

综 述

社交隔离调控本能行为的神经机制研究进展

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摘 要: 本能行为主要受遗传控制, 但也受到社交隔离等社交经历的调控。在果蝇和小鼠等模式动物的研究中已经发现社交隔离可以引起激素、神经递质、神经肽等分子水平以及神经环路层面的变化, 进而调控动物的本能行为。本文主要对社交隔离通过改变物种保守的神经肽和神经递质的表达进而调控动物睡眠、生殖行为、攻击行为等本能行为的最新进展进行综述, 以期深化理解社交隔离调控本能行为的关键且保守的信号通路。

关键词: 社交隔离; 本能行为; 神经肽; 神经递质

Research progress on the neural mechanism of the regulation of social isolation on innate behaviors

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Abstract: Innate behavior is mainly controlled by genetics, but is also regulated by social experiences such as social isolation. Studies in animal models such as *Drosophila* and mice have found that social isolation can regulate innate behaviors through the changes at the molecular level, such as hormone, neurotransmitter, neuropeptide level, and at the level of neural circuits. In this review, we summarized the research progress on the regulation of social isolation on various animal innate behaviors, such as sleep, reproduction and aggression by altering the expression of conserved neuropeptides and neurotransmitters, hoping to deepen the understanding of the key and conserved signal pathways that regulate innate behavior by social isolation.

Key words: social isolation; innate behavior; neuropeptide; neurotransmitter

本能行为是指动物与生俱来, 不需要任何训练就可以在个体中稳定表现出的各类行为。本能行为大致可以分为三类: 一是生物体维持自身生存状态的本能行为, 如摄食、睡眠等; 二是种族生殖繁衍相关的本能行为, 如求偶行为、接受行为、群体社交行为等; 三是生物体对外界刺激做出的趋利避害的反应, 如逃跑行为、防御行为、攻击行为等。本文将从三类本能行为中分别选取睡眠、生殖行为、攻击行为为例进行综述。

社交是影响群居动物行为表现的一个重要因素^[1]。

关于社交隔离的定义, 目前并没有达成一致, 在人类学的研究中将社交隔离定义为缺乏与家人、朋友或更广泛的人群的交流和互动^[2]。在动物实验中, 社交隔离更多的是指实验个体与其他个体的物理隔离, 即将实验动物单独饲养。现代社会中, 社交缺失和人口老龄化导致社交隔离越来越普遍, 人们普遍感到孤独, 而新型冠状病毒肺炎疫情的爆发导致的社交活动减少也可能会进一步加剧这种情况。孤独和社交隔离能够引起焦虑, 社交恐惧, 睡眠质量下降, 血压升高, 心血管功能和免疫系统异常, 抑

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郁症和痴呆的患病风险增加, 执行力降低, 认知能力衰退加快等各种不良影响^[3-6]。

社交隔离对动物神经环路层面和行为层面的影响会根据隔离发生年龄和隔离时间长度而变化。根据隔离时间的长短, 我们可以将社交隔离分为长期(慢性)社交隔离和短期(急性)社交隔离, 不同时间的社交隔离对行为改变的效果并不相同, 甚至可能相反。一般认为, 慢性社交隔离会给动物带来压力, 促进攻击^[7]、焦虑^[8]、抑郁^[9]等; 而急性社交隔离可促进应激小鼠海马区腹侧齿状回(ventral dentate gyrus, vDG)中颗粒细胞的激活, 起到一定的抗焦虑作用^[10]。社交隔离可以发生在幼年期、青春期、成年期等, 例如社交隔离以年龄依赖的方式改变了中脑边缘多巴胺(dopamine, DA)的释放与功能^[11]。青春期是大脑功能塑造的关键期, 对压力刺激异常敏感, 早期的社交隔离可能导致大脑结构和功能的长期甚至永久的改变, 引起成年后焦虑、成瘾、攻击性增强、社交障碍等一系列行为障碍^[12, 13]。

社交隔离调控行为的一个重要途径是影响神经递质和神经肽的表达水平^[14]。例如, 社交隔离的雄性小鼠海马区的5-羟色胺(5-hydroxytryptamine, 5-HT)神经元及其投射的数量和5-HT受体的表达水平降低^[15-17], 而5-HT被认为与动物的焦虑、抑郁、攻击等行为有关^[18, 19]。神经递质和神经肽在物种的进化中高度保守, 因此, 在果蝇、小鼠等模式生物中的研究结果通常也适用于哺乳动物甚至人类。对神经递质和神经肽信号如何响应社交隔离并调节多种行为的研究, 也将为我们理解抑郁、焦虑、社交恐惧等人类情绪和行为的机制提供潜在的研究方向。

