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综 述

腺嘌呤核苷酸及代谢产物在调节糖脂代谢稳态中的作用

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摘 要：糖脂代谢是高等生命体最基本的代谢活动，其过程受到环境和遗传的影响，并在器官、细胞和分子等不同水平上得到精确调控。脂质的过度摄取和积累导致肥胖，诱导糖代谢调节的失控，从而形成胰岛素抵抗和高血糖等代谢综合征。本文综述了游离脂肪酸诱导靶细胞释放腺嘌呤核苷酸的相关研究，回顾了过去数十年关于正常和特殊生理状态下腺嘌呤核苷酸信号发生、转导和作用方式的研究成果，提出了腺嘌呤核苷酸及其代谢产物是脂质代谢和糖代谢相互调节过程中的介导因子，其在2型糖尿病发生、发展中可能承担新角色。

关键词：糖脂代谢；腺嘌呤核苷酸；2型糖尿病；胰岛素抵抗；高血糖
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The role of adenine nucleotide and its metabolites in regulating the homeostasis of glucose and lipid metabolism

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Abstract: Glucose and lipid metabolism is the most fundamental metabolic activity of higher organisms. This process is affected by both genetic polymorphisms and environmental factors. Excessive uptake and accumulation of lipids lead to obesity and disorder of glucose metabolic homeostasis characterized by insulin resistance and hyperglycemia, suggesting that the cross-regulation between lipid and glucose metabolism happens precisely at organ, cellular and molecular levels by known mechanisms. Adenine nucleotides and their metabolites have emerged as mediators in the mutual regulation of glucose and lipid metabolism. This review summarizes the roles of purinergic signaling induced by fatty acids in glucose metabolism and the development of type 2 diabetes.

Key words: glucose and lipid metabolism; adenine nucleotide; type 2 diabetes; insulin resistance; hyperglycemia

高等生命的脂质代谢和糖代谢存在着密切相关的生理机制。能量摄取不足或特殊禁食状态下造成糖代谢减慢，触发组织脂质的分解和脂肪酸的利用增加；而脂质的过度摄取和积累导致肥胖和高血脂症，诱导糖代谢调节的失控，从而形成胰岛素抵抗和高血糖等代谢综合征。有大量的研究试图阐明高脂如何诱导高血糖形成的分子机制，但是仍然有许多问题没有解决。本文以腺嘌呤核苷酸代谢这个基本的生物学角度，综述了腺嘌呤核苷酸及其信号参与糖脂代谢的调节过程的研究成果。

1 腺嘌呤核苷酸代谢及其信号传导途径

腺嘌呤核苷酸系统在健康以及病理生理条件下 (如炎症、缺氧和癌症) 调节组织稳态 [1, 2]。三磷酸腺苷 (adenosine triphosphate, ATP) 除了是细胞的主要能量来源，还是一种已知的细胞外信使，它通过

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与受体相互作用或通过外切核苷酸酶降解为腺苷后触发一系列复杂的生理病理反应。ATP 以高浓度存在于细胞内，在细胞膜受损后可以通过囊泡释放或通过转运蛋白或离子通道释放出来 [3]。神经末梢、免疫细胞、平滑肌细胞和内皮细胞均可释放这些 ATP 和 5'- 二磷酸腺苷 (5'-adenosine diphosphate, ADP)[4]。如图 1 所示，一旦进入胞外空间，ATP 就能被离子型 (P2X) 或代谢型 (P2Y) 嘌呤受体感知 [5]。P2X 受体包括七个离子通道，这些通道与它们的优先配体 ATP 结合后，激活 Na^+ 和 Ca^{2+} 的细胞内流以及 K^+ 的外排。在八个 P2Y 受体中，ATP 仅是 P2Y2 和 P2Y11 的优选配体，而该家族其他蛋白的天然激动剂包括 ADP，UTP，UDP 或 UDP- 葡萄糖 [6, 7]。

