Advances in Psychology 心理学进展, 2019, 9(10), 1767-1777
Published Online October 2019 in Hans. http://www.hanspub.org/journal/ap
https://doi.org/10.12677/ap.2019.910214

Hans汉斯

Effect of Somatostatin-Expressing Interneuron Deficits in Depression

Chen Guo

School of Psychology, The Key Lab of Cognition and Personality of the Ministry of Education, The Southwest University, Chongqing
Email: 1107644895@qq.com

Received: Oct. 3rd, 2019; accepted: Oct. 18th, 2019; published: Oct. 25th, 2019

Abstract

Major depressive disorder is a common mental illness, but its pathological mechanism is still unclear. In recent years, studies have found that imbalance of neural network excitability and inhibition may be one of the important factors leading to depression, which is mainly caused by the incoordination between excitatory glutamatergic pyramidal neurons and inhibitory gamma-aminobutyric acid neurons. Somatostatin-expressing interneurons, the main inhibitory neurons, regulate pyramidal neuronal activity, participate in stress response, and have a high susceptibility to stress. In the dorsal ventral frontal lobes (dlPFC), cingulate gyrus (ACC), hippocampus and other brain regions in patients with depression, researchers have found a decrease in SST mRNA and protein levels. This article will review the function of somatostatin-expressing interneuron and how its functional reduction impacts depression, including causes and performance.

Keywords

Major Depressive Disorder, Gabaergic Interneurons, Somatostatin Interneurons, Prefrontal Cortex, Drug Development

SST中间神经元功能降低对抑郁症的影响

郭　沉

西南大学心理学部教育部认知与人格重点实验室，重庆
Email: 1107644895@qq.com

收稿日期：2019年10月3日；录用日期：2019年10月18日；发布日期：2019年10月25日

摘　要

抑郁症(major depressive disorder)是一种常见的精神疾病，但其病理机制尚不清楚。近年来，研究发

文章引用: 郭沉(2019). SST 中间神经元功能降低对抑郁症的影响. *心理学进展, 9(10),* 1767-1777.
DOI: 10.12677/ap.2019.910214

现神经网络的兴奋与抑制平衡失调可能是导致抑郁症的重要因素之一，该平衡主要由兴奋性谷氨酸能锥体神经元(pyramidal neuron)和抑制性γ-氨基丁酸(GABA)神经元协调完成。SST中间神经元是主要的抑制神经元，调节锥体神经元活动，参与应激反应，对应激有较高的易感性，在抑郁症患者背腹侧前额叶(dlPFC)、扣带回(ACC)、海马等脑区皆发现了SST mRNA或蛋白水平降低。本文将综述SST中间神经元功能及其功能降低对抑郁症影响的研究结果，包括在不同脑区(如前额叶、海马等)的表现、起因、相关的抑郁症药物研发。

关键词

抑郁症，GABA能中间神经元，SST中间神经元，前额叶，药物研发

1. 引言

全球人口中约有 5%患有抑郁症(Faron-Gorecka et al., 2016)，约有 20.6%的人口有患抑郁症的风险(Hasin et al., 2018)。抑郁症是自杀率升高的原因之一(Ebmeier, Donaghey, & Steele, 2006)，抑郁症已然成为威胁人类身心健康的重大疾病，因此对其病理生理机制和潜在药物靶点的研究至关重要。

抑郁症的病理机制主要有单胺能假说(Hirschfeld, 2000)、谷氨酸假说(Wang, Jing, Toledo-Salas, & Xu, 2015)、下丘脑－垂体－肾上腺(HPA)轴调节应激反应功能受损假说(Keller et al., 2017; Pariante & Lightman, 2008)。其中，单胺能假说认为抑郁症产生的原因是大脑内单胺类神经递质缺乏，如去甲肾上腺素、5-HT等，基于这一假说研发了 SSRI、三环类抗抑郁药物，通过增加大脑单胺水平治疗抑郁症状，其缺点主要是治疗效率低和复发率高(Marathe, D'Almeida P, Virmani, Bathini, & Alberi, 2018)。谷氨酸假说起源于快速抗抑郁药物 ketamine (NMDAR 受体拮抗剂)的发现，人类研究发现 ketamine 在 2 小时内具有快速抗抑郁功效(Zarate et al., 2012)，表明抑郁症可能与谷氨酸突触传递及可塑性的缺陷相关(Wang et al., 2015)。在80%抑郁症患者中发现 HPA 轴活动过度，糖皮质激素调节的 HPA 轴负反馈缺陷(Vincent et al., 2013)，而动物研究发现糖皮质激素受体拮抗剂 RU 43044 在调节 HPA 轴活动时能够减少抑郁行为(Ago et al., 2008)。

近年来，对抑郁症患者和动物实验的研究发现兴奋性锥体神经元和抑制性中间神经元之间功能的失衡可能是导致抑郁症的重要病理机制(Thompson et al., 2015)。神经元网络兴奋与抑制失衡可能对神经网络功能、信息处理与传输产生影响。长期的神经网络兴奋与抑制平衡异常可能引发诸多精神疾病临床症状，例如重度抑郁症(MDD)、双相情感障碍(BPD)、焦虑症以及精神分裂症(SCZ)。

在抑郁症患者大脑中发现 GABA 浓度降低(Gabbay et al., 2012)，$GABA_A$ 型受体($GABA_ARs$)减少(Klumpers et al., 2010)，谷氨酸脱羧酶(GAD)表达减少(Banasr et al., 2017)。患者在接受抗抑郁药物治疗(Shen et al., 2010)、电休克治疗(Sanacora et al., 2003)、经颅磁刺激治疗(TMS) (Dubin et al., 2016)或认知行为疗法(Sanacora et al., 2006)后大脑内 GABA 含量升高，且抑郁症状减轻，说明 GABA 还参与到抗抑郁作用中。

除了抑郁症，在其他精神障碍中也发现 GABA 中间神经元抑制功能降低，包括双相情感障碍(Atagun et al., 2017)、精神分裂症(Lewis & Sweet, 2009)等。

GABA 中间神经元占皮层神经元总量约 10%~20% (Rudy, Fishell, Lee, & Hjerling-Leffler, 2011)，大多为局部投射神经元，可以靶向其他神经元的树突、胞体和轴突，拥有密集的轴突分支，这使得 GABA 中间神经元能够调节整个神经网络(Fino, Packer, & Yuste, 2013)。

锥体神经元兴奋性信号的输入、输出和整合受不同分布、形态、电生理特性和分子特性的 GABA 中间神经元调控。根据不同的分子标记能将 GABA 中间神经元分为 20 个亚型，主要为以下几个类别：PV (小清蛋白)中间神经元，占比约为 40%；SST (生长抑素)中间神经元，占比约为 30%；离子型 5-HT3aR 中间神经元，占比约为 30%，其中包括 VIP (血管活性肠肽)中间神经元(Rudy et al., 2011)。

其中，SST 中间神经元主要由靶向 PN 远端树突细胞的 Martinotti 细胞组成，这类细胞具有低阈值常规放电特性和高自发活动水平，分布于皮层第 2 到第 6 层(Gonchar & Burkhalter, 1997)。在海马和新皮层中，SST 中间神经元介导反馈抑制和侧向抑制，维持静息状态下锥体神经元的活性，调控来自皮层第一层和丘脑输入的神经信号(Murayama et al., 2009)。

