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GPR119:治疗二型糖尿病和肥胖的新靶点

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摘 要:二型糖尿病(T2D)是当前严重威胁人类健康的一类重要疾病。多年来的流行病学分析显示,肥胖与T2D有着密切的联系。GPR119是近年来发现的抗T2D和肥胖的新靶点。在体外及动物模型中,GPR119具有调节葡萄糖代谢、影响食物摄取、降低体重的功能。近年来国外对其分子机理及激动剂的研究日益增多,本文对相关研究进展做一综述。

关键词:GPR119;激动剂;G蛋白偶联受体;二型糖尿病;肥胖

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GPR119:A Novel Therapeutic Receptor for Type 2 Diabetes and Obesity

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Abstract: Type 2 diabetes (T2D) is one of the leading causes of morbidity and mortality all over the world. Epidemiologic studies have demonstrated that the patients with obesity have increased risk of diabetes. A novel G protein-coupled receptor(GPCR), GPR119, was identified and has emerged as arguably one of the most exciting targets for the treatment of T2D and obesity. *In vitro* and *in vivo*, GPR119 play a key role in modulating glucose homeostasis, food intake, weight loss. This review summarizes the research leading to the identification of GPR119 as a potential drug target for T2D and related metabolic disorders. In addition, an overview of the recent progress made in the discovery of orally active GPR119 agonists is provided.

Key words: GPR119; agonist; G protein-coupled receptor; Type 2 diabetes; Obesity

在现代疾病中,糖尿病已成为继肿瘤和心脑血管疾病之后的第三大杀手。其中,90%以上的糖尿病患者为二型糖尿病(T2D)。肥胖是糖尿病发病的主要风险因素之一,而肥胖和糖尿病都将导致心血管疾病等并发症,进而诱发患者的死亡[1]。现在许多抗糖尿病药物导致体重增加,这将加剧糖尿病相关的心血管疾病[2]。由于许多糖尿病患者同时伴随有肥胖、高血脂等并发症[3],发现一种能够同时控制血糖和体重的抗糖尿病药物具有十分现实的意义。糖尿病靶点GPR119是G蛋白偶联受体(GPCR)家族成员;在体外及动物模型中,GPR119同时具有调节葡萄糖代谢、影响食物摄取、降低体重的功能[4],具有非常重要的研究价值和应用前景,基于该靶标的小分子激动剂也成为国内外医药公司的研究热点。

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1 GPR119的基因定位

2003年Fredriksson通过人类基因组序列比对,报道了一种I型(视紫质型)孤儿GPCR,命名为GPR119[5]。该基因的别名还有SNORF25[6,7]、RUP3[8]、GPCR2[9]、19AJ[10]、OSGPR116[11]和葡萄糖依赖的促胰岛素分泌受体[12]等。GPR119广泛存在于哺乳动物中,包括人、大鼠、小鼠、猕猴、鸡、牛、狗、黑猩猩、红鳍东方鲀等[13],其中研究最多的是人类GPR119。人类GPR119基因位于X染色体短臂26.1处,不含内含子,编码335个氨基酸,与小鼠GPR119有82%的同源性。

人和啮齿类动物GPR119的mRNA主要分布在胰脏和胃肠道中[6-8,11,14],其蛋白与小肠的胰高血糖素原阳性细胞中与GLP-1共定位[12]。而啮齿类动物的GPR119还在CNS系统中表达[12,14-17]。放射自显影和免疫组化显示胰腺中的GPR119分布于胰岛素分泌细胞中,并与胰岛素共定位[12,13]。还有研究指出GPR119分布于胰多肽分泌细胞中[18]。此外,

离体培养的胰腺细胞系和小肠 L-细胞系也表达 GPR119[12-14,17,19,20]。

2 GPR119 的信号通路及内源性配体

2.1 GPR119 的信号通路

GPR119 属于长链脂肪酸激活的 GPCR 家族,该家族成员还包括 GPR40 和 GPR120。GPR119 为 G_s 型 GPCR,通过腺苷酸环化酶提高 cAMP 水平起作用,而 GPR40 和 GPR120 为 G_q 型,通过肌醇三磷酸刺激 Ca^{2+} 起作用[21]。