本文主要对社交隔离通过改变神经肽和神经递质表达进而调控睡眠、生殖行为、攻击行为等动物本能行为的最新进展进行综述。

1 社交隔离与睡眠

睡眠对生物的生存至关重要, 是生物体维持自身生存状态的本能行为, 睡眠可能有助于动物处理在清醒时获得的信息^[20], 且睡眠行为在进化上是高度保守的。

社交隔离会影响果蝇的睡眠。Ganguly-Fitzgerald等人的研究发现群居饲养的果蝇通常比社交隔离的果蝇拥有更多的睡眠时长, 将群居饲养的果蝇单独饲养4天以上, 可以显著减少果蝇的睡眠时间; 相反,

将单独饲养的果蝇群居饲养后, 也可以增加果蝇的睡眠时间^[21]。这一行为学变化是由神经递质DA表达量的改变造成的^[21]。社交隔离通过改变睡眠结构来影响果蝇的睡眠, 在日间和夜晚产生差异性的变化, 社交隔离的果蝇日间睡眠时间和次数减少, 夜间睡眠变得分散、睡眠次数增加但持续时间减少^[22]。最近, Li等人以果蝇为模型对社交隔离影响果蝇睡眠的机制进行了进一步的研究^[5]。Li等人发现短时间的社交隔离(1天和3天)不会造成睡眠缺失, 长期社交隔离(5天和7天)则显著减少了每日总睡眠、日间睡眠以及开灯后4 h内的睡眠^[5]。长期社交隔离导致的果蝇睡眠减少与P2神经元的活性密切相关, P2神经元的表达与果蝇扇形体神经元部分重叠, 而已有研究发现果蝇扇形体神经元调节睡眠稳态并将能量代谢和睡眠相耦合^[23, 24]。更为有趣的是, 85%的P2神经元是神经肽F(neuropeptide F, NPF)阳性神经元。果蝇中的神经肽NPF是脊椎动物中神经肽Y(neuropeptide Y, NPY)的同源物, 而神经肽NPF/NPY参与调控摄食、睡眠觉醒、酒精摄食偏好、攻击等行为^[25-28]。P2神经元与神经肽NPF阳性神经元的高度重叠也提示神经肽NPF可能参与调控社交隔离导致的果蝇睡眠变化。

啮齿动物社交隔离也会导致与果蝇类似的睡眠行为异常。社交隔离的小鼠表现出睡眠中断增加, 慢波睡眠和快速动眼期明显减少^[29]。社交隔离压力减少了小鼠的睡眠时间, 但对睡眠潜伏期没有影响; 这种影响与GABA能神经递质系统的功能障碍和脑中神经甾体生物合成的减少有关^[30, 31]。同时也有研究表明, 在对小鼠睡眠剥夺的同时进行社交隔离, 会加剧睡眠剥夺对小鼠带来的损伤和不利影响^[29]。

对于人类来说, 长期社交隔离期间的高度紧张影响睡眠时长和睡眠质量并直接损害认知功能^[32]。尤其是在老年人群中, 睡眠质量与社交隔离和孤独感呈负相关^[33]。长期孤独的人类表现出的睡眠困难和贪食等相关行为也与长期隔离的果蝇的行为变化(睡眠减少和过度进食)具有高度的相似性^[5]。无论是果蝇、小鼠还是人类, 社交隔离导致的相似行为学变化背后的调控机制是否一致, 也是神经科学领域很重要的科学问题, 需要进行进一步的探究。

2 社交隔离与生殖行为

生殖行为是动物种族繁衍非常重要的本能行为, 包括雄性的求偶和雌性的接受等行为。自然界

中, 动物求偶行为的形式是极其丰富的, 诸如孔雀的开屏, 蛙类的鸣叫等, 但无论采取何种方式, 雄性的求偶模式往往是固定且刻板的, 以保证它所传递的求偶信息可以准确无误地被雌性接收。