大量对抑郁症患者的研究证明生长抑素(SST)与抑郁症的病理生理学机制有关，SST 广泛分布在中枢神经系统(CNS)中，既作为神经递质又作为神经调质(Engin & Treit, 2009)，与 γ-氨基丁酸(GABA)共同存在于神经末梢，参与调节应激的生理和行为反应(Lin & Sibille, 2013)。在对抑郁症患者背外侧前额叶研究中，发现 SST mRNA 表达下降，而 PV mRNA 表达则没有变化(Sibille, Morris, Kota, & Lewis, 2011)，此外，在其他脑区，如海马、杏仁核、扣带回等都发现了 SST mRNA 表达降低和 SST 神经元抑制功能降低(Guilloux et al., 2012; Tripp, Kota, Lewis, & Sibille, 2011; Tripp et al., 2012)，表明 SST 中间神经元功能降低是导致抑郁症的重要因素之一，因此本文将阐明 SST 中间神经元抑制功能降低对抑郁症的影响。

2. SST 中间神经元

作为中间神经元，SST 神经元的主要功能在于调节神经网络的兴奋与抑制平衡。SST 中间神经元有不同的类型，皮层中主要为 Martinotti 细胞，分布于皮层第 2 到第 6 层(Weckbecker et al., 2003)。在新皮层 L1 中，SST 中间神经元特异性靶向锥体神经元的远端树突(Gentet et al., 2012; Ma, Hu, Berrebi, Mathers, & Agmon, 2006)，对传入锥体神经元的兴奋性信号进行局部调节，在控制锥体神经元信息输入中发挥重要作用(Fino et al., 2013; Viollet et al., 2008)。对 GIN 小鼠和 X98 小鼠的研究部分阐明了 SST 中间神经元在大脑皮层中的作用，GIN 小鼠的 SST 中间神经元主要为 Martinotti 细胞，在皮层第 2/3 和 5 层表达绿色荧光蛋白，并投射到第 1 层，光遗传激活第 2、3、5 层的 SST 中间神经元能够抑制锥体神经元放电活动(Xu, Jeong, Tremblay, & Rudy, 2013)。X94 小鼠中的 GFP 表达 SST 中间神经元细胞主要位于皮层的第 4 层，为非 Martinotti 细胞，目标靶向第 4 层的 PV 中间神经元，通过抑制 PV 中间神经元活动激活锥体神经元，同时接受丘脑传入神经信息，光激活第 4 层的 SST 中间神经元使得锥体细胞产生去抑制作用(Xu et al., 2013)。

从大量的对抑郁症患各大脑区 SST mRNA 和含量降低的研究中可以推测抑郁患者 SST 中间神经元功能缺陷(Douillard-Guilloux, Lewis, Seney, & Sibille, 2017; Guilloux et al., 2012; Sibille et al., 2011; Tripp et al., 2011; Tripp et al., 2012)，在啮齿类动物研究中也有同样发现(Lin & Sibille, 2015)。

Fuchs 等人的研究对揭示 SST 中间神经元调节的神经网络兴奋与抑制平衡对抑郁症的影响发挥了重要作用。通过 Cre-loxp 技术条件性敲除小鼠前脑 SST 中间神经元中 $GABA_A$ 受体的 γ2 亚基基因，增加 SST 中间神经元的抑制性突触输入减少兴奋性突触输入增加，海马 CA1 区锥体神经元和扣带回第 2、3 层的抑制性突触输入增强，进而抑制锥体神经元的放电活动，在行为上表现为抑郁样行为减少，表明在不改变大脑 SST 含量的情况下，通过增加从 SST 中间神经元到锥体神经元的抑制性突触输入能够产生抗抑郁作用(Fuchs et al., 2017)。

在另一项动物研究中发现在前额叶中使用化学遗传方法急性抑制 SST 中间神经元放电活动使得动物焦虑行为增加，行为情绪性上升，而慢性抑制 SST 神经元活动却减少了焦虑行为和情绪性，表明在前额叶 SST 中间神经元对行为情绪的影响有复杂的时间依赖性(Soumier & Sibille, 2014)。

SST 中间神经元释放的神经递质为生长抑素(SST)，同时，SST 还是神经调质，是一种在多个器官中表达的神经肽，在皮层、杏仁核中央核、边缘系统和感觉系统、中央区灰质和下丘脑中大量表达。生长抑素参与调节应激的生理和行为反应，包括抑制下丘脑激素释放，如促肾上腺皮质激素释放激素(Lin & Sibille, 2013)、杏仁核中枢核输出和感觉输入的回路整合。

在人类抑郁症患者中发现生长抑素水平降低首先出现在对患者脑脊液(CSF)的研究中(Molchan et al., 1991)，该症状随着对抑郁症的治疗而改善(Post, Rubinow, Kling, Berrettini, & Gold, 1988)。此外，在抑郁症患者皮质边缘区中发现与生长抑素共标的两种神经肽(神经肽 Y 和皮质抑素)的表达均显著下降(Tripp et al., 2011; Tripp et al., 2012)。人类研究在抑郁症患者的多个脑区发现了 SST 含量、SST 蛋白水平和 SST mRNA 表达降低，如背外侧前额叶皮层(dlPFC)、前扣带皮层(sgACC)和杏仁核中(Guilloux et al., 2012; Sibille et al., 2011; Tripp et al., 2011)。

在动物研究中发现生长抑素受体敲除(SSTKO)小鼠表现出焦虑行为增加、皮质酮水平的升高，皮质抑素(Cortistatin)和 Gad67 的基因表达降低。对缺乏单个 SST1-5 受体的小鼠的研究有很多，其中对 SST2KO 的小鼠研究发现其在高架十字迷宫和旷场中焦虑行为增加，在强迫游泳试验中木僵率增加，垂体促肾上腺皮质激素释放增加而 SST 含量则相对减少(Viollet et al., 2000)，同样是 SST2 KO 小鼠，在慢性不可测应激模型中发现，相较于青年 SST2 KO 小鼠，老年 SST2 KO 小鼠表现出更高水平的空间学习能力和记忆力损伤以及焦虑行为，皮质酮水平也更高(Prevot et al., 2018)，这说明 SST2 受体基因的缺失不仅会加剧小鼠对应激源的敏感性，还会对正常的大脑老化过程产生负面影响。SST2 受体亚型的激活在大鼠和小鼠中具有强烈的抗焦虑作用(Engin & Treit, 2009; Prevot et al., 2017)。有研究认为，接受慢性应激后，大鼠纹状体和伏隔核(NAcc)中 SST2 受体结合位点的增加可能是受到了多巴胺 D2 受体的调节，说明这两种受体共同参与到了慢性应激引起的应激反应中(Faron-Gorecka et al., 2018)，另有研究发现在接受抗抑郁药地昔帕明(Desipramine) 21 天后，多巴胺 D2 受体和 SST5 受体异二聚体的形成增加，说明多巴胺 D2 受体和 SST5 受体异二聚体可能是抗抑郁作用的潜在介质(Szafran-Pilch et al., 2017)。

研究发现 SSTR4KO 小鼠在高架十字迷宫中焦虑行为增加，在强迫游泳实验中木僵水平上升，而在腹腔注射 SST4 受体激动剂 J-2156 后发现小鼠焦虑水平降低，悬尾测试中的抑郁行为减少，同时增加杏仁核、背侧中缝核、导水管周围灰质等脑区 Fos 免疫反应(Scheich et al., 2016)。近期动物研究发现 SST4 基因缺失的小鼠对慢性应激诱发的行为和神经内分泌改变具有较高的易感性(Scheich et al., 2017)。

