Bioprocess 生物过程, 2022, 12(1), 1-9
Published Online March 2022 in Hans. http://www.hanspub.org/journal/bp
https://doi.org/10.12677/bp.2022.121001

Hans汉斯

5-羟色胺在脂质代谢中的研究进展

吴钰婷，孙　诚*

南通大学，教育部/江苏省神经再生重点实验室/神经再生协同创新中心，国家药品监督管理局组织工程技术产品研究与评价重点实验室，江苏　南通

收稿日期：2022年2月15日；录用日期：2022年3月12日；发布日期：2022年3月22日

摘　要

血清素，又称5-羟色胺(5-hydroxytryptamine, 5-HT)，是一种高度保守的生物胺，主要在胃肠道和中枢神经系统中高表达，可以结合7种不同受体家族的受体，参与机体众多的生理及病理过程。研究表明，血清素是能量摄入与消耗的主要调节剂，外周血清素通过上调脂质合成促进能量有效储存，进而诱发胰岛素抵抗、血脂异常、肝脂肪变性、凝血病和高血压等肥胖症的不利代谢后果，而中枢血清素可抑制食欲并通过驱动交感神经增加棕色脂肪组织的能量消耗。因此，5-HT在肥胖疾病中的作用备受关注。本文结合最新的研究进展对5-HT在脂质代谢中的作用进行简要归纳。

关键词

血清素，脂质代谢，肥胖，能量稳态

Research Progresses for 5-Hydroxytryptamine in Lipid Metabolism

Yuting Wu, Cheng Sun*

NMPA Key Laboratory for Research and Evaluation of Tissue Engineering Technology Products, Key Laboratory of Neuroregeneration of Jiangsu and Ministry of Education, Co-Innovation Center of Neuroregeneration, Nantong University, Nantong Jiangsu

Received: Feb. 15th, 2022; accepted: Mar. 12th, 2022; published: Mar. 22nd, 2022

Abstract

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a highly conserved biogenic amine that is highly expressed in the gastrointestinal tract and central nervous system. It participates in nu-

*通讯作者。

文章引用: 吴钰婷, 孙诚. 5-羟色胺在脂质代谢中的研究进[J]. 生物过程, 2022, 12(1): 1-9.
DOI: 10.12677/bp.2022.121001

merous physiological and pathological processes by binding to seven different receptor families. Serotonin has been shown it is the main regulator of energy intake and consumption. Peripheral serotonin promotes effective energy storage by up-regulating lipid synthesis, inducing adverse metabolic consequences, such as obesity, insulin resistance, dyslipidemia, hepatic steatosis, coagulopathy and hypertension. Central serotonin suppresses appetite and increases energy expenditure by increasing sympathetic drive to brown adipose tissue. Therefore, the role of 5-HT in obesity has attracted much attention. In this review, we highlight the most recent advances for the roles of 5-HT in lipid metabolism.

Keywords

Serotonin, Lipid Metabolism, Obesity, Energy Balance

1. 引言

血清素，又称 5-羟色胺(5-hydroxytryptamine, 5-HT)，是一种高度保守的生物胺，因其在血清中的存在及其血管活性而得名[1]。它不仅是一种神经递质，还可以存在于非神经元组织中，作为一种激素通过其限速酶即色氨酸羟化酶 1 (tryptophan hydroxylase 1, Tph1)和色氨酸羟化酶 2 (tryptophan hydroxylase 2, Tph2)进行特异性调节[2] [3] [4]。缺乏 Tph1 的小鼠的外周血清素不能被中枢神经系统中 Tph2 合成的血清素补偿[4] [5] [6]。因此，血清素被认为不能通过血脑屏障[7]。在哺乳动物中，5-羟色胺是由色氨酸通过两次酶促反应合成。首先，色氨酸经过色氨酸羟化酶的催化作用生成 5-羟色氨酸[8]，再经氨基酸脱羧酶的催化作用生成 5-羟色胺。

5-羟色胺主要是通过与细胞表面 5-羟色胺受体(5-hydroxytryptamine receptor, 5-HTR)结合而发挥其生物学效应[9]。这些受体根据其结构、功能和信号转导可分为 7 个家族，分别是 HTR1、HTR2、HTR3、HTR4、HTR5、HTR6、HTR7 [9]。其中除了 HTR3 是一种配体门控离子通道外，其他 6 个家族都是 G 蛋白偶联受体[10]。由于受体具有独特的组织特异性，可以分为 4 个不同的下游信号通路。HTR1 和 HTR5 与 Gi/Go 蛋白偶联，通过抑制腺苷酸环化酶，从而降低 cAMP 水平[10]；而 HTR4、HTR6 和 HTR7 与 Gs 蛋白偶联进而增加 cAMP 的水平[11] [12] [13]；HTR2 与 Gq/G11 蛋白偶联诱导磷脂酶 C，使肌醇三磷酸、Ca^{2+}和甘油二酯表达上调，从而激活蛋白激酶 C [14]；HTR3 可通过增加细胞内阳离子的浓度使细胞去极化[15] [16]。

根据分布的不同，脂肪组织分为皮下(局部皮下)和内脏(分布于腹腔)脂肪组织。在啮齿类动物模型中，腹股沟脂肪组织(腹股沟周围)和附睾(或性腺)脂肪组织分别是皮下和内脏脂肪组织的主要类型。在本篇综述中，依然将皮下和内脏的脂肪组织代指脂肪组织的广泛类别。脂肪组织在生理或病理上也几乎与机体中每一个非神经器官相关，包括皮肤、肝脏、骨髓、骨骼肌、血管系统、肠道、肾上腺等。

过氧化物酶体增殖物激活受体 PPARγ 是一种配体依赖性转录因子，可协调与葡萄糖稳态和胰岛素敏感性相关基因的表达[17] [18] [19]。小鼠巨噬细胞特异性缺失 PPARγ 可导致饮食诱导的肥胖和胰岛素抵抗，表明该受体在调节葡萄糖和脂质稳态以及组织炎症方面具有重要的作用[20]。因此，PPARγ 是代谢综合征和炎症性疾病的治疗靶点[21]。5-HT 代谢物中存在吲哚醋酸盐，这一结构还存在于能直接激活