除了与 P2 受体相互作用外，ATP 还可以被质膜胞外核苷酸酶 (E-NTPDases) 迅速清除。在病理生理条件下 (例如缺氧或炎症)，ATP 的释放增加，并随即脱磷酸化形成腺苷，增加血浆腺苷含量 [8]。目前已经发现了四种质膜上的具有独特定位和生物学特性的 E-NTPDase (NTPDase 1、2、3 和 8)。ATP 主要由 NTPDase1 (CD39) 水解产生 5'- 单磷酸腺苷 (5'-adenosine monophosphate, AMP)，再由 ecto-5'- 核苷酸酶 (CD73) 水解为腺苷 [9, 10]。除了 CD39 和 CD73 去磷酸化 ATP，还存在一些研究较少的细胞表面相关酶在代谢腺嘌呤核苷酸的过程中起作用，如碱性磷酸酶、焦磷酸酶和磷酸二酯酶 [11]。在特定的生理病理条件下，CD39 和 CD73 的表达可能会改变。例如，缺氧上调两种胞外核苷酸酶：通过 SP1 依赖性途径上调 CD39 [12]；通过缺氧诱导因子 1α (hypoxia inducible factor 1α, HIF-1α) 依赖性途径上调 CD73 [13]。CD39 的活性是可逆的，而 CD73 的活性实际上是不可逆的。胞内腺苷也可以反过来通过腺苷激酶 (adenosine kinase, ADK) 快速磷酸化为 AMP，或通过腺苷脱氨酶 (adenosine deaminase, ADA) 的两个亚型 (ADA1 和 ADA2) 不可逆地脱氨，生成肌苷 [2, 11, 14, 15]。

腺苷系统包括核苷转运体和腺苷受体。胞内腺苷除了由 AMP 去磷酸化，还可以由 S- 腺苷同型半胱氨酸 (S adenosine homocysteine, SAH) 水解产生。腺苷通过平衡型核苷转运体 (equilibrative nucleoside transporters, ENTs) 和浓度型核苷转运体 (concentrative nucleoside transporters, CNTs) 进入胞内，转运体在控制胞外腺苷水平方面发挥关键作用 [14]。根据其分子和功能特性，这些转运体可分为两类：(1) ENTs (ENT1、ENT2、ENT3 和 ENT4)，它们根据浓度的不同携带核苷通过细胞膜；(2) CNTs (CNT1、CNT2 和 CNT3)，它们利用钠离子梯度作为能量来源，介导细胞内核苷的转运，对抗浓度梯度 [2]。结合胞外腺苷的 G 蛋白耦联受体存在四个不同亚型，分别为 A_1、A_{2A}、A_{2B} 和 A_3 [16, 17]。A_1 和 A_3 腺苷受体的激活降低了细胞内 cAMP 的水平，而 A_{2A} 和 A_{2B} 受体的刺激导致 cAMP 水平的增加。A_1 和 A_{2A} 是腺苷高亲和力受体，而 A_{2B} 和 A_3 受体显示出较低的腺苷亲和力。所有腺苷受体都能激活有丝分裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 途径，包括胞外信号调节激酶 1 (extracellular regulated protein kinase 1, ERK1)、ERK2、c-Jun N 末端激酶和 p38 MAPK。腺苷也可以不依赖受体发挥作用，例如通过 ADK 和 AMP 依赖的蛋白激酶 (adenosine 5'-monophosphate-activated protein kinase, AMPK) 途

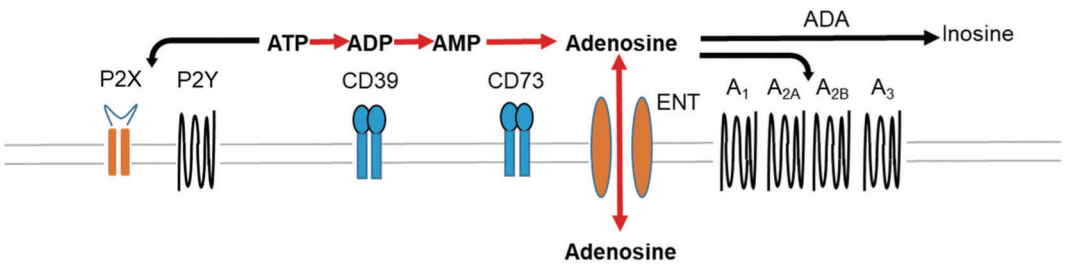

图 1. 腺嘌呤苷酸代谢系统通路

Fig. 1. Adenine nucleotide metabolic pathways. ATP activates purinergic receptors in the plasma membrane termed P2 (P2Y and P2X) receptors. ATP is mainly hydrolyzed by CD39. AMP, which is then hydrolyzed to adenosine by CD73. Adenosine mediates its effects via 4 receptor subtypes: the A_1, A_{2A}, A_{2B}, and A_3 adenosine receptors. Nucleoside transporters and adenosine deaminases (ADAs) are involved in adenosine signaling and modulate the extracellular concentration of adenosine. ENT, equilibrative nucleoside transporter.