从生长抑素(SST)和 SST 1-5 受体的研究中我们可以推测出 SST 中间神经元抑制功能的下降对抑郁症的影响。

3. SST 中间神经元功能降低在各脑区的表现

在前额叶皮层(PFC)中，对抑郁症患者大脑组织研究发现，PFC 中 GABA 合成酶 GAD67mRNA 和蛋白水平减少(Karolewicz et al., 2010)，在抑郁症患者的 dlPFC 中发现 SST mRNA 表达显著降低(Sibille et al., 2011)，使用化学遗传技术急性抑制额叶 SST 中间神经元活动使得小鼠行为情绪异常增加，而慢性抑制额叶 SST 中间神经元活动却能够有效地抑制行为情绪异常，这表明 SST 中间神经元有调节情绪的作用，并且行为情绪调节可能涉及到复杂的神经网络功能(Soumier & Sibille, 2014)。

杏仁核是情绪调节的皮质边缘环路的关键组成部分，在抑郁症患者杏仁核中发现 GABA 合成酶 GAD67mRNA 表达和蛋白水平的减少，在杏仁核外侧和基底内侧发现 SST mRNA 表达下降(Guilloux et al., 2012)和 SST 中间神经元数量的减少(Douillard-Guilloux et al., 2017)，以及几种 GABA 转录物的减少，包括 GABA 合成酶、谷氨酸脱羧酶 1(GAD1)和 GABA 受体亚基 $GABAR_A1$ (Guilloux et al., 2012)，但只在女性患者杏仁核中发现了 SST 基因表达和蛋白水平降低(Guilloux et al., 2012; Sibille et al., 2009)，男性 MDD

受试者杏仁核中 SSTRNA 表达无显著变化，这表明女性与男性在抑郁症中的差异。

海马区有大量的糖皮质激素受体，对 HPA 轴上的负反馈调节起着关键作用(Herman, Ostrander, Mueller, & Figueiredo, 2005)，因而在情绪调节中发挥重要作用(McEwen, Nasca, & Gray, 2016)。在重度抑郁症患者海马中发现糖皮质激素水平升高，这导致海马功能障碍，并且可能导致海马体积萎缩(Sheline, 1996)。慢性应激通过影响海马背侧和腹侧 PV 中间神经元(Hu, Zhang, Czeh, Flugge, & Zhang, 2010)和 SST 中间神经元(Czeh et al., 2015)，损害海马 GABA 中间神经元的抑制功能。动物研究还发现慢性应激减少了海马 CA1-2-3 区域 15%~25%的 SST 中间神经元(Czeh et al., 2015)。

扣带回(ACC)皮层是情绪调节的关键脑区，包括情绪信息与认知的控制整合，扣带回参与调节的情绪皮质激素环路已经进入到 MDD 的病理生理学和治疗研究中，抗抑郁治疗常伴随着 sgACC 活动降低(Mayberg, 2002)。对抑郁症患者扣带回研究显示，扣带回皮层中细胞的 SST 含量降低(Seney, Tripp, McCune, Lewis, & Sibille, 2015; Tripp et al., 2011)。抑郁症中的 sgACC 功能异常可能是由 GABA 中间神经元抑制功能缺陷导致的(Valentine & Sanacora, 2009)，另有研究显示与正常受试者相比，抑郁症男性和女性受试者 sgACC 中 SSTRNA 水平下降约 30%，与男性患者相比，女性患者扣带回中 SST 下降更多(Seney et al., 2013)，约为男性患者的两倍(Kessler et al., 2003)。

4. 导致 SST 中间神经元功能降低的因素

生物应激源，如足底电击可选择性影响 SST 中间神经元或 SST 表达进而导致抑郁(Ponomarev, Rau, Eger, Harris, & Fanselow, 2010)，一项动物研究发现在接受慢性应激模型后 PFC 区生长激素抑制素-28 表达下降(Li et al., 2018)。慢性应激抑郁模型通过破坏细胞内部稳态机制而改变 SST 中间神经元功能，而且 SST 中间神经元的固有细胞特性可能决定了它们对各种损伤的选择易感性，包括内质网(ER)应激(Lin & Sibille, 2013)、对神经营养性环境的高度依赖以及神经细胞的发育和衰老过程。

内质网应激是一种与正常老化和神经退行性疾病有关的细胞应激，过量的 ER 负荷或细胞外刺激会引起 ER 蛋白翻译受损，进而导致未折叠蛋白的积累，最后造成内质网应激。内质网应激是由蛋白激酶 RNA 内质网(Perk)介导的真核起始因子 2α (Eif2a)的磷酸化造成的蛋白应答信号传导途径异常引起的。在 UCMS 和慢性升高皮质酮的小鼠模型中观察到 SST 中间神经元的 Eif2a 信号抑制，而通过 PERK 抑制 Eif2a 磷酸化降低了 UCMS 小鼠行为情绪(Lin & Sibille, 2015)，表明改变蛋白稳态可能导致 SST 细胞选择易感性。产生反应性氧化性物质两种酶(一氧化氮合酶(nNOS)和 NADPH 黄递酶(NADPHd))与生长激素抑制素和神经肽 Y 共定位(Jaglin, Hjerling-Leffler, Fishell, & Batista-Brito, 2012)，且在 SST 中间神经元中拥有高表达，表明 SST 中间神经元对应激的高敏感性与氧化应激有关。

脑源性神经营养因子(BDNF)与额叶和杏仁核细胞数量降低(Bowley, Drevets, Ongur, & Price, 2002; Rajkowska, Halaris, & Selemon, 2001)以及海马体积减小有关(Campbell, Marriott, Nahmias, & MacQueen, 2004)，此外，BDNF 及其受体神经营养酪氨酸激酶受体 2 型(TrkB)还与多种情绪障碍有关(Guilloux et al., 2012; Tripp et al., 2012)，其中 BDNF-TrkB 信号传导对维持生长抑素基因表达很关键(Martinowich, Schloesser, Jimenez, Weinberger, & Lu, 2011)，BDNF 对 SST 神经元发育、数量增加起重要作用(Du et al., 2018)，研究显示抑郁症患者海马组织中 BDNF 水平降低(Thompson Ray, Weickert, Wyatt, & Webster, 2011)，将抑郁症人类患者与 BDNF 信号传导基因变异的小鼠进行比较，发现生长抑素、神经肽 Y 和皮质抑素都减少(Guilloux et al., 2012)，此外，在人类和动物研究中发现 SST 或 GABA 合成酶基因表达降低发生在 BDNF 信号缺陷的下游机制(Guilloux et al., 2012; Tripp et al., 2012)，即 SST 基因表达降低是由 BDNF 信号缺陷导致的(Glorioso et al., 2006)，表明在参与调节生理和病理过程中，SST 中间神经元的功能和易感性可能由 BDNF-TrkB 信号介导。BDNF-TrkB 信号本身易受炎症(Goshen et al., 2008; Song & Wang, 2011)和