PPARγ 的化合物吲哚美辛中[22]。有研究表明，脂肪酸代谢物通过 Ω 环的构象变化激活 PPARγ；5-HT 代谢物作为 PPARγ 的内源性激动剂，同样也是通过直接结合螺旋 H12 来调节巨噬细胞的功能和脂肪生成，并且抑制 5-HT 代谢物后，内源性 PPARγ 的表达下降[23]。因此，阐明 5-羟色胺在脂质合成中的作用是当前的重要方向，也是本文综述的重点内容。

2. 5-HT 与白色脂肪组织脂质代谢

在营养过剩的情况下，剩余热量超过能量消耗时，多余的热量便以甘油三酯(triglycerides, TGs)的形式储存于白色脂肪组织(white adipose tissue, WAT)中。WAT 是能量稳态的关键调节器，它能够合成和储存 TGs 以满足长期的能量需求，在机体能量匮乏时从 TGs 中释放游离脂肪酸(FFA)。WAT 也是一个内分泌器官，分泌调节全身代谢的脂肪因子，如瘦素[24]和脂联素[25]，以调节全身的代谢[26] [27]。

3T3-L1 是一种成纤维细胞，具有前体脂肪细胞的相关特性，被广泛应用于脂肪细胞分化方面的研究[28] [29]。体外研究发现，HTR2A 在由 3T3-L1 分化的脂肪细胞中表达上调，导致脂联素表达降低，纤溶酶原激活物抑制剂(PAI-1)表达增加[30] [31]。脂联素具有胰岛素增敏作用，肥胖会降低脂联素敏感性，从而导致胰岛素抵抗，进而加剧高胰岛素血症[32]。使用小干扰 RNA(siRNA)抑制 HTR2A 基因可抑制由 sarpogrelate (HTR2A 拮抗剂)导致的脂联素表达增强作用[33]。这些发现证明，HTR2A 信号级联负性调节脂联素的表达，进而促进脂肪生成[33]。逆转录病毒介导 3T3-L1 随机突变，从中筛选出在添加脂肪诱导剂后无法分化的突变的 3T3-L1，发现 Tph1 是 3T3-L1 脂肪分化所必需的；再通过 Cre-loxp 切除病毒介导插入的序列，恢复 Tph1 基因表达后反向证明了 3T3-L1 脂肪分化需要 Tph1 [34]。并且，在此研究中，作者还发现 5-HT 促进了 3T3-L1 和小鼠血管基质部分中的前脂肪细胞的分化，而 Tph1 抑制剂、5-HTR 拮抗剂或者 Tph1 基因缺失，均可导致 5-HT 信号途径中断，进而降低 3T3-L1 向脂肪细胞分化的能力[34]。

众所周知，PI3K-Akt 信号通路是参与脂肪细胞分化的重要途径[35]。Yun 等研究发现，当用 HTR2A siRNA 转染前体脂肪细胞后，*HTR2A* 基因表达沉默，磷酸化 Akt (Ser473)水平降低，AKT 信号通路受到抑制[36]。由于磷酸化 Akt (Ser473)信号通路在脂肪细胞增殖、生长和分化中具有重要作用，一些研究已证明 Akt 通路的激活可调节脂肪生成中 PPARγ 和 C/EBPα 的表达，进而促进或抑制脂肪细胞的分化[37] [38]。因此，在 *HTR2A* 基因沉默或过度表达后，Akt 信号通路的调节可能会影响脂肪生成，这表明 HTR2A 是脂肪生成的调控因子；并且，HTR2A 极有可能通过 Akt 磷酸化，作为一种潜在的调节方式来调节脂肪生成。

蛋白酶的功能失活减少了哺乳动物脂肪细胞分化过程中的脂肪积累[39]。Sohle 等人研究发现，在秀丽隐杆线虫和小鼠模型中，敲除肠道和皮下组织中的蛋白酶 L 基因(*CPL-1*)可促进神经元中的 5-HT 的合成，并通过中枢 5-HT 信号通路诱导体内脂肪分解[40]。并且腹腔注射组织蛋白酶 L 抑制剂 CLIK195 同样可以抑制体重增加和 WAT 脂肪生成，同时提高大脑血清素的水平，增强了 WAT 脂肪分解和脂肪酸氧化[41]。这些结果都证明了外周 CPL-1 的功能失活可通过激活中枢 5-HT 信号减少脂肪储存。

3. 5-HT 与棕色脂肪组织脂质代谢

在过去的几年里，棕色脂肪组织(BAT)的生物学特性和发育起源以及 WAT 和 BAT 之间的差异已经得到了清晰而深入的剖析[42] [43] [44]。BAT 因适应性产热而成为肥胖研究领域的热点，即调节产热的过程中，部分由能量底物的分解代谢介导，而不释放三磷酸腺苷分解产生的化学能，这一过程由解偶联蛋白 1 (UCP1)主导。UCP1 是一种跨膜蛋白，大量表达于棕色脂肪细胞线粒体的线粒体内膜中。UCP1 通过脂质和碳水化合物的分解代谢途径解偶联三磷酸腺苷产生，参与适应性产热[44]。由于 BAT 丰富的血管化，棕色脂肪细胞释放出的能量以热量的形式在体内扩散。以棕色脂肪细胞介导的产热为治疗目标，增加能量消耗，可能是对抗肥胖和代谢疾病的可行方法[45] [46]。

中枢 5-HT 具有厌食作用，因为 5-HT 可通过激活受体 HTR1B 和 HTR2C 来调节下丘脑的摄食回路[47]。5-HT 还可以影响下丘脑中 BAT 的代谢，因为背内侧核(DMH)的神经元与中缝苍白球有突触联系，中缝苍白球通过 5-HT 能回路调节交感神经的激活。在小鼠中，当连接 DMH 和中缝苍白球的胆碱能毒蕈碱受体被拮抗时，该回路促进产热[48]。此外，小鼠体内 5-HT 能神经元的缺失会导致葡萄糖和脂质代谢改变，导致棕色和米色脂肪细胞的产热能力严重受损[49]。因此，中枢 5-HT 是控制食欲和能量平衡的基础。