径，但这方面机制一直不明确 [1]。

2 糖脂代谢紊乱与腺嘌呤核苷酸代谢异常的关联

2.1 尿酸升高与糖脂代谢紊乱

在人体中，尿酸是嘌呤核苷酸分解代谢的最终氧化产物。血清尿酸水平是基于嘌呤及嘌呤核苷酸的吸收、产生和排泄之间的平衡。肥胖常伴有高尿酸血症 [18]。血清尿酸升高与内脏脂肪积累和各种代谢疾病密切相关 [19–21]，如葡萄糖耐受不良、血压升高、血脂异常和动脉粥样硬化性心血管疾病等代谢综合征 [22–26]。有文献报道，尿酸的增加与 2 型糖尿病 (type 2 diabetes mellitus, T2D) 的发生具有一定的相关性 [27]。血清尿酸升高是糖尿病最好的独立预测因子之一，通常预示着胰岛素抵抗和糖尿病的发生 [28]。

2.2 游离脂肪酸(free fat acid, FFA)、腺嘌呤核苷酸代谢和胰岛素抵抗

FFA 的升高被认为是肥胖诱导胰岛素抵抗的重要因素。最新的研究表明血浆腺嘌呤核苷酸是 FFA 引起胰岛素抵抗的介导因子。首先，FFA 诱导细胞释放腺嘌呤核苷酸。在体外细胞实验中，FFA 通过损伤细胞引起腺嘌呤核苷酸的释放，导致胞外 AMP 上升 [29]。FFA 诱导人脐静脉内皮细胞释放腺嘌呤核苷酸先于诱导细胞凋亡 [30]。另外，FFA 降低了红细胞对活性氧 (reactive oxygen species, ROS) 的抵抗力，对氧化应激敏感，对溶血的敏感性增加 [31]，从而增加血浆腺嘌呤核苷酸的浓度 [30]。在缺氧等条件下，红细胞会向细胞外释放 ATP [32, 33]。肥胖的 *db/db* 小鼠的血样往往表现出溶血特征 [34]。在正常小鼠实验中，通过滴注脂肪乳等方法短时间内迅速提高血浆中 FFA 的浓度时，血浆腺嘌呤核苷酸浓度升高，高血糖产生 [29]。血浆腺嘌呤核苷酸浓度的升高被认为是饮食诱导 T2D 和自发的 *db/db* 小鼠高血糖的原因 [29]。给野生型小鼠注射 AMP 可使体内腺苷水平升高，并导致高血糖 [29]，其发生高血糖的机制与肝细胞中 ATP 及代谢物的积累，并进一步导致细胞内环境的酸碱度发生变化有关 [35]。这样，血浆腺嘌呤核苷酸可能扮演了 FFA 引起胰岛素抵抗、高血糖出现的中间角色。