糖皮质激素水平的影响。此外，轻度氧化应激抑制酪氨酸磷酸酶活性，这可能损害 TrkB 的下游信号，可直接影响 SST 中间神经元的特性，进而导致其功能缺陷。动物研究发现抗抑郁治疗能够增加脑部 BDNF 蛋白水平以及其 mRNA 表达，向海马区注射 BDNF 能够起到抗抑郁作用(Shirayama, Chen, Nakagawa, Russell, & Duman, 2002)。

年龄与 SST 表达水平高度相关，海马和皮层区域的 SST 神经元对衰老似乎比其他中间神经元亚型更敏感(French, Ma, Oh, Tseng, & Sibille, 2017; Rozycka & Liguz-Lecznar, 2017)，在人类大脑皮质中生长抑素的基因表达随着年龄增长显著降低(Erraji-Benchekroun et al., 2005)，而小清蛋白基因表达并未因年龄而改变(Glorioso, Oh, Douillard, & Sibille, 2011)。衰老往往伴随着 BDNF 循环水平下降(Erickson et al., 2010)、炎症(Bruunsgaard & Pedersen, 2003)和氧化应激损伤增加(Barja, 2002)。在人类抑郁症患者研究中发现与正常衰老受试者相比，抑郁症患者 sgACC 区中生长抑素基因表达减少的速度更快(Tripp et al., 2012)，抑郁症可能是导致早期衰老现象的重要原因(Douillard-Guilloux, Guilloux, Lewis, & Sibille, 2013)。

5. 药物研发

抑郁症是一种复杂的精神疾病，具有高度异质性的临床表现和病理学特征，其治疗药物的研发主要基于单胺能假说(Millan, 2006)。针对抑郁症的治疗尽管有许多药理学和非药理学疗法，但依旧约 35%的患者的症状无法通过常规的药物治疗得到缓解(Rush et al., 2006)。

药理学研究认为生长抑素有抗抑郁的作用，如大鼠脑室内注射泛生长抑素激动剂(ODT8-SST)可减少应激诱导血浆中 ACTH、肾上腺素和去甲肾上腺素的升高(Brown, Rivier, & Vale, 1984; Fisher & Brown, 1980)，在大鼠静脉注射生长抑素，观察发现在高架十字迷宫和强迫游泳试验中，大鼠产生了抗焦虑和抗抑郁样行为，以及类似抗焦虑药物的神经生理学特征(Engin, Stellbrink, Treit, & Dickson, 2008)。脑室内注射 SST2 受体激动剂减少了大鼠在高架十字迷宫中的焦虑行为，而其他四种受体亚型激动剂没有类似作用，注射 SST2 受体激动剂和 SST3 受体激动剂后大鼠在强迫游泳中的木僵行为减少，产生了抗抑郁作用(Engin & Treit, 2009)。在小鼠脑部杏仁核和隔膜中微量输入生长抑素-14 和-28，发现在高架十字迷宫和休克-探针测试中小鼠焦虑行为降低(Yeung, Engin, & Treit, 2011)，注射 SST2 受体拮抗剂 PRL2903 可抵消生长抑素的抗焦虑作用(Yeung & Treit, 2012)。SST2R 和 SST3R 受体激动剂在高架十字迷宫测试和强制游泳测试中起到了抗焦虑和抗抑郁的作用，这表明这些 SST 受体亚型是研究抗抑郁作用的潜在靶点(Nilsson et al., 2012)。

持续给药丙咪嗪(imipramine) (一种三环类抗抑郁药物)发现在产生抗抑郁作用的同时，SST-14 和 SST-18(1-11)表达增加，SST1 受体拮抗剂 SRA880 能与丙咪嗪协同作用，可增加大脑皮质中的 BDNF mRNA 表达，在悬尾试验中引起抗抑郁作用，这可能是由于 SST 增加血清素释放导致的(Nilsson et al., 2012)。另一项研究发现地昔帕明(desipramine) (一种抗抑郁药物和丙咪嗪的活性代谢物)治疗后，大鼠海马 CA1 区 SST1 受体表达增加(Pallis et al., 2009)。

持续给药西酞普兰(citalopram) (一种选择性 5-羟色胺再摄取抑制剂抗抑郁药物)发现在尾状核壳、海马、伏隔核和前额叶皮质中 SST 水平增加，海马 CA1 区 SST1、4 受体表达显著增加，而额叶皮质表层和深层的 SST2 受体密度显着下降，表明西酞普兰在产生抗抑郁效果的同时，还影响生长激素抑制素系统对情绪、动机和认知的功能(Pallis et al., 2009)。

快速抗抑郁药物的研究为抑郁症治疗提供了新的途径，氯胺酮(ketamine)和东莨菪碱(scopolamine)通过快速增加体内谷氨酸水平、BDNF 通路激活和突触生成产生快速的抗抑郁作用。研究发现氯胺酮增强内侧前额叶皮质(mPFC)中抑制性突触的作用，进而逆转 $GABA_AR\gamma2^{+/-}$小鼠的抑郁行为(Ren et al., 2016)，但是氯胺酮会产生游离和拟态副作用，在较高剂量下易上瘾(Machado-Vieira, Salvadore, DiazGranados, & Zarate, 2009)，其药用价值还有待研究。一项小鼠实验中发现，东莨菪碱通过拮抗 mPFC SST 中间神经元

中代谢型乙酰胆碱受体(mAChR)起到抗抑郁作用(Wohleb et al., 2016)，这似乎与抑郁症相关 SST 降低的研究证据不一致，其速效抗抑郁药疗效还需进一步证实。此外，最近的一项研究表明，内侧前额叶皮质的生长抑素中间神经元对于氯胺酮的快速作用抗抑郁机制是必需的(Wohleb 等，2016)。

6. 结论

越来越多的研究在抑郁症中发现 SST 表达和 SST 中间神经元功能的降低，以及 SST 和 SST 中间神经元在抑郁症治疗中的抗抑郁作用，说明 SST 中间神经元很有可能成为下一个抑郁症重要研究靶点，为了解精神病理学的机制提供了一个契机，为抑郁症治疗新药的研发提供了有效的途径。

参考文献

Ago, Y., Arikawa, S., Yata, M., Yano, K., Abe, M., Takuma, K., & Matsuda, T. (2008). Antidepressant-Like Effects of the Glucocorticoid Receptor Antagonist RU-43044 Are Associated with Changes in Prefrontal Dopamine in Mouse Models of Depression. *Neuropharmacology, 55,* 1355-1363. https://doi.org/10.1016/j.neuropharm.2008.08.026

Atagun, M. I., Sikoglu, E. M., Soykan, C., Serdar Suleyman, C., Ulusoy-Kaymak, S., Caykoylu, A., Moore, C. M. et al. (2017). Perisylvian GABA Levels in Schizophrenia and Bipolar Disorder. *Neuroscience Letters, 637,* 70-74. https://doi.org/10.1016/j.neulet.2016.11.051

Banasr, M., Lepack, A., Fee, C., Duric, V., Maldonado-Aviles, J., DiLeone, R., Sanacora, G. et al. (2017). Characterization of GABAergic Marker Expression in the Chronic Unpredictable Stress Model of Depression. *Chronic Stress (Thousand Oaks), 1*. https://doi.org/10.1177/2470547017720459

Barja, G. (2002). Endogenous Oxidative Stress: Relationship to Aging, Longevity and Caloric Restriction. *Ageing Research Reviews, 1,* 397-411. https://doi.org/10.1016/S1568-1637(02)00008-9