如前所述，中枢 5-HT 是刺激产热和招募米色脂肪细胞的重要因素；因此，影响中枢 5-HT 能回路的药物可能会增加 5-HT 介导的对脂肪组织的调控作用[50]。选择性 5-HT 再摄取抑制剂通常被用作抗抑郁药物，但它们也可以应用于肥胖症治疗中。Sibutramine 是一种抑制中枢突触中 5-HT 和去甲肾上腺素(norepinephrine, NE)再摄取的药物；它可转化为两种活性代谢物，通过降低食欲和增加产热来达到减肥效果[51]。副作用包括严重的心血管后果，如心率和血压升高，以及非致命性心肌梗死或中风[52]。Fluoxetine 是另一种选择性 5-HT 再摄取抑制剂类药物。最近的一项研究表明，长期服用 fluoxetine 可以减少大鼠体重和 WAT 的质量，而不会影响动物的食物摄入量，其 BAT、UCP1 表达和线粒体代谢率也有所增加[53]。Fenfluramine 及其异构体 dexfenfluramine 是 5-HT 能药物，可通过增加 5-HT 的突触释放来抑制食欲[50]。

外周血清素对 BAT 的作用与中枢血清素具有相反效果。Crane 等人研究发现高脂喂养的野生型小鼠的 5-HT 含量升高，但 *TPH1* 敲除(*Tph1*$^{-/-}$)小鼠的 5-HT 含量没有升高[54]。与代谢活性增加和 5-HT 含量降低一致，高脂喂养的 *Tph1*$^{-/-}$小鼠的肩胛间棕色脂肪组织(iBAT)比野生型小鼠的 UCP1 表达更高。此外，5-HT 减弱异丙肾上腺素刺激的 cAMP 积累和 PKA 底物激素敏感脂肪酶的磷酸化；5-HT 前体(色氨酸、5-羟基色氨酸)或终产物(5HIAA、褪黑素)均未发现这种效应，说明血清素可直接作用于棕色脂肪细胞，抑制肾上腺素能诱导的 UCP1 表达[54]。

4. 5-HT 与米色脂肪脂质代谢

UCP1 在 BAT 中大量表达，且与产热过程呈正相关；因此，肥胖患者 BAT 的增加可能会改善能量消耗。增加脂肪组织中富含 UCP1 的功能性细胞的可能方法之一是将白色(前)脂肪细胞转化为棕色样脂肪细胞，称为 WAT 褐变[43]。在 WAT 中出现分散的棕色样脂肪细胞团，称为米色脂肪细胞(beige adipocytes)。这些细胞与棕色脂肪细胞有许多共同特征，如脂肪储备的多腔室聚集，富含线粒体，表达高水平的 UCP1，增加产热关键蛋白的转录因子的表达[44]。然而，米色脂肪细胞仍具有独特的基因表达谱，与白色和棕色脂肪细胞不同[45] [55] [56]。研究表明，在冷暴露或 β3-激动剂处理后，除现有的成熟脂肪细胞外，大多数米色脂肪细胞是由前体细胞群体从头分化诱导而成，而不是由成熟的白色脂肪细胞转分化诱导的[57]。

中枢神经系统中的 5-HT 能神经元对体温调节至关重要，因此可控制产热脂肪的代谢活动[58] [59]。McGlashon 等人的研究发现，小鼠中枢 5-HT 能神经元的缺失，可导致体温调节紊乱，BAT 脂肪变性，WAT 褐变受损，并伴随着棕色脂肪和米色脂肪产热所必需基因的表达降低[49]。Lorcaserin 是一种 5HT2C 受体激动剂，可减轻体重并改善血糖控制，已批准用于治疗肥胖。在小鼠中 5-HTR2C 受体基因缺失会导致肥胖[60]。中枢 5-HT 会促使白色脂肪细胞转化为活跃的米色脂肪细胞，以及从祖细胞中招募新的米色脂肪细胞[49]。Han 等人的研究发现，由一组下丘脑刺鼠相关蛋白(agouti-related protein, AgRP)神经元的亚群调节能量消耗[61] [62] [63]，证明该亚群向中缝背核背外侧(dlDRN)表达黑皮素 4 受体(MC4R)的神经元发出非侧向投射，而这些神经元又支配着附近的 5-HT 神经元，从而建立一个功能性神经回路，在不影响进食的情况下控制产热和能量消耗。揭示了中枢 AgRP^{ARC}→MC4R^{dlDRN}→5-HT^{dmDRN} 神经回路通过靶向外周 iBAT 和米色 scWAT 的线粒体机制双向控制产热和能量消耗，能有效逆转肥胖[64] [65] [66]。