社交隔离可以影响动物的生殖行为, 不同的果蝇物种响应于社交隔离产生的求偶和接受行为的改变不尽相同^[34, 35]。Marie-Orleach 等人的研究发现, 相比于社交隔离的雄蝇, 群居饲养的雄蝇与雌蝇接触时求偶强度更高, 单位时间内会产生更多的扇翅鸣叫, 从而提高求偶的成功率^[36]。而且, 最新的研究发现, 在竞争交配的实验中, 群居饲养的性成熟雄蝇与单独饲养(社交隔离)的性成熟雄蝇相比, 在追求雌性方面具有明显的优势。进一步的机制研究发现, 群居促进性成熟雄蝇的求偶行为依赖果蝇的 Or47b 嗅觉受体神经元, 群居后的信息素信号结合保幼激素信号可以提高 Or47b 神经元内 FruM 蛋白的表达, 导致 Or47b 神经元的敏感性提高, 进而调控雄蝇的求偶行为^[37]。

更为有趣的是, 本实验室的研究发现社交隔离可以引起雄蝇无效求偶行为的增加, 并且这种增加可能是由于神经肽 Drosulfakinin (Dsk) 表达降低造成的^[38]。我们分别将单独饲养雄蝇以及群居饲养雄蝇与去头的雌蝇配对, 并检测雄蝇的求偶行为, 结果发现, 单独饲养雄蝇的求偶指数显著高于群居饲养果蝇的求偶行为, 显然这种求偶并不是有效的, 因为雄蝇无法与无头雌蝇完成交尾。同时, 我们也发现社交隔离状态下的雄性果蝇 *Dsk* 的转录水平显著降低。因此, 我们将 *Dsk* 基因表达敲低的雄蝇分别进行单独饲养和群居饲养, 检测两组雄蝇对去头的雌蝇的求偶, 结果发现群居饲养雄蝇的求偶行为有所增加, 求偶指数与单独饲养的雄蝇没有差异^[38]。我们的免疫组化结果在雄蝇脑中标记到了 4 对 *Dsk* 肽能神经元, 分别为 2 对 MP3 神经元、1 对 MP1a 神经元和 1 对 MP1b 神经元(图 1A)。进一步的行为学结果显示, MP1a 神经元和 MP1b 神经元对雄蝇求偶行为非常关键。神经肽 *Dsk* 是哺乳动物中胆囊收缩素(cholecystokinin, CCK)的同源物, 已有研究发现神经肽 CCK 参与调节焦虑、攻击等行为, 并与抑郁症和恐慌症等疾病相关^[39-41]。

在大鼠中的研究发现, 断奶后的社交隔离导致成年后大鼠性行为减少^[42]。同样低, 在小鼠的研究中也发现, 发育过程中的社交隔离使雄鼠对雌鼠的性偏好降低, 并延长交配潜伏期, 从而减少了交配

行为^[43]。在雌性小鼠中, 青春期长时间的社交隔离导致成年后雌鼠的接受行为降低, 即使是成年后再重新社会化也不足以挽救这种影响。在经历过这种社交隔离的雌性中, 下丘脑雌激素受体 α (estrogen receptor α , ER α) 表达发生改变, 表明青春期的社交隔离可能会影响这一时期的性类固醇激素依赖性的脑重塑和重组^[44]。

社交隔离在成年大鼠中还可以导致类焦虑行为相关的性行为缺陷, 具体表现为开始性行为前的潜伏期和在第一次交配中射精前的潜伏期增长; 一旦交配完成, 社交隔离的大鼠开始第二次交配的潜伏期则恢复正常, 伏隔核(nucleus accumbens, NAc)内 cAMP 应答元件(cAMP response element, CRE)依赖性转录减少可能是长期社交隔离导致行为改变的机制之一^[45]。值得一提的是, NAc 接受来自富含神经肽 NPY 的下丘脑室旁核(paraventricular nucleus, PVN)的信号输入, 这些输入也可以提供与压力相关的信息^[46], 而神经肽 NPY 是否参与了社交隔离引起的大鼠类焦虑行为相关的性行为缺陷需要后续进一步的研究。

3 社交隔离与攻击行为

攻击行为在动物群体中非常常见。攻击行为可以是同物种个体之间由于争夺食物、配偶, 抢占巢区、领地而发生的相互攻击或战斗, 也可以是不同物种间由于捕食、争夺领地等发生的相互攻击。