Bowley, M. P., Drevets, W. C., Ongur, D., & Price, J. L. (2002). Low Glial Numbers in the Amygdala in Major Depressive Disorder. *Biological Psychiatry, 52,* 404-412. https://doi.org/10.1016/S0006-3223(02)01404-X

Brown, M. R., Rivier, C., & Vale, W. (1984). Central Nervous System Regulation of Adrenocorticotropin Secretion: Role of Somatostatins. *Endocrinology, 114,* 1546-1549. https://doi.org/10.1210/endo-114-5-1546

Bruunsgaard, H., & Pedersen, B. K. (2003). Age-Related Inflammatory Cytokines and Disease. *Immunology and Allergy Clinics of North America, 23,* 15-39. https://doi.org/10.1016/S0889-8561(02)00056-5

Campbell, S., Marriott, M., Nahmias, C., & MacQueen, G. M. (2004). Lower Hippocampal Volume in Patients Suffering from Depression: A Meta-Analysis. *American Journal of Psychiatry, 161,* 598-607. https://doi.org/10.1176/appi.ajp.161.4.598

Czeh, B., Varga, Z. K., Henningsen, K., Kovacs, G. L., Miseta, A., & Wiborg, O. (2015). Chronic Stress Reduces the Number of GABAergic Interneurons in the Adult Rat Hippocampus, Dorsal-Ventral and Region-Specific Differences. *Hippocampus, 25,* 393-405. https://doi.org/10.1002/hipo.22382

Douillard-Guilloux, G., Guilloux, J. P., Lewis, D. A., & Sibille, E. (2013). Anticipated Brain Molecular Aging in Major Depression. *The American Journal of Geriatric Psychiatry, 21,* 450-460. https://doi.org/10.1016/j.jagp.2013.01.040

Douillard-Guilloux, G., Lewis, D., Seney, M. L., & Sibille, E. (2017). Decrease in Somatostatin-Positive Cell Density in the Amygdala of Females with Major Depression. *Depress Anxiety, 34,* 68-78. https://doi.org/10.1002/da.22549

Du, X., Serena, K., Hwang, W., Grech, A. M., Wu, Y. W. C., Schroeder, A., & Hill, R. A. (2018). Prefrontal Cortical Parvalbumin and Somatostatin Expression and Cell Density Increase during Adolescence and Are Modified by BDNF and Sex. *Molecular and Cellular Neuroscience, 88,* 177-188. https://doi.org/10.1016/j.mcn.2018.02.001

Dubin, M. J., Mao, X., Banerjee, S., Goodman, Z., Lapidus, K. A., Kang, G., Shungu, D. C. et al. (2016). Elevated Prefrontal Cortex GABA in Patients with Major Depressive Disorder after TMS Treatment Measured with Proton Magnetic Resonance Spectroscopy. *Journal of Psychiatry & Neuroscience, 41,* E37-E45. https://doi.org/10.1503/jpn.150223

Ebmeier, K. P., Donaghey, C., & Steele, J. D. (2006). Recent Developments and Current Controversies in Depression. *The Lancet, 367,* 153-167. https://doi.org/10.1016/S0140-6736(06)67964-6

Engin, E., & Treit, D. (2009). Anxiolytic and Antidepressant Actions of Somatostatin: The Role of sst2 and sst3 Receptors. *Psychopharmacology (Berl), 206,* 281-289. https://doi.org/10.1007/s00213-009-1605-5

Engin, E., Stellbrink, J., Treit, D., & Dickson, C. T. (2008). Anxiolytic and Antidepressant Effects of Intracerebroventricularly Administered Somatostatin: Behavioral and Neurophysiological Evidence. *Neuroscience, 157,* 666-676. https://doi.org/10.1016/j.neuroscience.2008.09.037

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Heo, S., McLaren, M., Kramer, A. F. et al. (2010). Brain-Derived Neurotrophic Factor Is Associated with Age-Related Decline in Hippocampal Volume. *Journal of Neuroscience, 30,* 5368-5375. https://doi.org/10.1523/JNEUROSCI.6251-09.2010

Erraji-Benchekroun, L., Underwood, M. D., Arango, V., Galfalvy, H., Pavlidis, P., Smyrniotopoulos, P., Sibille, E. et al. (2005). Molecular Aging in Human Prefrontal Cortex Is Selective and Continuous throughout Adult Life. *Biological Psychiatry, 57,* 549-558. https://doi.org/10.1016/j.biopsych.2004.10.034

Faron-Gorecka, A., Kusmider, M., Kolasa, M., Zurawek, D., Szafran-Pilch, K., Gruca, P., Dziedzicka-Wasylewska, M. et al. (2016). Chronic Mild Stress Alters the Somatostatin Receptors in the Rat Brain. *Psychopharmacology (Berl), 233,* 255-266. https://doi.org/10.1007/s00213-015-4103-y

Faron-Gorecka, A., Kusmider, M., Solich, J., Kolasa, M., Pabian, P., Gruca, P., Dziedzicka-Wasylewska, M. et al. (2018). Regulation of Somatostatin Receptor 2 in the Context of Antidepressant Treatment Response in Chronic Mild Stress in Rat. *Psychopharmacology (Berl), 235,* 2137-2149. https://doi.org/10.1007/s00213-018-4912-x

Fino, E., Packer, A. M., & Yuste, R. (2013). The Logic of Inhibitory Connectivity in the Neocortex. *Neuroscientist, 19,* 228-237. https://doi.org/10.1177/1073858412456743

Fisher, D. A., & Brown, M. R. (1980). Somatostatin Analog: Plasma Catecholamine Suppression Mediated by the Central Nervous System. *Endocrinology, 107,* 714-718. https://doi.org/10.1210/endo-107-3-714

French, L., Ma, T., Oh, H., Tseng, G. C., & Sibille, E. (2017). Age-Related Gene Expression in the Frontal Cortex Suggests Synaptic Function Changes in Specific Inhibitory Neuron Subtypes. *Frontiers in Aging Neuroscience, 9,* 162. https://doi.org/10.3389/fnagi.2017.00162

Fuchs, T., Jefferson, S. J., Hooper, A., Yee, P. H., Maguire, J., & Luscher, B. (2017). Disinhibition of Somatostatin-Positive GABAergic Interneurons Results in an Anxiolytic and Antidepressant-Like Brain State. *Molecular Psychiatry, 22,* 920-930. https://doi.org/10.1038/mp.2016.188

Gabbay, V., Mao, X., Klein, R. G., Ely, B. A., Babb, J. S., Panzer, A. M., Shungu, D. C. et al. (2012). Anterior Cingulate Cortex Gamma-Aminobutyric Acid in Depressed Adolescents: Relationship to Anhedonia. *Archives of General Psychiatry, 69,* 139-149. https://doi.org/10.1001/archgenpsychiatry.2011.131

Gentet, L. J., Kremer, Y., Taniguchi, H., Huang, Z. J., Staiger, J. F., & Petersen, C. C. (2012). Unique Functional Properties of Somatostatin-Expressing GABAergic Neurons in Mouse Barrel Cortex. *Nature Neuroscience, 15,* 607-612. https://doi.org/10.1038/nn.3051

Glorioso, C., Oh, S., Douillard, G. G., & Sibille, E. (2011). Brain Molecular Aging, Promotion of Neurological Disease and Modulation by Sirtuin 5 Longevity Gene Polymorphism. *Neurobiology of Disease, 41,* 279-290. https://doi.org/10.1016/j.nbd.2010.09.016