外周血清素被证明是一种促肥胖因子[67]，可促进 WAT 中的脂质积累，并抑制 WAT 褐变和 BAT

产热[54]。在小鼠体内进行的一项研究表明，抑制色氨酸羟化酶 1 (负责外周 5-HT 合成的酶)，可通过激活 BAT 和招募米色脂肪细胞抑制体重增加[48]。Zhang 等人的研究显示，在高胆固醇饮食喂养的小鼠体内，肥大细胞(MC)失活可改善肥胖和胰岛素抵抗，并提高代谢率[68]。肾上腺素受体激动剂去甲肾上腺素刺激可增强 MC 功能性缺陷小鼠代谢率和皮下脂肪组织褐变；而在 MC 功能性缺陷小鼠的皮下脂肪组织中注射重组 MC 可阻断这些变化[69]。已有前人证明，表达血小板衍生生长因子受体 A(PDGFRα^{+})的细胞是脂肪细胞祖细胞，这类细胞能够分化为米色脂肪细胞[70]。进一步研究发现，使用 TPH1 抑制剂或 TPH1 缺陷的 MCs 增加了 UCP1 及米色脂肪细胞基因 Pdgfr*α* 表达，表明 MC 衍生的血清素可以抑制皮下脂肪组织褐变和机体能量消耗。进而证明皮下脂肪组织中 MC 的功能失活或 MC 中 5-HT 合成的抑制，可促进小鼠脂肪细胞褐变和全身能量代谢[68]。Yabut 和 Desjardins 等人也证明了具有分化米色脂肪细胞能力的白色脂肪组织因热中性条件[71]而导致肥大细胞的浸润[72] [73]，肥大细胞中表达可调节外周血清素合成的限速酶 Tph1。将 *Tph1*$^{-/-}$肥大细胞移植到肥大细胞缺陷小鼠中或选择性缺失 Tph1 肥大细胞可增强白色脂肪组织中 UCP1 的表达，并保护小鼠免受肥胖和胰岛素抵抗的影响[54] [74]，这些结果进一步证明外周 5-HT 是脂肪组织产热的重要抑制剂[75]。

5. 5-HT 与非酒精性脂肪肝脂质代谢

肝脏是循环葡萄糖和脂质的重要调节剂。在禁食期间，肝脏会增加糖原分解和糖异生以维持血浆中葡萄糖的水平。相反，肝脏在进食后储存大量的葡萄糖和脂肪酸，形成糖原和甘油三酯。非酒精性脂肪性肝病(NAFLD)是一种严重的疾病，涉及肝脏脂质过多积累[76] [77]。NAFLD 与肥胖和慢性肝病密切相关，被认为是肝损伤的主要原因[78] [79]。不少研究表明，外周 5-HT 可以调节肝脏脂质平衡[54] [80] [81] [82]。与对照组相比，用脂肪酸和 5-HT 处理的原代肝细胞会出现更多的甘油三酯[82]。此外，用 HTR3 的拮抗剂处理 ob/ob 小鼠可减少肝脏脂肪沉积[83]。上述结果表明外周 5-HT 具有促进肝内脂质积累的作用。

有研究证明，对氯苯丙氨酸和 LP533401 作为 Tph 的抑制剂，可以通过抑制脂质摄取，减少脂质在肝脏中积累[80]。随后研究发现，肠道来源的 5-HT 可以调节高脂饮食诱导的肝脂肪变性，其作用机制是通过肝细胞表达的 HTR2A 调节肝脏脂质代谢[81]。用 HTR2A 拮抗剂 sarpogrelate 处理小鼠，可以对 NAFLD 起到一定的保护作用，但与棕色/米色脂肪组织形态、UCP1 含量或是能量消耗(已知的肝脏脂质沉积的负调节因子)的变化无关[54] [74]。同样，一项最近的研究表明，Kim 等人设计合成的新型 HTR2A 拮抗剂，通过抑制 HTR2A 的功能发挥，降低肝脏重量，并减轻脂质积聚和肝脏脂肪变性[84]。Crane 等人的研究也发现，与野生型小鼠相比，高脂喂养的 *Tph1*$^{-/-}$小鼠的肝脏重量也较低，并表现出脂质积累减少，这表明抑制外周 5-HT 对 NAFLD 确实具有保护作用[54]。血清素转运蛋白(SERT)可调节 5-HT 的生物利用度，从而调节其生理效应。SERT 功能降低与啮齿类动物和人胃肠运动的改变有关[82]。另有研究表明，HTR3 受体依赖性途径可触发小肠 SERT 蛋白的减少或丢失，增加糖的摄入，进而增加 NAFLD 发生风险[85]。

6. 总结与展望

综上所述，5-HT 广泛参与了全身的能量稳态和脂质合成的过程。目前为止，作为治疗肥胖相关代谢性疾病研发的新方向，5-HT 受体特异性抑制剂已部分进入临床试验。然而，虽然靶向抑制 5-HT 在肥胖相关疾病中具有一定的保护作用，其药物对身体产生的副作用及安全性尚有争议。未来研究着重于应用组织特异性敲除 TPH1 或 HTR 小鼠，揭示 5-HT 综合调控网络，将有助于开发新型的药物，用于治疗脂质代谢紊乱相关的疾病如肥胖、2 型糖尿病和 NAFLD。

基金项目

本综述受到国家自然科学基金(No. 81970747)资助。

参考文献

[1] Rapport, M.M., Green, A.A. and Page, I.H. (1948) Serum Vasoconstrictor, Serotonin; Isolation and Characterization. *The Journal of Biological Chemistry*, **176**, 1243-1251. https://doi.org/10.1016/S0021-9258(18)57137-4

[2] Berger, M., Gray, J.A. and Roth, B.L. (2009) The Expanded Biology of Serotonin. *Annual Review of Medicine*, **60**, 355-366. https://doi.org/10.1146/annurev.med.60.042307.110802

[3] Khan, W.I. and Ghia, J.E. (2010) Gut Hormones: Emerging Role in Immune Activation and Inflammation. *Clinical and Experimental Immunology*, **161**, 19-27. https://doi.org/10.1111/j.1365-2249.2010.04150.x

[4] Walther, D.J., Peter, J.U., Bashammakh, S., *et al*. (2003) Synthesis of Serotonin by a Second Tryptophan Hydroxylase Isoform. *Science*, **299**, 76. https://doi.org/10.1126/science.1078197

[5] Zhang, X., Beaulieu, J.M., Sotnikova, T.D., *et al*. (2004) Tryptophan Hydroxylase-2 Controls Brain Serotonin Synthesis. *Science*, **305**, 217. https://doi.org/10.1126/science.1097540

[6] Côté, F., Thévenot, E., Fligny, C., *et al*. (2003) Disruption of the Nonneuronal tph1 Gene Demonstrates the Importance of Peripheral Serotonin in Cardiac Function. *Proceedings of the National Academy of Sciences of the United States of America*, **100**, 13525-13530. https://doi.org/10.1073/pnas.2233056100