研究发现, 社交隔离后, 攻击性行为在两性果蝇中都有所增加。雌性果蝇在面对食物资源时表现出更强的攻击性^[47], 而雄性对同性的领土入侵者表现更强的攻击性^[48]。Agrawal 等人的研究发现, 神经肽 *Dsk* 参与调控社交隔离导致的攻击增加, 社交隔离会降低 *Dsk* 基因的表达; 同时, 使用 RNA 干扰技术敲低 *Dsk* 基因的表达也会诱导社交隔离的果蝇产生更高的攻击行为^[49]。值得注意的是, Wu 等人的研究却发现, 敲低 *Dsk* 及其受体 *CCKLR-17D1* 可以降低果蝇的攻击行为^[50]。当激活和失活表达 *Dsk* 的神经元时会分别增加和减少雄性果蝇的攻击行为^[50]。基于神经肽 *Dsk* 同时参与社交隔离导致的攻击行为和求偶行为的变化, 我们推测, 社交隔离会导致雄蝇中 *Dsk* 的表达降低, 从而引起雄蝇无效求偶行为的增加和攻击行为的增加。同时, 本实验室免疫组化的结果显示雄蝇特异的调控求偶行为和攻击行为的 P1 神经元与 MP1b 神经元有明显

的突触联系^[38], 因此, 我们推测神经肽 Dsk 通过 MP1b 神经元调控社交隔离后雄蝇求偶行为和攻击行为的变化 (图 1B)。

2018 年, Zelikowsky 及其同事发现, 社交隔离引发的攻击行为增加以及对外界压力刺激的过度敏感会伴随着 *Tachykinin 2 (Tac2)* 基因编码的神经肽 Neurokinin B (NkB) 的表达量升高, 而神经肽 NkB 再通过其受体 Nk3R 调控攻击行为和应激反应^[7]。给予小鼠 Nk3R 特异性拮抗剂可以有效地降低社交隔离对小鼠产生的行为影响, 进而为社交隔离导致的负面行为影响的治疗提供了新靶点。需要提及的是, 早在 2014 年, 已经有研究发现 *Tac2* 的同源基因 *Tachykinin* 编码的神经肽 Tachykinin (Tk) 调控果蝇的攻击行为, Tk 及其受体 Takr86C 在社交隔离果蝇中的表达显著上调^[51, 52]。不管是神经肽 Dsk/CCK 还是神经肽 Tk/NkB 对攻击行为的调控, 都说明了社交隔离引起的攻击行为增加在神经肽层面的调控机制上可能具有一定的保守性。

社交隔离可以诱导神经递质如 5-HT、DA 等水平的变化, 这些神经递质对于啮齿类动物的攻击行

为具有重要的调节作用。断奶后的社交隔离诱导小鼠攻击行为增强及首次攻击潜伏期缩短, 这些行为学表现可能与前额叶皮层、下丘脑、中脑、海马等脑区突触后 5-HT 受体数量的减少密切相关^[53, 54], 例如下丘脑区域大多数 5-HT₃ 受体蛋白在 GABA 能神经元上表达, 而社交隔离诱导 5-HT₃ 受体减少^[54], 使 GABA 释放减少, 导致神经元过度活化, 从而增强慢性社交隔离小鼠的攻击性。而海马体中突触后 5-HT_{1A} 受体结合增加^[55], 突触前 5-HT_{1B} 受体活性降低^[56], 则可能是社交隔离大鼠海马 5-HT 反应性低的代偿机制。在社交隔离大鼠脑图谱研究中 c-Fos 的免疫反应性也表明, 内侧和基底外侧杏仁核、下丘脑攻击区和下丘脑室旁核的激活参与了对入侵者的攻击行为^[57]。

早在上个世纪, 人们就发现社交隔离的小鼠诱导出的高攻击性与纹状体中多巴胺 D1 受体密度增加有关^[58]。体内电生理实验也表明, 断奶后社交隔离大鼠中脑腹侧被盖区 (ventral tegmental area, VTA) 自发活跃的 DA 能神经元数量增加, 且 DA 能神经元不规则和爆发性放电的比例更高^[59]。在草原田鼠