现在研究指出 GPR119 在体内有两条信号通路。第一条通路是 GPR119 与配体结合,促使胞内 cAMP 上升,诱导胰岛素分泌。该通路的具体机制是通过 ATP-敏感的 K^+ 和电压-依赖的 Ca^{2+} 通道,增加胞内 cAMP,刺激腺苷酸环化酶,增加蛋白激酶 A 活性,进而调节葡萄糖代谢(图 1)[19,20,22]。第二条通路是 GPR119 在激动剂刺激下通过增加 GLP-1(glucagon-like peptide)和 GIP(glucose-dependent insulinotropic peptide)的分泌,调节葡萄糖代谢(图 1)[23,24]。

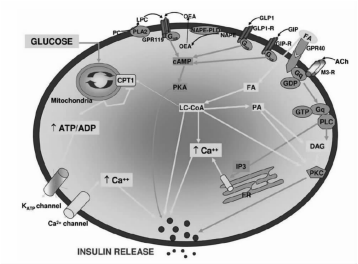

图 1 GPR119 介导的信号通路[24]

Fig. 1 GPR119-mediated signal pathway

2.2 GPR119 的配体

2001 年 Bonini 发现了 GPR119 的第一个配体:全反式-视黄酸[6]。该配体能够提高 COS-7 细胞内的 cAMP 水平,其 EC_{50} 为 909nM,E_{max} 为 202%。但是 Griffin 的报道又指出全反式-视黄酸在 10 nM ~ 10 μM 范围内,对 GPR119/HEK 293 没有激活作用[6]。该配体的具体活性需要进一步确证。此外,Bonini 还报道血小板活化因子(PAF)和溶血血小板激活因子(Lyso-PAF)也能够增加 GPR119 稳转株胞内 cAMP[7]。

2005 年 Soga 等人报道,多种脂肪酸[油酰、硬脂酰、棕榈酰-溶血磷脂胆碱(LPC)、溶血磷脂酰乙醇胺、溶血磷脂酰肌醇]为 GPR119 激动剂,它们的 EC_{50} 都小于 6 μM[14],而且油酰-LPC 在酵母报告基因检测模型中也被证实具有 GPR119 激动作用。

由于同源分析显示 GPR119 与大麻素受体的氨基酸序列有一定的同源性[11],所以研究者检测了脂肪酰胺与其的受配体活性[4,11,25]。结果显示油酰乙醇胺(OEA)具有较高的结合活性。已知 OEA 通过激动 PPARα,调节禁食行为和活动性[26,27];还可激活潜在的香草素 I 型受体瞬时感受器[28],增加脂肪酸转位酶表达[29],提高脂肪细胞和肠道细胞脂肪酸摄取。故研究人员推测 GPR119 有可能通过介导 OEA 或其他未知内源性配体的部分生理功能。随后又发现内源性香草素物质 N-油酰多巴胺和奥代尼的体外活性与 OEA 相似[30]。部分 GPR119 内源性配体及合成配体的活性见表 1[31]。

现在发现的内源性配体 EC_{50} 相较其他 GPCR 的受配体反应,EC_{50} 值较高,而选择性、亲和性较差,一般情况下无法到达反应浓度。但是 OEA 在小肠中具有高浓度[26],且 GPR119 在胃肠道中高表达,这提示二者的生理反应可能在胃肠道中进行。

表 1 部分 GPR119 内源性配体及合成配体的活性[31]

Table 1 Pharmacological profile of compounds tested as GPR119 ligands

化合物 Compound	细胞株 Cell strain	反应方式 Reaction	EC_{50} EC_{50}	参考文献 Reference
大麻素类				
花生四烯酸乙醇胺	hGPR119-酵母	荧光检测	很低	[84]
OEA	hGPR55-HEK293	cAMP 上升	EC_{50} 2.9μM	[84]
	hGPR55-酵母	荧光检测	EC_{50} 3.2μM	[84]
	mGPR55-酵母	荧光检测	EC_{50} 2.9μM	[84]
	hGPR119-酵母	荧光检测	EC_{50} 3.2μM	[4]
PEA	hGPR55-酵母	荧光检测	EC_{50} 3.2μM	[84]