[7] Yabut, J.M., Crane, J.D., Green, A.E., *et al*. (2019) Emerging Roles for Serotonin in Regulating Metabolism: New Implications for an Ancient Molecule. *Endocrine Reviews*, **40**, 1092-1107. https://doi.org/10.1210/er.2018-00283

[8] Fitzpatrick, P.F. (1999) Tetrahydropterin-Dependent Amino Acid Hydroxylases. *Annual Review of Biochemistry*, **68**, 355-381. https://doi.org/10.1146/annurev.biochem.68.1.355

[9] Walther, D.J., Peter, J.U., Winter, S., *et al*. (2003) Serotonylation of Small GTPases Is a Signal Transduction Pathway that Triggers Platelet Alpha-Granule Release. *Cell*, **115**, 851-862. https://doi.org/10.1016/S0092-8674(03)01014-6

[10] Nichols, D.E. and Nichols, C.D. (2008) Serotonin Receptors. *Chemical Reviews*, **108**, 1614-1641. https://doi.org/10.1021/cr078224o

[11] King, M.V., Marsden, C.A. and Fone, K.C. (2008) A Role for the 5-HT(1A), 5-HT4 and 5-HT6 Receptors in Learning and Memory. *Trends in Pharmacological Sciences*, **29**, 482-492. https://doi.org/10.1016/j.tips.2008.07.001

[12] Eglen, R.M., Wong, E.H., Dumuis, A., *et al*. (1995) Central 5-HT4 Receptors. *Trends in Pharmacological Sciences*, **16**, 391-398. https://doi.org/10.1016/S0165-6147(00)89081-1

[13] Cortes-Altamirano, J.L., Olmos-Hernandez, A., Jaime, H.B., *et al*. (2018) Review: 5-HT1, 5-HT2, 5-HT3 and 5-HT7 Receptors and Their Role in the Modulation of Pain Response in the Central Nervous System. *Current Neuropharmacology*, **16**, 210-221. https://doi.org/10.2174/1570159X15666170911121027

[14] Sah, V.P., Seasholtz, T.M., Sagi, S.A., *et al*. (2000) The Role of Rho in G Protein-Coupled Receptor Signal Transduction. *Annual Review of Pharmacology and Toxicology*, **40**, 459-489. https://doi.org/10.1146/annurev.pharmtox.40.1.459

[15] Barnes, N.M., Hales, T.G., Lummis, S.C., *et al*. (2009) The 5-HT3 Receptor—The Relationship between Structure and Function. *Neuropharmacology*, **56**, 273-284. https://doi.org/10.1016/j.neuropharm.2008.08.003

[16] Machu, T.K. (2011) Therapeutics of 5-HT3 Receptor Antagonists: Current Uses and Future Directions. *Pharmacology & Therapeutics*, **130**, 338-347. https://doi.org/10.1016/j.pharmthera.2011.02.003

[17] Evans, R.M., Barish, G.D. and Wang, Y.X. (2004) PPARs and the Complex Journey to Obesity. *Nature Medicine*, **10**, 355-361. https://doi.org/10.1038/nm1025

[18] Lehrke, M. and LAZAR, M.A. (2005) The Many Faces of PPARgamma. *Cell*, **123**, 993-999. https://doi.org/10.1016/j.cell.2005.11.026

[19] Mckenna, N.J., Cooney, A.J., Demayo, F.J., *et al*. (2009) Minireview: Evolution of NURSA, the Nuclear Receptor Signaling Atlas. *Molecular Endocrinology*, **23**, 740-746. https://doi.org/10.1210/me.2009-0135

[20] Odegaard, J.I., Ricardo-Gonzalez, R.R., Goforth, M.H., *et al*. (2007) Macrophage-Specific PPARgamma Controls Alternative Activation and Improves Insulin Resistance. *Nature*, **447**, 1116-1120. https://doi.org/10.1038/nature05894

[21] Walczak, R. and Tontonoz, P. (2002) PPARadigms and PPARadoxes: Expanding roles for PPARgamma in the Control of Lipid Metabolism. *Journal of Lipid Research*, **43**, 177-186. https://doi.org/10.1016/S0022-2275(20)30159-0

[22] Hirai, H., Tanaka, K., Takano, S., *et al*. (2002) Cutting Edge: Agonistic Effect of Indomethacin on a Prostaglandin D2 Receptor, CRTH2. *Journal of Immunology*, **168**, 981-985. https://doi.org/10.4049/jimmunol.168.3.981

[23] Waku, T., Shiraki, T., Oyama, T., *et al*. (2010) The Nuclear Receptor PPARγ Individually Responds to Serotonin- and Fatty Acid-Metabolites. *The EMBO Journal*, **29**, 3395-3407. https://doi.org/10.1038/emboj.2010.197

[24] Skurk, T., Alberti-Huber, C., Herder, C., *et al*. (2007) Relationship between Adipocyte Size and Adipokine Expression and Secretion. *The Journal of Clinical Endocrinology and Metabolism*, **92**, 1023-1033. https://doi.org/10.1210/jc.2006-1055

[25] Benrick, A., Chanclón, B., Micallef, P., *et al*. (2017) Adiponectin Protects against Development of Metabolic Disturbances in a PCOS Mouse Model. *Proceedings of the National Academy of Sciences of the United States of America*, **114**, E7187-E7196. https://doi.org/10.1073/pnas.1708854114

[26] Rosene, D. and Spiegelman, B.M. (2014) What We Talk about When We Talk about Fat. *Cell*, **156**, 20-44. https://doi.org/10.1016/j.cell.2013.12.012

[27] Zhao, G.N., Tian, Z.W., Tian, T., *et al*. (2021) TMBIM1 is an Inhibitor of Adipogenesis and Its Depletion Promotes Adipocyte Hyperplasia and Improves Obesity-Related Metabolic Disease. *Cell Metabolism*, **33**, 1640-1654.E8. https://doi.org/10.1016/j.cmet.2021.05.014