Glorioso, C., Sabatini, M., Unger, T., Hashimoto, T., Monteggia, L. M., Lewis, D. A., & Mirnics, K. (2006). Specificity and Timing of Neocortical Transcriptome Changes in Response to BDNF Gene Ablation during Embryogenesis or Adulthood. *Molecular Psychiatry, 11,* 633-648. https://doi.org/10.1038/sj.mp.4001835

Gonchar, Y., & Burkhalter, A. (1997). Three Distinct Families of GABAergic Neurons in Rat Visual Cortex. *Cerebral Cortex, 7,* 347-358. https://doi.org/10.1093/cercor/7.4.347

Goshen, I., Kreisel, T., Ben-Menachem-Zidon, O., Licht, T., Weidenfeld, J., Ben-Hur, T., & Yirmiya, R. (2008). Brain Interleukin-1 Mediates Chronic Stress-Induced Depression in Mice via Adrenocortical Activation and Hippocampal Neurogenesis Suppression. *Molecular Psychiatry, 13,* 717-728. https://doi.org/10.1038/sj.mp.4002055

Guilloux, J. P., Douillard-Guilloux, G., Kota, R., Wang, X., Gardier, A. M., Martinowich, K., Sibille, E. et al. (2012). Molecular Evidence for BDNF- and GABA-Related Dysfunctions in the Amygdala of Female Subjects with Major Depression. *Molecular Psychiatry, 17,* 1130-1142. https://doi.org/10.1038/mp.2011.113

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry, 75,* 336-346. https://doi.org/10.1001/jamapsychiatry.2017.4602

Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic System Mechanisms of Stress Regulation: Hypothalamo-Pituitary-Adrenocortical Axis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 29,* 1201-1213. https://doi.org/10.1016/j.pnpbp.2005.08.006

Hirschfeld, R. M. (2000). History and Evolution of the Monoamine Hypothesis of Depression. *The Journal of Clinical Psychiatry, 61,* 4-6.

Hu, W., Zhang, M., Czeh, B., Flugge, G., & Zhang, W. (2010). Stress Impairs GABAergic Network Function in the Hippocampus by Activating Nongenomic Glucocorticoid Receptors and Affecting the Integrity of the Parvalbumin-Expressing Neuronal Network. *Neuropsychopharmacology, 35,* 1693-1707. https://doi.org/10.1038/npp.2010.31

Jaglin, X. H., Hjerling-Leffler, J., Fishell, G., & Batista-Brito, R. (2012). The Origin of Neocortical Nitric Oxide Synthase-Expressing Inhibitory Neurons. *Frontiers in Neural Circuits, 6,* 44. https://doi.org/10.3389/fncir.2012.00044

Karolewicz, B., Maciag, D., O'Dwyer, G., Stockmeier, C. A., Feyissa, A. M., & Rajkowska, G. (2010). Reduced Level of Glutamic Acid Decarboxylase-67 kDa in the Prefrontal Cortex in Major Depression. *International Journal of Neuropsychopharmacology, 13,* 411-420. https://doi.org/10.1017/S1461145709990587

Keller, J., Gomez, R., Williams, G., Lembke, A., Lazzeroni, L., Murphy, G. M., & Schatzberg, A. F. (2017). HPA Axis in Major Depression: Cortisol, Clinical Symptomatology and Genetic Variation Predict Cognition. *Molecular Psychiatry, 22,* 527-536. https://doi.org/10.1038/mp.2016.120

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., National Comorbidity Survey, R. et al. (2003). The Epidemiology of Major Depressive Disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA, 289,* 3095-3105. https://doi.org/10.1001/jama.289.23.3095

Klumpers, U. M., Veltman, D. J., Drent, M. L., Boellaard, R., Comans, E. F., Meynen, G., Hoogendijk, W. J. et al. (2010). Reduced Parahippocampal and Lateral Temporal GABAA-[11C]flumazenil Binding in Major Depression: Preliminary Results. *European Journal of Nuclear Medicine and Molecular Imaging, 37,* 565-574. https://doi.org/10.1007/s00259-009-1292-9

Lewis, D. A., & Sweet, R. A. (2009). Schizophrenia from a Neural Circuitry Perspective: Advancing toward Rational Pharmacological Therapies. *The Journal of Clinical Investigation, 119,* 706-716. https://doi.org/10.1172/JCI37335

Li, W., Papilloud, A., Lozano-Montes, L., Zhao, N., Ye, X., Zhang, X., Rainer, G. et al. (2018). Stress Impacts the Regulation Neuropeptides in the Rat Hippocampus and Prefrontal Cortex. *Proteomics, 18,* e1700408. https://doi.org/10.1002/pmic.201700408

Lin, L. C., & Sibille, E. (2013). Reduced Brain Somatostatin in Mood Disorders: A Common Pathophysiological Substrate and Drug Target? *Frontiers in Pharmacology, 4,* 110. https://doi.org/10.3389/fphar.2013.00110

Lin, L. C., & Sibille, E. (2015). Somatostatin, Neuronal Vulnerability and Behavioral Emotionality. *Molecular Psychiatry, 20,* 377-387. https://doi.org/10.1038/mp.2014.184

Ma, Y., Hu, H., Berrebi, A. S., Mathers, P. H., & Agmon, A. (2006). Distinct Subtypes of Somatostatin-Containing Neocortical Interneurons Revealed in Transgenic Mice. *Journal of Neuroscience, 26,* 5069-5082. https://doi.org/10.1523/JNEUROSCI.0661-06.2006

Machado-Vieira, R., Salvadore, G., DiazGranados, N., & Zarate, C. A. (2009). Ketamine and the Next Generation of Antidepressants with a Rapid Onset of Action. *Pharmacology & Therapeutics, 123,* 143-150. https://doi.org/10.1016/j.pharmthera.2009.02.010

Marathe, S. V., D'Almeida P, L., Virmani, G., Bathini, P., & Alberi, L. (2018). Effects of Monoamines and Antidepressants on Astrocyte Physiology: Implications for Monoamine Hypothesis of Depression. *Journal of Experimental Neuroscience, 12,* 1179069518789149. https://doi.org/10.1177/1179069518789149

Martinowich, K., Schloesser, R. J., Jimenez, D. V., Weinberger, D. R., & Lu, B. (2011). Activity-Dependent Brain-Derived Neurotrophic Factor Expression Regulates Cortistatin-Interneurons and Sleep Behavior. *Molecular Brain, 4,* 11. https://doi.org/10.1186/1756-6606-4-11

Mayberg, H. S. (2002). Modulating Limbic-Cortical Circuits in Depression: Targets of Antidepressant Treatments. *Seminars in Clinical Neuropsychiatry, 7,* 255-268. https://doi.org/10.1053/scnp.2002.35223

McEwen, B. S., Nasca, C., & Gray, J. D. (2016). Stress Effects on Neuronal Structure: Hippocampus, Amygdala, and Prefrontal Cortex. *Neuropsychopharmacology, 41,* 3-23. https://doi.org/10.1038/npp.2015.171

Millan, M. J. (2006). Multi-Target Strategies for the Improved Treatment of Depressive States: Conceptual Foundations and Neuronal Substrates, Drug Discovery and Therapeutic Application. *Pharmacology & Therapeutics, 110,* 135-370. https://doi.org/10.1016/j.pharmthera.2005.11.006