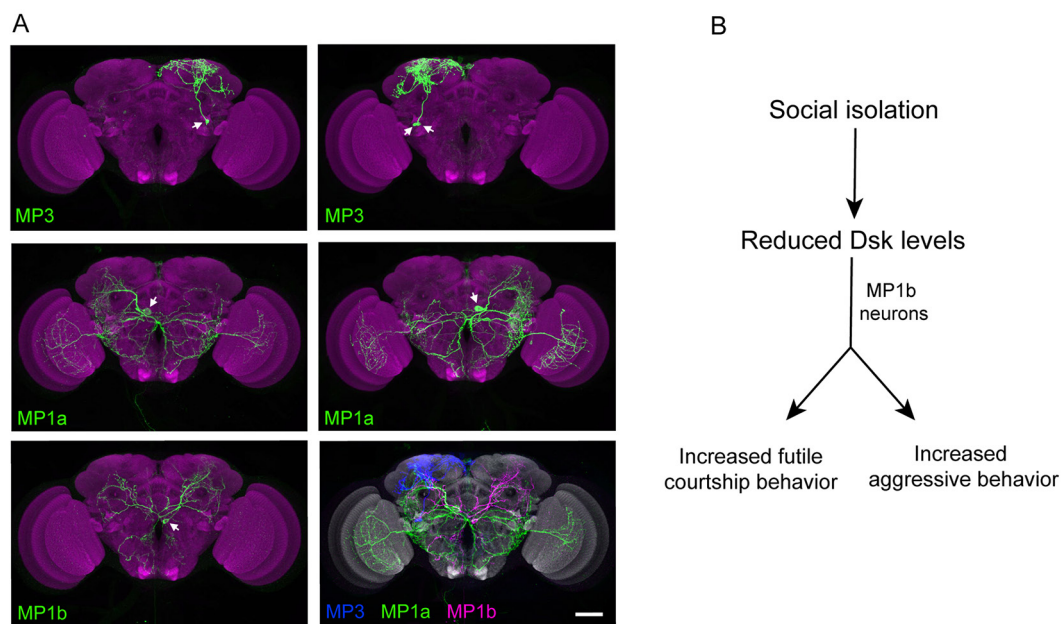


图 1. Dsk神经元的表达及对求偶和攻击行为的调控

Fig. 1. The expression of Dsk neurons and regulatory mechanisms on courtship behavior and aggressive behavior. A: Single-neuron labeling of Dsk neurons in the medial protocerebrum (MP). Stochastic labeling of single MP3 (upper left), two MP3 (upper right), single MP1a (middle row) and single MP1b neurons (lower left). Two MP3, one MP1a and one MP1b neurons are registered in a standard brain (lower right). Scale bar, 50 μ m. B: Social isolation leads to a decrease in the expression of the neuropeptide Dsk, resulting in increases in futile courtship behavior and aggressive behavior of male flies. Dsk: Drosulfakinin. Fig. 1A is from our previous findings^[38].

中的研究发现, 社交隔离导致 NAc 多巴胺 D1 受体结合增加, 甚至在群居的田鼠中, 具有较高多巴胺 D1 受体结合的个体会表现出社交回避增加^[60]。断奶后隔离饲养的大鼠在 NAc 中的突触前 DA 和 5-HT 功能增强^[61, 62], 而在海马中的突触前 5-HT 功能下降^[56], 这些神经化学失衡可能导致隔离大鼠对新刺激或预测危险的刺激的过度反应, 以及隔离诱导的行为变化, 如过度攻击等^[63]。

社交隔离应激可诱发多种内分泌变化, 包括下丘脑-垂体-肾上腺 (hypothalamic-pituitary-adrenocortical, HPA) 轴的激活、儿茶酚胺的释放, 最终导致糖皮质激素的释放和交感神经-肾上腺髓质系统的激活^[14]。社交隔离引起的不适当的攻击形式与 HPA 轴活性高或低以及成年期 5-HT 系统功能普遍较低有关。社交隔离导致 HPA 轴参数明显改变, 但不同的研究结果之间存在争议。一项研究报道, 断奶后社交隔离成年雄性大鼠基线促肾上腺皮质激素 (adrenocorticotrophic hormone, ACTH) 水平升高, ACTH 和皮质酮释放增加, 焦虑相关行为增强, 产生 HPA 轴功能的亢进^[64]。但另一项研究发现, 社交隔离降低了基线 ACTH 和皮质酮水平, 可能是由于 PVN 内神经元的自发电活动减少^[65]。HPA 轴在攻击性的调节中发挥重要作用, 长期高或低活性的 HPA 轴通常与攻击性增加和异常攻击模式有关^[66-68], 这些研究表明 HPA 轴功能升高或减退可能与社交隔离大鼠的异常攻击模式之间存在联系, 但仍需进一步研究证实。