[28] Foti, M., Porcheron, G., Fournier, M., *et al*. (2007) The Neck of Caveolae Is a Distinct Plasma Membrane Subdomain that Concentrates Insulin Receptors in 3T3-L1 Adipocytes. *Proceedings of the National Academy of Sciences of the United States of America*, **104**, 1242-1247. https://doi.org/10.1073/pnas.0610523104

[29] Reed, B.C., Kaufmann, S.H., Mackall, J.C., *et al*. (1977) Alterations in Insulin Binding Accompanying Differentiation of 3T3-L1 Preadipocytes. *Proceedings of the National Academy of Sciences of the United States of America*, **74**, 4876-4880. https://doi.org/10.1073/pnas.74.11.4876

[30] KOHLER, H.P. and GRANT, P.J. (2000) Plasminogen-Activator Inhibitor type 1 and Coronary Artery Disease. *The New England Journal of Medicine*, **342**, 1792-1801. https://doi.org/10.1056/NEJM200006153422406

[31] Eriksson, P., Reynisdottir, S., Lönnqvist, F., *et al*. (1998) Adipose Tissue Secretion of Plasminogen Activator Inhibitor-1 in Non-Obese and Obese Individuals. *Diabetologia*, **41**, 65-71. https://doi.org/10.1007/s001250050868

[32] Yamauchi, T., Kamon, J., Ito, Y., *et al*. (2003) Cloning of Adiponectin Receptors that Mediate Antidiabetic Metabolic Effects. *Nature*, **423**, 762-769. https://doi.org/10.1038/nature01705

[33] Uchida-Kitajima, S., Yamauchi, T., Takashina, Y., *et al*. (2008) 5-Hydroxytryptamine 2A Receptor Signaling Cascade Modulates Adiponectin and Plasminogen Activator Inhibitor 1 Expression in Adipose Tissue. *FEBS Letters*, **582**, 3037-3044. https://doi.org/10.1016/j.febslet.2008.07.044

[34] Kinoshita, M., Ono, K., Horie, T., *et al*. (2010) Regulation of Adipocyte Differentiation by Activation of Serotonin (5-HT) Receptors 5-HT2AR and 5-HT2CR and Involvement of MicroRNA-448-Mediated Repression of KLF5. *Molecular Endocrinology*, **24**, 1978-1987. https://doi.org/10.1210/me.2010-0054

[35] Kim, S.P., Ha, J.M., Yun, S.J., *et al*. (2010) Transcriptional Activation of Peroxisome Proliferator-Activated Receptor-Gamma Requires Activation of Both Protein Kinase A and Akt during Adipocyte Differentiation. *Biochemical and Biophysical Research Communications*, **399**, 55-59. https://doi.org/10.1016/j.bbrc.2010.07.038

[36] Yun, J., Jin, H., Cao, Y., *et al*. (2018) RNA-Seq Analysis Reveals a Positive Role of HTR2A in Adipogenesis in Yan Yellow Cattle. *International Journal of Molecular Sciences*, **19**, Article No. 1760. https://doi.org/10.3390/ijms19061760

[37] Peng, X.D., Xu, P.Z., Chen, M.L., *et al*. (2003) Dwarfism, Impaired Skin Development, Skeletal Muscle Atrophy, Delayed Bone Development, and Impeded Adipogenesis in Mice Lacking Akt1 and Akt2. *Genes & Development*, **17**, 1352-1365. https://doi.org/10.1101/gad.1089403

[38] Mota de Sá, P., Richard, A.J., Hang, H., *et al*. (2017) Transcriptional Regulation of Adipogenesis. *Comprehensive Physiology*, **7**, 635-674. https://doi.org/10.1002/cphy.c160022

[39] Yang, M., Sun, J., Zhang, T., *et al*. (2008) Deficiency and Inhibition of Cathepsin K Reduce Body Weight Gain and Increase Glucose Metabolism in Mice. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **28**, 2202-2208. https://doi.org/10.1161/ATVBAHA.108.172320

[40] Söhle, J., Machuy, N., Smailbegovic, E., *et al*. (2012) Identification of New Genes Involved in Human Adipogenesis and Fat Storage. *PLoS ONE*, **7**, e31193. https://doi.org/10.1371/journal.pone.0031193

[41] Lin, Y., Bao, B., Yin, H., *et al*. (2019) Peripheral Cathepsin L Inhibition Induces Fat Loss in C. Elegans and Mice through Promoting Central Serotonin Synthesis. *BMC Biology*, **17**, Article No. 93. https://doi.org/10.1186/s12915-019-0719-4

[42] Cannon, B. and Nedergaard, J. (2004) Brown Adipose Tissue: Function and Physiological Significance. *Physiological Reviews*, **84**, 277-359. https://doi.org/10.1152/physrev.00015.2003

[43] Kajimura, S., Seale, P. and Spiegelman, B.M. (2010) Transcriptional Control of Brown Fat Development. *Cell Meta-*

bolism, **11**, 257-262. https://doi.org/10.1016/j.cmet.2010.03.005

[44] Bargut, T.C., Aguila, M.B. and Mandarim-DE-Lacerda, C.A. (2016) Brown Adipose Tissue: Updates in Cellular and Molecular Biology. *Tissue & Cell*, **48**, 452-460. https://doi.org/10.1016/j.tice.2016.08.001

[45] Harms, M. and Seale, P. (2013) Brown and Beige Fat: Development, Function and Therapeutic Potential. *Nature Medicine*, **19**, 1252-1263. https://doi.org/10.1038/nm.3361

[46] Kajimura, S. and Saito, M. (2014) A New Era in Brown Adipose Tissue Biology: Molecular Control of Brown Fat Development and Energy Homeostasis. *Annual Review of Physiology*, **76**, 225-249. https://doi.org/10.1146/annurev-physiol-021113-170252

[47] Oh, C.M., Park, S. and Kim, H. (2016) Serotonin as a New Therapeutic Target for Diabetes Mellitus and Obesity. *Diabetes & Metabolism Journal*, **40**, 89-98. https://doi.org/10.4093/dmj.2016.40.2.89