2-AG	hGPR55-酵母	荧光检测	无效	[84]
CP5594	hGPR55-酵母	荧光检测	无效	[84]
WIN55212-2	hGPR55-酵母	荧光检测	无效	[84]
JWH133	hGPR55-酵母	荧光检测	无效	[84]
溶血磷脂				
油酰-LPC	hGPR119-RH7777	cAMP 上升	EC_{50} 1.5μM	[85]
	hGPR55-酵母	荧光检测	EC_{50} >30μM	[84]
	mGPR55-酵母	荧光检测	EC_{50} >30μM	[84]
棕榈酰-LPC	hGPR119-RH7777	cAMP 上升	EC_{50} 1.6μM	[85]
硬脂酰-LPC	hGPR119-RH7777	cAMP 上升	EC_{50} 3.3μM	[85]
LP-乙醇胺	hGPR119-RH7777	cAMP 上升	EC_{50} 5.7μM	[85]
LPI	hGPR119-RH7777	cAMP 上升	EC_{50} 5.7μM	[85]
合成配体				
PSN632408	hGPR55-HEK293	cAMP 上升	EC_{50} 1.9μM	[84]
	hGPR55-酵母	荧光检测	EC_{50} 5.6μM	[84]
	mGPR55-酵母	荧光检测	EC_{50} 7.9μM	[84]
AR231453	hGPR55-HEK293	cAMP 上升	EC_{50} 5.7nM	[86]
	HIT-T15	cAMP 上升	EC_{50} 4.7nM	[86]
	HIT-T15	胰岛素释放	EC_{50} 3.5nM	[86]
	GLUtag	cAMP 上升	EC_{50} 4.3nM	[86]
	GLUtag	GLP-1 释放	EC_{50} 56nM	[86]

3　GPR119 的生理功能

3.1　GPR119 与胰岛素分泌

T2D 主要病因是胰岛素抵抗和胰岛 β-细胞分泌的胰岛素不足。GPR119 在 β-细胞中高表达,可以通过配体刺激促进葡萄糖依赖的胰岛素分泌(GSIS),该活性已经被多个实验证实[8,12,23,32,33]。Chu 等报道 GPR119 的小分子化合物激动剂 AR231453 能够提高正常小鼠的血浆胰岛素,提高正常和患糖尿病小鼠的葡萄糖耐受能力,而对 GPR119 基因敲除小鼠无影响[12,15]。LPC 处理胰岛 β-细胞 NIT-1,胰岛素分泌增加,而腺苷酸环化酶抑制剂或 GPR119-选择性 siRNA 都可以抑制该活性[14,34]。

另一方面,肠内分泌细胞 GLUTag 也表达 GPR119, AR231453 刺激细胞后,胞内 cAMP 水平上升,刺激 GLP-1 分泌,进而参与葡萄糖的代谢[35,33,36]。而且 GLP-1 拮抗剂 exendin 可以降低 AR231453 的作用[37]。OEA 在小肠 L 细胞中也可通过 GPR119 增加 GLP-1 分泌[16]。即 GPR119 在体内表现出双重降血糖作用。首先可以直接通过 β-细胞的 GSIS 作用降血糖,其次还可以间接在肠内分泌细胞中刺激 GLP-1 和 GIP 分泌,通过它们的下游通路抑制进食联系的葡萄糖分泌,实现降血糖[38-40]。具体机理见图 2[15]。

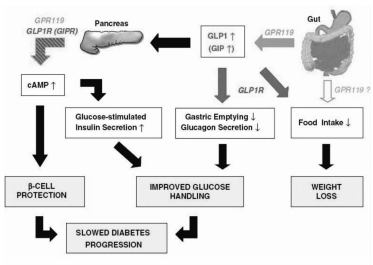

图 2　GPR119 可能的生理功能[15]