2.3 糖脂代谢紊乱与腺嘌呤核苷酸代谢酶的异常反应

肥胖个体的尿酸水平升高 [21, 36]。肥胖可增强脂肪组织中的腺嘌呤核苷酸的分解代谢 [18]。在 T2D 患者的血浆中，与腺嘌呤核苷酸代谢相关的酶的活性呈现异常升高 [37–39]。在代谢紊乱的 T2D 患者的外周血单个核细胞 (peripheral blood mononuclear cell, PBMC) 中，$CD39^+$ 和 $CD39^+$ $CD19^+$ 细胞的比例提高，CD39 酶活性升高 [40]。$CD39^+$ 细胞或 $CD39^+$ $CD19^+$ 细胞的百分比与空腹血糖水平和 HbA1c 百分比之间存在显著相关性 [40]。T2D 和 T2D/ 高血压患者的血小板 CD39 和 CD73 活性显著增加 [37]。腺苷和腺苷类似物通过 cAMP 通路诱导 CD73 表达上调 [41]。升高的 CD37 和 CD73 可能是由于血浆内核苷酸升高介导的胞内 cAMP 上升造成的。另外，T2D 患者的 ADA 活性增加 [38, 39]，T2D 患者的 ADA2 亚型活性明显高于低血糖值的患者 [42]。T1D 和 T2D 患者血清中 ADA2 水平明显增加 [43]。在 T2D 患者中，ADA2 的活性与 HbA1C 水平直接相关 [43]。T2D 受试者中，ADA2 等位基因的比例和身体质量指数 (body mass index, BMI) 正相关 [44]。同样，高酸性磷酸酶基因位点 1 (acid phosphatase locus 1, ACP1) 活性 /ADA 活性低基因型与高血糖水平呈正相关，而高 BMI 和 ACP1 活性 /ADA 活性低基因型与血脂异常呈正相关 [45]。ADA 活性的升高可能是高水平腺苷的反馈调节，但这种调节似乎没有降低腺苷水平。

脂肪组织中黄嘌呤氧化还原酶 (xanthine oxidoreductase, XOR) 代谢产生尿酸，肥胖小鼠脂肪组织的 XOR 活性高于正常小鼠 [18]。在非酒精性脂肪性肝病的细胞和小鼠模型中，XOR 的表达和活性显著升高 [46]。肥胖上调了脂肪组织 XOR 的 mRNA 表达和活性以及尿酸的分泌 [18, 47]。喂食高脂肪食物的大鼠皮下 XOR 活性同样有所增加 [48]。升高的 XOR 也可能是由于上游代谢物增多自然产生的变化。XOR 位于过氧化物酶体增殖物激活受体 -γ (peroxisome proliferators-activated receptor-γ, PPAR-γ) 的上游，可调节该蛋白的活性，从而调控脂肪生成 [47]。抑制 XOR 活性可显著降低 HepG2 细胞中尿酸的产生，并减弱 FFA 诱导的脂肪积累 [46]，提示腺苷酸代谢酶的变化可能会进一步加重糖脂代谢的紊乱。

2.4 糖脂代谢紊乱与腺嘌呤核苷酸相关受体的异常表达

肥胖患者的胰腺 β 细胞存在高水平的 P2X7，而在糖尿病患者的胰腺几乎检测不到 P2X7 的存在 [49]。在非肥胖糖尿病 (non-obese diabetic, NOD) 小鼠中，随着糖尿病的发展，P2X7 的表达逐渐减少 [50]。但是，在任何情况下，无论是雄性还是雌性小鼠，NOD 中 P2X7 的基因消融都不会改变 T1D 发

生率[51]。研究显示，长期暴露于外源性 ATP 可导致 P2X7 依赖的细胞坏死[52]。炎症因子促进 P2X7 受体的表达[53]。肥胖引起的 P2X7 减少一方面可能是高浓度核苷酸导致的细胞坏死，另一方面源于长期的慢性炎症，但具体机制仍需要进一步研究。在 NOD 小鼠胰岛中，腺苷 A_1 受体表达下调，A_{2A} 表达上调[54]。Guzman-Flores 等研究显示，T2D 患者的 $CD8^+$、$CD19^+$ 和 $CD14^+$ 细胞中 $A_{2A}{}^+$ 细胞百分比增加[55]。研究显示，糖尿病大鼠肝脏中 A_{2A} 和 A_3 受体水平显著升高；给予链脲佐菌素 (streptozocin, STZ) 大鼠 4 天胰岛素后，腺苷受体的表达恢复到正常水平[56, 57]。Johnston-Cox 等研究显示，高脂饮食 (high fat diet, HFD) 小鼠的内脏脂肪中 A_{2B} 腺苷受体的表达增加，提示 A_{2B} 受体可能与代谢综合征和 T2D 的特征发展有关[58]。在肥胖症患者中，皮下脂肪中的 A_{2B} 受体表达与 BMI 和胰岛素受体底物 2 (insulin receptor substrate 2, IRS-2) mRNA 表达呈正相关，这表明该腺苷受体亚型与人类的脂肪组织代谢有关[58]。但也有文献报道糖尿病大鼠肝脏 A_{2B} 受体水平下降[56, 57]。Liu 等研究显示，STZ 诱导的糖尿病大鼠肝脏中腺苷 A_1 受体表达增加，而另一项研究则显示糖尿病大鼠肝脏中 A_1 受体表达没有变化[56, 57]。这些变化在不同的糖脂代谢紊乱的模型中呈现不同甚至相互矛盾，可能和不同实验模型中核苷酸浓度的差别相关。腺苷受体可能在调节正常的糖脂代谢稳态中的作用比在病理情况下的作用更大。