长期社交隔离会导致雌、雄小鼠表现出不同的行为变化, 雄性小鼠的攻击行为增加, 而雌性小鼠则表现为社交退缩, 造成行为变化的原因是前额叶皮层作用的下游靶区不同。前额叶皮层的下游靶区基底外侧杏仁核主神经元的过度活跃造成了社交隔离后雌性小鼠攻击行为增加; 而在雌性小鼠中, 前额叶皮层的下游靶区中脑 VTA DA 能神经元活性降低则造成了社交隔离后雌性小鼠社交退缩行为^[69, 70]。

最近对仓鼠的研究也发现, 社交隔离增强了雄性和雌性仓鼠的攻击性, 主要通过性别依赖的方式影响了加压素 V1a 受体、催产素 (oxytocin, OT) 受体和 5-HT_{1a} 受体的结合^[71], 这三个主要受体也对社交经历诱导的攻击行为可塑性调节具有重要意义。有趣的是, 在大鼠中的研究发现, 断奶后的社交隔离不仅增强了雌雄大鼠的攻击性^[72, 73], 而且诱导出了异常的攻击模式, 使大鼠更倾向于攻击对手

脆弱的身体部位, 如头部、喉部和腹部^[74]。对社交隔离诱导的异常攻击行为的大脑机制进行研究, 可能对人类童年时期的社会忽视导致的异常攻击相关问题的理解具有重要意义。

4 讨论

公共卫生研究表明, 社交隔离可以对人类心理、身体健康以及行为等方面造成负面影响^[75, 76], 但这些研究缺乏分子以及神经环路层面的机制支持。动物模型可以通过遗传学、基因组学、分子和神经科学等方法, 在基因、神经递质、激素、神经环路、行为等各个层面进行研究, 从而可以更加深入地阐述社交隔离如何影响动物个体的行为。

社交隔离影响神经发育和神经可塑性, 而大脑发育异常被认为会增加成年后患精神类疾病的风险^[77]。社交隔离的大鼠海马中 CA1 锥体细胞树突长度减短, 且内侧前额叶皮层和海马的锥体细胞中树突棘密度均降低^[78]。在鸟类 (斑胸草雀) 中的研究也发现, 社交隔离会使端脑区域树突棘密度降低^[79]。此外, 早期的社交隔离会影响神经系统的发育, 尤其是 DA、5-HT 递质系统的发育成熟, 从而在成年后发生严重的行为障碍, 如过度攻击等。脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF) 是神经营养因子家族的重要成员, 在大脑中发挥多种神经营养和神经保护功能^[80], 也是一种普遍存在的有效神经元可塑性调节剂^[81], Han 等人^[82]报道了青春期社交隔离会增加 BDNF 在前额叶皮层中的表达, 同时降低其在 NAc 以及海马的 CA1 和齿状回区中的表达, 这与前额叶皮层和 NAc 这两个区域的 DA 浓度变化平行^[77]。DA 能和谷氨酸能系统在前额叶皮层和边缘系统的成熟发生在青春期^[83], 这是一个由神经营养因子系统支持的过程, 而在此关键发育阶段的社交隔离诱导的 BDNF 水平异常可能会长期或永久地破坏大脑相关神经系统, 尤其是 DA 能和谷氨酸能系统的发育和成熟, 造成成年后的多种行为障碍, 甚至产生类似精神分裂症患者中观察到的信息加工缺陷的情况^[77]。

社交隔离对人类的另一大危害是“孤独感”, 区别于社交隔离本身, 孤独是对社交隔离的感知, 是人类的一种情绪。基于人群的纵向研究表明, 除客观社交隔离外, 感到孤独也是发病率和死亡率的一个风险因素, 研究表明慢性社交隔离增加了 HPA 轴的激活, 并且这些影响更多地取决于人与人之间