Fig. 2　Proposed physiologic function of GPR119

最近研究还指出 GPR119 与 PPY 在胰岛细胞中共定位,PPY 在食物摄取时从胞质中分泌,抑制胰岛素内分泌和旁分泌,调节胆囊活动,增加饱感,加快能量代谢,抑制餐后血糖提高的作用[41],所以推测 GPR119 能够通过调节 PPY 在胰腺中调节能量代谢。这有可能是 GPR119 调节能量代谢的又一通路。

3.2 GPR119 与肥胖

GPR119 是可能的肥胖治疗靶标。使用 GPR119 选择性激动剂 PSN632408 喂食小鼠,可降低小鼠的食物摄取量。喂食脂肪的雄性小鼠,长期给药 PSN632408 也降低食物摄入和体重[4]。GPR119 内源性配体 OEA 喂食可以降低小鼠体重[4]。但 Lan 指出[17]OEA 在野生型和 GPR119$^{-/-}$小鼠中均能降低食物摄取,没有表现出 GPR119 的选择性。这可能是由于 OEA 相对低的选择性和较低的激动活性,所以 OEA 在动物模型中未能表现出活性。此外,OEA 也具有非 PPARα 介导的生理功能,例如小肠蠕动抑制作用[42],减轻内脏和炎性疼痛[43]。另外有报道指出[4,25,33],以 LPC 处理大鼠,能抑制胃排空,阻止食物摄取,但不会引起味觉败坏或身体不适,长期喂食还可导致体重降低,脂肪堆积。

OEA 和 LPC 是否能够通过 GPR119 降低体重还需要进一步的确证。为了阐明 GPR119 与肥胖的关系,需要在野生型和 GPR119 $^{-/-}$小鼠中研究其激动剂的生理作用。此外还要进一步区别 GPR119 与 PPARα 介导的厌食作用[27,44,45],脂代谢[46],神经保护作用[47,48]等。

4 GPR119 激动剂

GPR119 激动剂为小分子化合物,不同于 GLP-1R 的多肽激动剂,因此更加适合开发口服制剂。由于 GPR119 激动剂具有良好的药效和清楚的药物作用机理,众多制药公司正在研发新型口服类 GPR119 激动剂用于治疗 T2D、肥胖等。

4.1 Arena 公司开发的激动剂

Arena 公司是 GPR119 激动剂研究最活跃的公司之一。AR231453 是其早期合成的一个激动剂,在小鼠中具有良好的抗糖尿病效果(10 mg/kg, po; T_{max} = 0.5 h, C_{max} = 9.84 μM, AUC = 19803 h · ng/mL, $t_{1/2}$ = 3.4 h),该化合物在 GPR119 功能研究中起到了关键作用。

2008 年 AR231453 的结构式被公布(图 3)[22],通过对其嘧啶环右边加入-OR 基团(其中 R 为一个异丙基-氨基甲酸酯修饰的吡啶环),合成了一系列 AR231453 类似物(图 3)[8,49-51]。之后,在此基础上合成了 APD668 和 APD597[52,53]。APD668 在体外[54]该化合物能够激动多个种属的 GPR119(hEC$_{50}$ = 0.47 nM, mouse EC$_{50}$ = 0.98 nM, rat EC$_{50}$ = 2.51 nM)。在大、小鼠的口服葡萄糖耐受实验(oGTT)中,其初始有效剂量为 3 mg/kg,最大有效剂量为 10 ~ 30 mg/kg,且在 11d 的给药中无耐药现象。在 Zucker 糖尿病/肥胖大鼠(ZDF)中,它能降低血糖,延迟高血糖症发病,延迟患病期的 HbA1c 升高,显著降低食物摄取,降低血浆三酰甘油和游离脂肪酸,在 I 期临床试验中能改善 T2D 患者的葡萄糖控制[55]。但是由于其低活性停止进行 II 期临床实验[56]。