[48] Jeong, J.H., Lee, D.K., Blouet, C., *et al*. (2015) Cholinergic Neurons in the Dorsomedial Hypothalamus Regulate Mouse Brown Adipose Tissue Metabolism. *Molecular Metabolism*, **4**, 483-492. https://doi.org/10.1016/j.molmet.2015.03.006

[49] Mcglashon, J.M., Gorecki, M.C., Kozlowski, A.E., *et al*. (2015) Central Serotonergic Neurons Activate and Recruit Thermogenic Brown and Beige Fat and Regulate Glucose and Lipid Homeostasis. *Cell Metabolism*, **21**, 692-705. https://doi.org/10.1016/j.cmet.2015.04.008

[50] Montanari, T., Pošćić, N. and Colitti, M. (2017) Factors Involved in White-to-Brown Adipose Tissue Conversion and in Thermogenesis: A Review. *Obesity Reviews*: *An Official Journal of the International Association for the Study of Obesity*, **18**, 495-513. https://doi.org/10.1111/obr.12520

[51] Nisoli, E. and Carruba, M.O. (2000) An Assessment of the Safety and Efficacy of Sibutramine, an Anti-Obesity Drug with a Novel Mechanism of Action. *Obesity Reviews*: *An Official Journal of the International Association for the Study of Obesity*, **1**, 127-139. https://doi.org/10.1046/j.1467-789x.2000.00020.x

[52] Li, M.F. and Cheung, B.M. (2011) Rise and Fall of Anti-Obesity Drugs. *World Journal of Diabetes*, **2**, 19-23. https://doi.org/10.4239/wjd.v2.i2.19

[53] Da Silva, A.I., Braz, G.R., Pedroza, A.A., *et al*. (2015) Fluoxetine Induces Lean Phenotype in Rat by Increasing the Brown/White Adipose Tissue Ratio and UCP1 Expression. *Journal of Bioenergetics and Biomembranes*, **47**, 309-318. https://doi.org/10.1007/s10863-015-9617-9

[54] Crane, J.D., Palanivel, R., Mottillo, E.P., *et al*. (2015) Inhibiting Peripheral Serotonin Synthesis Reduces Obesity and Metabolic Dysfunction by Promoting Brown Adipose Tissue Thermogenesis. *Nature Medicine*, **21**, 166-172. https://doi.org/10.1038/nm.3766

[55] Wu, J., Boström, P., Sparks, L.M., *et al*. (2012) Beige Adipocytes Are a Distinct Type of Thermogenic Fat Cell in Mouse and Human. *Cell*, **150**, 366-376. https://doi.org/10.1016/j.cell.2012.05.016

[56] Garcia, R.A., Roemmich, J.N. and Claycombe, K.J. (2016) Evaluation of Markers of Beige Adipocytes in White Adipose Tissue of the Mouse. *Nutrition & Metabolism*, **13**, Article No. 24. https://doi.org/10.1186/s12986-016-0081-2

[57] Steinberg, G.R. (2018) Cellular Energy Sensing and Metabolism-Implications for Treating Diabetes: The 2017 Outstanding Scientific Achievement Award Lecture. *Diabetes*, **67**, 169-179. https://doi.org/10.2337/dbi17-0039

[58] Nakamura, K. and Morrison, S.F. (2011) Central Efferent Pathways for Cold-Defensive and Febrile Shivering. *The Journal of Physiology*, **589**, 3641-3658. https://doi.org/10.1113/jphysiol.2011.210047

[59] Nakamura, K., Matsumura, K., Hübschle, T., *et al*. (2004) Identification of Sympathetic Premotor Neurons in Medullary Raphe Regions Mediating Fever and Other Thermoregulatory Functions. *The Journal of Neuroscience*: *The Official Journal of the Society for Neuroscience*, **24**, 5370-5380. https://doi.org/10.1523/JNEUROSCI.1219-04.2004

[60] O'Neil, P.M., Smith, S.R., Weissman, N.J., *et al*. (2012) Randomized Placebo-Controlled Clinical Trial of Lorcaserin for Weight Loss in Type 2 Diabetes Mellitus: The BLOOM-DM Study. *Obesity*, **20**, 1426-1436. https://doi.org/10.1038/oby.2012.66

[61] Krashes, M.J., Koda, S., Ye, C., *et al*. (2011) Rapid, Reversible Activation of AgRP Neurons Drives Feeding Behavior in Mice. *The Journal of Clinical Investigation*, **121**, 1424-1428. https://doi.org/10.1172/JCI46229

[62] Small, C.J., Liu, Y.L., Stanley, S.A., *et al*. (2003) Chronic CNS Administration of Agouti-Related Protein (Agrp) Reduces Energy Expenditure. *International Journal of Obesity and Related Metabolic Disorders*: *Journal of the International Association for the Study of Obesity*, **27**, 530-533. https://doi.org/10.1038/sj.ijo.0802253

[63] Ruan, H.B., Dietrich, M.O., Liu, Z.W., *et al*. (2014) O-GlcNAc Transferase Enables AgRP Neurons to Suppress Browning of White Fat. *Cell*, **159**, 306-317. https://doi.org/10.1016/j.cell.2014.09.010

[64] Burke, L.K., Darwish, T., Cavanaugh, A.R., *et al*. (2017) mTORC1 in AGRP Neurons Integrates Exteroceptive and Interoceptive Food-Related Cues in the Modulation of Adaptive Energy Expenditure in Mice. *eLife*, **6**, e22848.