Molchan, S. E., Lawlor, B. A., Hill, J. L., Martinez, R. A., Davis, C. L., Mellow, A. M., Sunderland, T. et al. (1991). CSF Monoamine Metabolites and Somatostatin in Alzheimer's Disease and Major Depression. *Biological Psychiatry, 29,* 1110-1118. https://doi.org/10.1016/0006-3223(91)90253-I

Murayama, M., Perez-Garci, E., Nevian, T., Bock, T., Senn, W., & Larkum, M. E. (2009). Dendritic Encoding of Sensory Stimuli Controlled by Deep Cortical Interneurons. *Nature, 457,* 1137-1141. https://doi.org/10.1038/nature07663

Nilsson, A., Stroth, N., Zhang, X., Qi, H., Falth, M., Skold, K., Svenningsson, P. et al. (2012). Neuropeptidomics of Mouse Hypothalamus after Imipramine Treatment Reveal Somatostatin as a Potential Mediator of Antidepressant Effects. *Neuropharmacology, 62,* 347-357. https://doi.org/10.1016/j.neuropharm.2011.08.004

Pallis, E., Vasilaki, A., Fehlmann, D., Kastellakis, A., Hoyer, D., Spyraki, C., & Thermos, K. (2009). Antidepressants Influence Somatostatin Levels and Receptor Pharmacology in Brain. *Neuropsychopharmacology, 34,* 952-963. https://doi.org/10.1038/npp.2008.133

Pariante, C. M., & Lightman, S. L. (2008). The HPA Axis in Major Depression: Classical Theories and New Developments. *Trends in Neurosciences, 31,* 464-468. https://doi.org/10.1016/j.tins.2008.06.006

Ponomarev, I., Rau, V., Eger, E. I., Harris, R. A., & Fanselow, M. S. (2010). Amygdala Transcriptome and Cellular Mechanisms Underlying Stress-Enhanced Fear Learning in a Rat Model of Posttraumatic Stress Disorder. *Neuropsychopharmacology, 35,* 1402-1411. https://doi.org/10.1038/npp.2010.10

Post, R. M., Rubinow, D. R., Kling, M. A., Berrettini, W., & Gold, P. W. (1988). Neuroactive Substances in Cerebrospinal Fluid. Normal and Pathological Regulatory Mechanisms. *Annals of the New York Academy of Sciences, 531,* 15-28. https://doi.org/10.1111/j.1749-6632.1988.tb31808.x

Prevot, T. D., Gastambide, F., Viollet, C., Henkous, N., Martel, G., Epelbaum, J., Guillou, J. L. et al. (2017). Roles of Hippocampal Somatostatin Receptor Subtypes in Stress Response and Emotionality. *Neuropsychopharmacology, 42,* 1647-1656. https://doi.org/10.1038/npp.2016.281

Prevot, T. D., Viollet, C., Epelbaum, J., Dominguez, G., Beracochea, D., & Guillou, J. L. (2018). sst2-Receptor Gene Deletion Exacerbates Chronic Stress-Induced Deficits: Consequences for Emotional and Cognitive Ageing. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 86,* 390-400. https://doi.org/10.1016/j.pnpbp.2018.01.022

Rajkowska, G., Halaris, A., & Selemon, L. D. (2001). Reductions in Neuronal and Glial Density Characterize the Dorsolateral Prefrontal Cortex in Bipolar Disorder. *Biological Psychiatry, 49,* 741-752. https://doi.org/10.1016/S0006-3223(01)01080-0

Ren, Z., Pribiag, H., Jefferson, S. J., Shorey, M., Fuchs, T., Stellwagen, D., & Luscher, B. (2016). Bidirectional Homeostatic Regulation of a Depression-Related Brain State by Gamma-Aminobutyric Acidergic Deficits and Ketamine Treatment. *Biological Psychiatry, 80,* 457-468. https://doi.org/10.1016/j.biopsych.2016.02.009

Rozycka, A., & Liguz-Lecznar, M. (2017). The Space Where Aging Acts: Focus on the GABAergic Synapse. *Aging Cell, 16,* 634-643. https://doi.org/10.1111/acel.12605

Rudy, B., Fishell, G., Lee, S., & Hjerling-Leffler, J. (2011). Three Groups of Interneurons Account for Nearly 100% of Neocortical GABAergic Neurons. *Developmental Neurobiology, 71,* 45-61. https://doi.org/10.1002/dneu.20853

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Fava, M. et al. (2006). Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *American Journal of Psychiatry, 163,* 1905-1917. https://doi.org/10.1176/ajp.2006.163.11.1905

Sanacora, G., Fenton, L. R., Fasula, M. K., Rothman, D. L., Levin, Y., Krystal, J. H., & Mason, G. F. (2006). Cortical Gamma-Aminobutyric Acid Concentrations in Depressed Patients Receiving Cognitive Behavioral Therapy. *Biological Psychiatry, 59,* 284-286. https://doi.org/10.1016/j.biopsych.2005.07.015

Sanacora, G., Mason, G. F., Rothman, D. L., Hyder, F., Ciarcia, J. J., Ostroff, R. B., Krystal, J. H. et al. (2003). Increased Cortical GABA Concentrations in Depressed Patients Receiving ECT. *American Journal of Psychiatry, 160,* 577-579. https://doi.org/10.1176/appi.ajp.160.3.577

Scheich, B., Cseko, K., Borbely, E., Abraham, I., Csernus, V., Gaszner, B., & Helyes, Z. (2017). Higher Susceptibility of Somatostatin 4 Receptor Gene-Deleted Mice to Chronic Stress-Induced Behavioral and Neuroendocrine Alterations. *Neuroscience, 346,* 320-336. https://doi.org/10.1016/j.neuroscience.2017.01.039

Scheich, B., Gaszner, B., Kormos, V., Laszlo, K., Adori, C., Borbely, E., Helyes, Z. et al. (2016). Somatostatin Receptor Subtype 4 Activation Is Involved in Anxiety and Depression-Like Behavior in Mouse Models. *Neuropharmacology, 101,* 204-215. https://doi.org/10.1016/j.neuropharm.2015.09.021

Seney, M. L., Chang, L. C., Oh, H., Wang, X., Tseng, G. C., Lewis, D. A., & Sibille, E. (2013). The Role of Genetic Sex in Affect Regulation and Expression of GABA-Related Genes across Species. *Frontiers in Psychiatry, 4,* 104. https://doi.org/10.3389/fpsyt.2013.00104

Seney, M. L., Tripp, A., McCune, S., Lewis, D. A., & Sibille, E. (2015). Laminar and Cellular Analyses of Reduced Somatostatin Gene Expression in the Subgenual Anterior Cingulate Cortex in Major Depression. *Neurobiology of Disease, 73,* 213-219. https://doi.org/10.1016/j.nbd.2014.10.005

Sheline, Y. I. (1996). Hippocampal Atrophy in Major Depression: A Result of Depression-Induced Neurotoxicity? *Molecular Psychiatry, 1,* 298-299.