3 腺嘌呤核苷酸代谢和糖代谢稳态

3.1 ATP与糖代谢稳态的关系

ATP 已被证明对几乎所有葡萄糖的生产和存储元素都有影响，包括糖原分解、糖异生和糖酵解[59]。糖原分解主要是通过胰高血糖素的作用介导的，但 ATP 同样可以刺激糖原分解[60–64]。事实上，胰高血糖素通过诱导 ATP 的释放作用于 P2 受体导致肝细胞膜极化[65]。大鼠和人肝脏中 P2Y1 受体的激活刺激糖原磷酸化酶[66, 67]，其机制包括细胞内钙的增加以及活化磷脂酶 D，这些都可能增强肝糖原分解。ATP 在分离的大鼠肝细胞中可以促进糖异生，腺苷也具有同样作用[68]。ATP 引起的 $[Ca^{2+}]$ 的初始瞬时升高在触发糖异生中起重要作用[69]。然而，这种影响受糖异生的碳源或细胞外 ATP 的浓度控制。在分离的肝细胞中，丙酮酸和乳酸 (但不包括甘油或果糖) 的糖异生被细胞外高浓度的 ATP 抑制，腺苷产生类似的效果[70]。胰岛素刺激的肝细胞糖酵解被 ATP 通过抑制磷酸果糖激酶 2 减弱[71]。肝细胞糖代谢的嘌呤调控 (主要是 P2Y1 和 P2Y2) 可能通过 mTOR 通路控制[59]。ATP 还被证明可以增加正常小鼠和四氧嘧啶糖尿病大鼠的胰岛素分泌[72]。ATP 通过胞内机制和激活胰腺 β 细胞表面的 P2 受体影响胰岛素分泌[73]，而这种作用还取决于血糖浓度[74, 75]。在人的胰岛，小鼠和大鼠的 β 细胞和胰腺中都发现了 P2X 和 P2Y 受体的表达[76–81]。P2Y 受体影响胰岛素分泌。在大鼠胰岛素瘤 INS-1 细胞系中，P2Y 受体的激活会导致胰岛素分增多[82]。P2Y4 受体的激活被证明可以独立于血糖水平之外，单独刺激胰岛素分泌[82]。在低葡萄糖水平下，P2Y1 和 P2Y6 受体的激活会刺激胰岛素分泌[83]。但与之相对应的是，在高葡萄糖水平下，刺激 P2Y1 和 P2Y6 会抑制胰岛素释放[84]。这些研究结果表明，ATP 介导体内 β 细胞胰岛素释放的自分泌阳性信号，并提示 P2Y 受体的活化可能在胰岛素分泌的调节中起作用。Madsen 等在 NOD 小鼠模型中，发现两个 P2Y 受体 (P2Y2 和 P2Y6) 存在于胰岛素依赖性糖尿病区域[85]。NOD 小鼠中 P2X 和 P2Y 受体的 UTR 区、外显子和内含子区的单核苷酸多态性 (single nucleotide polymorphism, SNP) 存在差异[85]。