[65] Deng, J., Yuan, F., Guo, Y., *et al*. (2017) Deletion of ATF4 in AgRP Neurons Promotes Fat Loss Mainly via Increasing Energy Expenditure. *Diabetes*, **66**, 640-650. https://doi.org/10.2337/db16-0954

[66] Dodd, G.T., Andrews, Z.B., Simonds, S.E., *et al*. (2017) A Hypothalamic Phosphatase Switch Coordinates Energy Expenditure with Feeding. *Cell Metabolism*, **26**, 375-393.E7. https://doi.org/10.1016/j.cmet.2017.07.013

[67] Berglund, E.D., Liu, C., Sohn, J.W., *et al*. (2013) Serotonin 2C Receptors in Pro-Opiomelanocortin Neurons Regulate Energy and Glucose Homeostasis. *The Journal of Clinical Investigation*, **123**, 5061-5070. https://doi.org/10.1172/JCI70338

[68] Zhang, X., Wang, X., Yin, H., *et al*. (2019) Functional Inactivation of Mast Cells Enhances Subcutaneous Adipose Tissue Browning in Mice. *Cell Reports*, **28**, 792-803.E4. https://doi.org/10.1016/j.celrep.2019.06.044

[69] Lim, S., Honek, J., Xue, Y., *et al*. (2012) Cold-Induced Activation of Brown Adipose Tissue and Adipose Angiogenesis in Mice. *Nature protocols*, **7**, 606-615. https://doi.org/10.1038/nprot.2012.013

[70] Lee, Y.H., Petkova, A.P., Mottillo, E.P., *et al*. (2012) *In Vivo* Identification of Bipotential Adipocyte Progenitors Recruited by *β*3-Adrenoceptor Activation and High-Fat Feeding. *Cell Metabolism*, **15**, 480-491. https://doi.org/10.1016/j.cmet.2012.03.009

[71] Roh, H.C., Tsai, L.T.Y., Shao, M., *et al*. (2018) Warming Induces Significant Reprogramming of Beige, but Not Brown, Adipocyte Cellular Identity. *Cell Metabolism*, **27**, 1121-1137.E5. https://doi.org/10.1016/j.cmet.2018.03.005

[72] Hellman, B., Larsson, S. and Westman, S. (1963) Mast Cell Content and fatty Acid Metabolism in the Epididymal Fat Pad of Obese Mice. *Acta Physiologica Scandinavica*, **58**, 255-262. https://doi.org/10.1111/j.1748-1716.1963.tb02647.x

[73] Divoux, A., Moutel, S., Poitou, C., *et al*. (2012) Mast Cells in Human Adipose Tissue: Link with Morbid Obesity, Inflammatory Status, and Diabetes. *The Journal of Clinical Endocrinology and Metabolism*, **97**, E1677-E1685. https://doi.org/10.1210/jc.2012-1532

[74] Oh, C.M., Namkung, J., Go, Y., *et al*. (2015) Regulation of Systemic Energy Homeostasis by Serotonin in Adipose Tissues. *Nature Communications*, **6**, Article No. 6794. https://doi.org/10.1038/ncomms7794

[75] Yabut, J.M., Desjardins, E.M., Chan, E.J., *et al*. (2020) Genetic Deletion of Mast Cell Serotonin Synthesis Prevents the Development of Obesity and Insulin Resistance. *Nature Communications*, **11**, Article No. 463. https://doi.org/10.1038/s41467-019-14080-7

[76] Younossi, Z., Anstee, Q.M., Marietti, M., *et al*. (2018) Global Burden of NAFLD and NASH: Trends, Predictions, Risk Factors and Prevention. *Nature Reviews Gastroenterology & Hepatology*, **15**, 11-20. https://doi.org/10.1038/nrgastro.2017.109

[77] Musso, G., Gambino, R. and Cassader, M. (2009) Recent Insights into Hepatic Lipid Metabolism in Non-Alcoholic Fatty Liver Disease (NAFLD). *Progress in Lipid Research*, **48**, 1-26. https://doi.org/10.1016/j.plipres.2008.08.001

[78] Pais, R., Barritt, A.S.T., Calmus, Y., *et al*. (2016) NAFLD and Liver Transplantation: Current Burden and Expected Challenges. *Journal of Hepatology*, **65**, 1245-1257. https://doi.org/10.1016/j.jhep.2016.07.033

[79] Michelotti, G.A., Machado, M.V. and Diehl, A.M. (2013) NAFLD, NASH and Liver Cancer. *Nature Reviews Gastroenterology & Hepatology*, **10**, 656-665. https://doi.org/10.1038/nrgastro.2013.183

[80] Namkung, J., Shong, K.E., Kim, H., *et al*. (2018) Inhibition of Serotonin Synthesis Induces Negative Hepatic Lipid Balance. *Diabetes & Metabolism Journal*, **42**, 233-243. https://doi.org/10.4093/dmj.2017.0084

[81] Choi, W., Namkung, J., Hwang, I., *et al*. (2018) Serotonin Signals through a Gut-Liver Axis to Regulate Hepatic Steatosis. *Nature Communications*, **9**, Article No. 4824. https://doi.org/10.1038/s41467-018-07287-7

[82] Osawa, Y., Kanamori, H., Seki, E., *et al*. (2011) L-tryptophan-Mediated Enhancement of Susceptibility to Nonalcoholic Fatty Liver Disease Is Dependent on the Mammalian Target of Rapamycin. *The Journal of Biological Chemistry*, **286**, 34800-34808. https://doi.org/10.1074/jbc.M111.235473

[83] Haub, S., Ritze, Y., Ladel, I., *et al*. (2011) Serotonin Receptor Type 3 Antagonists Improve Obesity-Associated Fatty Liver Disease in Mice. *The Journal of Pharmacology and Experimental Therapeutics*, **339**, 790-798. https://doi.org/10.1124/jpet.111.181834

[84] Kim, M., Hwang, I., Pagire, H.S., *et al*. (2020) Design, Synthesis, and Biological Evaluation of New Peripheral 5HT(2A) Antagonists for Nonalcoholic Fatty Liver Disease. *Journal of Medicinal Chemistry*, **63**, 4171-4182. https://doi.org/10.1021/acs.jmedchem.0c00002

[85] Coates, M.D., Johnson, A.C., Greenwood-Van Meerveld, B., *et al*. (2006) Effects of Serotonin Transporter Inhibition on Gastrointestinal Motility and Colonic Sensitivity in the Mouse. *Neurogastroenterology and Motility*: *The Official Journal of the European Gastrointestinal Motility Society*, **18**, 464-471. https://doi.org/10.1111/j.1365-2982.2006.00792.x