的社会关系的破裂，而不是客观隔离本身^[4]。而与社会密切联系产生的“幸福感”则来源于内源性阿片肽系统与 DA 能系统。内源性阿片肽系统与 DA 能系统，具有奖赏和缓解疼痛的作用^[84]，阿片样物质可以减少社交隔离所经历的痛苦，主要表现为与母亲分离的大鼠幼崽发声减少^[85]；而社会联系增加内源性阿片释放^[86]。啮齿动物的社交隔离还伴随着海马和杏仁核中 μ 和 κ 阿片受体的表达减少，而全身注射 δ 阿片受体激动剂可逆转社交隔离诱导的焦虑样行为^[87]。在人类中，阻断阿片受体会降低社会联系感，降低情感和身体温暖感，并降低腹侧纹状体的活动^[88–90]。

社交隔离与社会等级也有关联，对雌性小鼠社会等级的研究揭示了社交隔离诱导的行为改变与社会地位之间的紧密联系，社会等级较低的小鼠容易受到社会不稳定性的影响，社会等级较高的小鼠更容易受到社交隔离或孤独的影响^[91]，这一结果可能有助于我们理解人类群体广泛性焦虑症和严重抑郁症等精神疾病及其潜在影响因素。

本文主要总结了社交隔离对果蝇、小鼠、大鼠睡眠、生殖行为、攻击行为等本能行为的影响及调

控机制(表 1)。事实上，社交隔离对动物的影响是广泛而普遍的，例如，在斑马鱼中的社交隔离就产生了一些有趣的现象。低密度的饲养条件会增加斑马鱼的应激反应和攻击性^[92]。短期的社交隔离引起成年斑马鱼强烈的焦虑样行为和皮质醇反应^[93]，呈现与哺乳动物相似的反应，但斑马鱼和哺乳动物中的慢性社交隔离压力则产生了不同的影响。在哺乳动物中，慢性社交隔离会增加精神障碍(如焦虑)的风险^[8, 94]，但在斑马鱼中慢性社交隔离引起类似抗焦虑的作用^[95, 96]。这种差异可能是由于鱼类对新环境和大脑调节的适应更快^[97, 98]。所以，我们可以通过社交隔离进行诱导，在斑马鱼、哺乳动物包括非人灵长类中建立起焦虑、抑郁、精神分裂等精神类疾病的动物模型^[99–101]。使用这些动物模型对社交隔离压力的神经内分泌、神经生物学和表观遗传等进行更全面的研究，以便更好地理解在暴露于社交压力如遗弃、孤独的人类中观察到的精神缺陷及行为障碍的机制。

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表1. 社交隔离对动物本能行为的影响及调控机制
Table 1. Effects and regulatory mechanisms of social isolation on animal innate behaviors

	<i>Drosophila</i>		Mice		Rat	
	Behavioral effects	Regulatory mechanism	Behavioral effects	Regulatory mechanism	Behavioral effects	Regulatory mechanism
Sleep	Reduced sleep	Activity of NPF ⁺ P2 neurons ^[23, 24] Neurotransmitter DA↓ ^[21]	Reduced sleep	GABAergic neuron dysfunction ^[30]	—	—
Reproductive behavior	Weakened male courtship-competition Increased futile courtship behavior	Reduced Ca ²⁺ levels in Or47b ORNs ^[37] Neuropeptide Dsk↓ ^[38]	Reduced female sexual behavior	ERα↑ ^[44]	Reduced male mating behavior	Reduced CRE-dependent transcription ^[45]
Aggressive behavior	Increased aggressive behavior	Neuropeptide Dsk↓ ^[49] Neuropeptide Tk↑ ^[51, 52]	Increased aggressive behavior	Neuropeptide NkB↑ ^[7] Neurotransmitter 5-HT↓ ^[53, 54] Neurotransmitter DA↑ ^[58] PFC-BLA neural circuit ^[69, 70]	Increased aggressive behavior	Neurotransmitter 5-HT↓ ^[55, 56] Neurotransmitter DA↑ ^[59]

NPF: neuropeptide F; DA: dopamine; Or47b: Odorant receptor 47b; ORNs: olfactory receptor neurons; ERα: estrogen receptor α; CRE: cAMP response element; Dsk: Drosulfakinin; Tk: Tachykinin; NkB: Neurokinin B; PFC: prefrontal cortex; BLA: basal lateral amygdala.

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