Shen, Q., Lal, R., Luellen, B. A., Earnheart, J. C., Andrews, A. M., & Luscher, B. (2010). Gamma-Aminobutyric Acid-Type A Receptor Deficits Cause Hypothalamic-Pituitary-Adrenal Axis Hyperactivity and Antidepressant Drug Sensitivity Reminiscent of Melancholic Forms of Depression. *Biological Psychiatry, 68,* 512-520. https://doi.org/10.1016/j.biopsych.2010.04.024

Shirayama, Y., Chen, A. C., Nakagawa, S., Russell, D. S., & Duman, R. S. (2002). Brain-Derived Neurotrophic Factor Produces Antidepressant Effects in Behavioral Models of Depression. *Journal of Neuroscience, 22,* 3251-3261. https://doi.org/10.1523/JNEUROSCI.22-08-03251.2002

Sibille, E., Morris, H. M., Kota, R. S., & Lewis, D. A. (2011). GABA-Related Transcripts in the Dorsolateral Prefrontal Cortex in Mood Disorders. *International Journal of Neuropsychopharmacology, 14,* 721-734. https://doi.org/10.1017/S1461145710001616

Sibille, E., Wang, Y., Joeyen-Waldorf, J., Gaiteri, C., Surget, A., Oh, S., Lewis, D. A. et al. (2009). A Molecular Signature of Depression in the Amygdala. *American Journal of Psychiatry, 166,* 1011-1024. https://doi.org/10.1176/appi.ajp.2009.08121760

Song, C., & Wang, H. (2011). Cytokines Mediated Inflammation and Decreased Neurogenesis in Animal Models of Depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 35,* 760-768. https://doi.org/10.1016/j.pnpbp.2010.06.020

Soumier, A., & Sibille, E. (2014). Opposing Effects of Acute versus Chronic Blockade of Frontal Cortex Somatostatin-Positive Inhibitory Neurons on Behavioral Emotionality in Mice. *Neuropsychopharmacology, 39,* 2252-2262. https://doi.org/10.1038/npp.2014.76

Szafran-Pilch, K., Faron-Gorecka, A., Kolasa, M., Zurawek, D., Szlachta, M., Solich, J., Dziedzicka-Wasylewska, M. et al. (2017). Antidepressants Promote Formation of Heterocomplexes of Dopamine D2 and Somatostatin Subtype 5 Receptors in the Mouse Striatum. *Brain Research Bulletin, 135,* 92-97. https://doi.org/10.1016/j.brainresbull.2017.10.003

Thompson Ray, M., Weickert, C. S., Wyatt, E., & Webster, M. J. (2011). Decreased BDNF, trkB-TK+ and GAD67 mRNA Expression in the Hippocampus of Individuals with Schizophrenia and Mood Disorders. *Journal of Psychiatry & Neuroscience, 36,* 195-203. https://doi.org/10.1503/jpn.100048

Thompson, S. M., Kallarackal, A. J., Kvarta, M. D., Van Dyke, A. M., LeGates, T. A., & Cai, X. (2015). An Excitatory Synapse Hypothesis of Depression. *Trends in Neurosciences, 38,* 279-294. https://doi.org/10.1016/j.tins.2015.03.003

Tripp, A., Kota, R. S., Lewis, D. A., & Sibille, E. (2011). Reduced Somatostatin in Subgenual Anterior Cingulate Cortex in Major Depression. *Neurobiology of Disease, 42,* 116-124. https://doi.org/10.1016/j.nbd.2011.01.014

Tripp, A., Oh, H., Guilloux, J. P., Martinowich, K., Lewis, D. A., & Sibille, E. (2012). Brain-Derived Neurotrophic Factor Signaling and Subgenual Anterior Cingulate Cortex Dysfunction in Major Depressive Disorder. *American Journal of Psychiatry, 169,* 1194-1202. https://doi.org/10.1176/appi.ajp.2012.12020248

Valentine, G. W., & Sanacora, G. (2009). Targeting Glial Physiology and Glutamate Cycling in the Treatment of Depression. *Biochemical Pharmacology, 78,* 431-439. https://doi.org/10.1016/j.bcp.2009.04.008

Vincent, M. Y., Hussain, R. J., Zampi, M. E., Sheeran, K., Solomon, M. B., Herman, J. P., Jacobson, L. et al. (2013). Sensitivity of Depression-Like Behavior to Glucocorticoids and Antidepressants Is Independent of Forebrain Glucocorticoid Receptors. *Brain Research, 1525,* 1-15. https://doi.org/10.1016/j.brainres.2013.05.031

Viollet, C., Lepousez, G., Loudes, C., Videau, C., Simon, A., & Epelbaum, J. (2008). Somatostatinergic Systems in Brain: Networks and Functions. *Molecular and Cellular Endocrinology, 286,* 75-87. https://doi.org/10.1016/j.mce.2007.09.007

Viollet, C., Vaillend, C., Videau, C., Bluet-Pajot, M. T., Ungerer, A., L'Heritier, A., Epelbaum, J. et al. (2000). Involvement of sst2 Somatostatin Receptor in Locomotor, Exploratory Activity and Emotional Reactivity in Mice. *European Journal of Neuroscience, 12,* 3761-3770. https://doi.org/10.1046/j.1460-9568.2000.00249.x

Wang, J., Jing, L., Toledo-Salas, J. C., & Xu, L. (2015). Rapid-Onset Antidepressant Efficacy of Glutamatergic System Modulators: The Neural Plasticity Hypothesis of Depression. *Neuroscience Bulletin, 31,* 75-86. https://doi.org/10.1007/s12264-014-1484-6

Weckbecker, G., Lewis, I., Albert, R., Schmid, H. A., Hoyer, D., & Bruns, C. (2003). Opportunities in Somatostatin Research: Biological, Chemical and Therapeutic Aspects. *Nature Reviews Drug Discovery, 2,* 999-1017. https://doi.org/10.1038/nrd1255

Wohleb, E. S., Wu, M., Gerhard, D. M., Taylor, S. R., Picciotto, M. R., Alreja, M., & Duman, R. S. (2016). GABA Interneurons Mediate the Rapid Antidepressant-Like Effects of Scopolamine. *The Journal of Clinical Investigation, 126,* 2482-2494. https://doi.org/10.1172/JCI85033

Xu, H., Jeong, H. Y., Tremblay, R., & Rudy, B. (2013). Neocortical Somatostatin-Expressing GABAergic Interneurons Disinhibit the Thalamorecipient Layer 4. *Neuron, 77,* 155-167. https://doi.org/10.1016/j.neuron.2012.11.004

Yeung, M., & Treit, D. (2012). The Anxiolytic Effects of Somatostatin Following Intra-Septal and Intra-Amygdalar Microinfusions Are Reversed by the Selective sst2 Antagonist PRL2903. *Pharmacology Biochemistry and Behavior, 101,* 88-92. https://doi.org/10.1016/j.pbb.2011.12.012

Yeung, M., Engin, E., & Treit, D. (2011). Anxiolytic-Like Effects of Somatostatin Isoforms SST 14 and SST 28 in Two Animal Models (*Rattus norvegicus*) after Intra-Amygdalar and Intra-Septal Microinfusions. *Psychopharmacology (Berl), 216,* 557-567. https://doi.org/10.1007/s00213-011-2248-x

Zarate, C. A., Brutsche, N. E., Ibrahim, L., Franco-Chaves, J., Diazgranados, N., Cravchik, A., Luckenbaugh, D. A. et al. (2012). Replication of Ketamine's Antidepressant Efficacy in Bipolar Depression: A Randomized Controlled Add-On Trial. *Biological Psychiatry, 71,* 939-946. https://doi.org/10.1016/j.biopsych.2011.12.010