4.2 Prosidion 公司开发的激动剂

PSN632408 是 Prosidion 公司早期研发的 GPR119 激动剂(图 4)[4,57]。随后在此基础上合成了一系列相关激动剂,包括 PSN-119-1、PSN-119-1M、PSN-119-2 等(图 4)[58,59]。前期研究结果表明,PSN632408 和西布曲明(Sibutramine)效果相似,能降低食欲减少体重。21 d 喂食,增加 cAMP 水平,提高葡萄糖耐受力和胰岛素敏感性。PSN-119-1 能够增加 HIT-T15 β-细胞 cAMP 水平,EC$_{50}$为 253 nM,E$_{max}$为 3.3 倍。50 mg/kg 口服剂量显著降低大鼠 24 h 的进食。30 mg/kg 口服剂量提高多个肥胖/ T2D 小鼠模型的口服葡萄糖耐受力。与 DPP-4 抑制剂联用,能显著增强大鼠血浆 GLP-1 的水平。30 mg/kg 口服剂量抑制胃排空。在高脂喂食大鼠的葡萄糖耐受试验中,100 mg/kg 口服剂量处理 21 d,显著降低血浆葡萄糖和胰岛素水平,减少脂肪形成和血浆来普汀水平[60]。

PSN-IV/119-1 具有 DPP-IV 抑制剂和 GPR119 激动剂双重功能[55]。临床前研究指出,在糖尿病 ZDF 小鼠中,30 mg/kg 的 PSN632408 与 sitagliptin 对 DPP-IV 抑制效果相当,但降糖作用更佳(AUC 58% vs 22%)。对 DPP-IV 的 IC$_{50}$为 0.2 μmol/L,对 GPR119 的 EC$_{50}$为 0.62 μmol/L[61]。

PSN-821 是 2008 年宣布进入 I 期临床的药物[62],目前已进入 II 期临床阶段[56]。临床前试验指出,PSN-821 促进释放内源性 GLP-1,增加 β-细胞 cAMP,提高葡萄糖耐受,延迟胃排空,抑制食欲,引起体重减轻[63]。在糖尿病 ZDF 大鼠中,PSN-821 显著抑制葡萄糖漂移(oGTT)。DIO(Diet-induced obese)大鼠中,30 mg/kg 剂量 ×4 周喂食,能降低体重 8.8%[64]。

