the hippocampus, cortex and spinal cord, under stress or non-stressconditions. However, the plasticity of neurons or immune cells induced by stress is usually poor. Meanwhile, the induced GC overexpression induces and enhances chronic pain through different signaling pathways, and associated with neuropsychiatric diseases such as depression. In addition, understanding the dual analgesic or pain-inducing mechanisms of GC in chronic pain should focus on determining how GC acts on different cell types in the peripheral and central nervous systems. At the same time, further research on the dual mechanism of GC in the central nervous system will undoubtedly contribute to the treatment of chronic pain and have obvious clinical significance.

Key words chronic pain, glucocorticoid, receptors, analgesia, pain-inducing

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