4.3 Metabolex 公司开发的激动剂

MBX-2982 是 Metabolex 公司开发的 GPR119 激

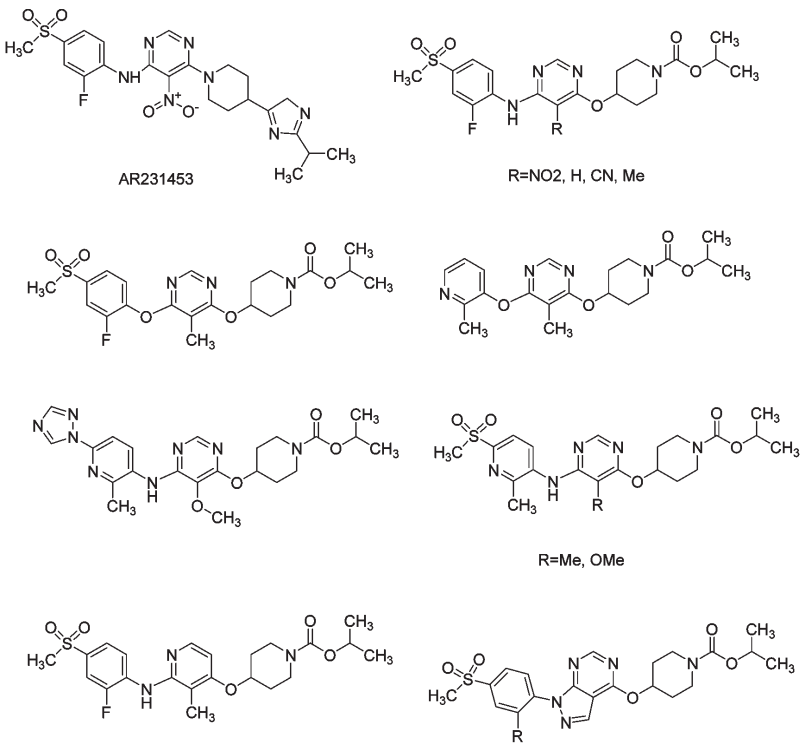

图 3　Arena 公司开发 GPR119 激动剂

Fig. 3　Chemical structures of GPR119 agonists from Arena

动剂,已经进入 II 期临床研究[56]。MBX-2982 以五元杂环为核心,与 PSN-632408 结构相比,将吡啶与芳香基团位置互换。在啮齿类动物模型的葡萄糖耐受试验中,能刺激 GSIS 反应,增加血浆 GLP-1 和胃抑制性多肽(GIP)水平。在喂食高脂食物的大鼠中,能显著降低胃排空,延迟糖尿病发病。在表达 GPR119 的 CHO 细胞中,MBX-2982 可增加 cAMP 水平[65]。I 期临床试验中,MBX-2982 以 10 ~ 1000 mg,每天一次的剂量口服,能被快速吸收,体内代谢良好,没有剂量依赖的副作用;具有剂量依赖的降血糖作用,能增加 GLP-1 水平。空腹血糖异常(impaired fasting glycaemia,IFG)患者中所做的混合餐糖赖量试验显示(mixed-meal tolerance test,MMTT),口服剂量 100 或 300 mg,药物耐受良好,降低血糖波动和胰高血糖素,增加 GSIS 反应[66,67]。图 5 为 MBX-2982 的类似物。

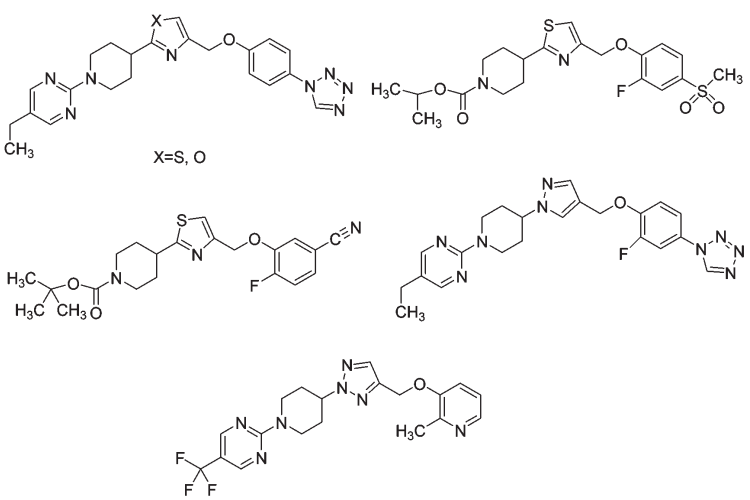

图 4　Metabolex 公司开发 GPR119 激动剂

Fig. 4　Chemical structures of GPR119 agonists from Metabolex

4.4 其它公司开发的激动剂

此外,还有许多公司开发了 GPR119 激动剂。如 Bristol-Myers Squibb[68-71]、Astellas[72]、GlaxoSmith-Kline[73-78]、Schering-Plough[79,80]、Novartis/IRM[81,83]、Merck[84,85]、Biovitrum[70,86]、等。

5 展望

前期研究结果表明 GPR119 激动剂能够有效改善糖尿病患者的葡萄糖控制,并且 GPR119 激动剂能够增加 DPP-IV 抑制剂的药效,由于两者都是葡萄糖依赖形式起效,联合用药相较于磺脲,能够更有效的降低高血糖偶发率。然而,由于 GPR119 激动剂的低活性和安全性,GPR119 激动作为治疗 2 型糖尿病有效药物单独成药仍需进一步的研究。但其展现了良好的前景,有可能成为治疗糖尿病药物的下一个重磅炸弹。

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