P2X 受体同样影响胰岛素分泌。在大鼠胰岛素瘤 INS-1 细胞系中直接激活 P2X 受体不能刺激胰岛素分泌，但抑制 P2X 受体会阻止胰岛素分泌[82]。同时用胰岛素和 ATP 处理人胰岛 β 细胞，可刺激 P2X3 受体，导致细胞内 Ca^{2+} 浓度增加和胰岛素释放增加[80]。P2X7 是 P2X 受体中最受关注的。研究显示，*P2X7*$^{-/-}$ 小鼠对连续 5 天 STZ 诱导的 T1D 有抵抗力，*P2X7*$^{-/-}$ T1D 小鼠血糖水平更低[86]。*P2X7*$^{-/-}$ T1D 小鼠的胰腺促炎因子 (如 IL-1β 和 IFN-γ) 并没有增加[86]。*P2X7*$^{-/-}$ 小鼠的胰腺淋巴结免疫细胞浸润减少[86]。在体内用 P2X7 拮抗剂治疗可预防 STZ 诱导的糖尿病[86]，提示 P2X7 可能是预防或治疗糖尿病的良好药理靶标。但是用葡萄糖、棕榈酸或 BzATP (P2X 激动剂) 处理人胰岛 30 min，会导致 P2X7 表达增加，并诱导 IL-1Ra 和胰岛素分泌[49]。此外，与野生型小鼠相比，喂食 HFD 的 *P2X7*$^{-/-}$ 小鼠更易于表现出高血糖、高胰岛素血症、β 细胞凋亡增加和功能受损[49]。这些研究结果表明，P2X7 可能参与 β 细胞提高胰岛素分泌的补偿机制。除此之外，研究显示，位于内含子区域的 P2X3、P2X4

和 P2X5 基因变异与糖尿病风险的增加和空腹血糖的升高显著相关，P2Y1 基因多态性与葡萄糖稳态有关 [87]。在 P2Y1 敲除小鼠上的研究显示，*P2Y1*$^{-/-}$ 小鼠血糖升高，胰岛素水平上升，表明 P2Y1 受体在葡萄糖稳态中起作用，并与胰岛素释放增加有关 [88]。

3.2 腺苷与糖代谢

腺苷通过 A_1 受体的作用，增加细胞内 cAMP 和钙离子浓度，从而激活糖原磷酸化酶。尽管腺苷和胰高血糖素对糖原磷酸化酶的激活效应相似，但在葡萄糖产生的效用上，腺苷不如胰高血糖素有效，甚至拮抗胰高血糖素和 cAMP 对糖原分解的刺激作用 [89]。在正常或高水平葡萄糖浓度下，腺苷都能促进胰岛分泌胰岛素。腺苷信号传导与葡萄糖稳态以及 T2D 的病理生理有紧密联系 [4, 90, 91]。腺苷在脂肪细胞功能的调节中起作用 [92]。A_1 受体激动剂诱导脂肪细胞分化，A_{2B} 受体的刺激抑制了脂肪形成 [93]。Dong 等研究显示，过表达 A_1 受体的转基因小鼠脂肪组织中 FFA 水平较低，且未出现胰岛素抵抗 [94]。A_3 受体激动剂显著降低 βTC-6 细胞增殖和胰岛细胞活力，用选择性 A_3 受体拮抗剂 VUF5574 对 βTC-6 细胞进行预处理可部分拮抗这种作用 [95]。研究显示，A_{2A} 受体激动剂可保护与淋巴细胞共培养的胰岛，并改善糖尿病个体中边缘胰岛团的植入 [96]。在 CD1 小鼠的多次低剂量 STZ (multiple low-dose STZ, MLDS) 注射诱导模型和环磷酰胺诱导的 NOD 小鼠 T1D 中，用非选择性腺苷受体激动剂 NECA 进行的治疗可延缓糖尿病的发展 [97]。在过表达 CD39 的 C57BL/6 小鼠的胰岛中，胰岛不受 MLDS 诱导的糖尿病的侵袭，A_{2B} 受体表达水平显著上调，并且在 MLDS 处理后不会下调 [98]。

腺苷受体在小鼠胰岛以及啮齿动物胰岛素瘤细胞系 (大鼠 INS-1 和小鼠 βTC-6 细胞) 中均有表达，提示腺苷参与 β 细胞功能的调节。在 INS-1 细胞以及小鼠和大鼠胰岛中激活 A_1 受体可促进胰岛素释放 [99]。在高葡萄糖浓度下，用 A_{2A} 受体拮抗剂预处理胰岛可阻止胰岛素分泌，而 A_{2B} 和 A_3 受体拮抗剂则不能阻止胰岛素分泌，而使用 A_1 受体拮抗剂则可增强胰岛素分泌 [95]。尽管单独施用 A_1、A_{2A} 和 A_3 受体的选择性激动剂没有显示出保护作用，但非选择性 AR 激动剂 NECA 改善了 MLDS 诱导的野生型和 $A_{2A}^{-/-}$ 小鼠的高血糖症，使用 A_{2B} 受体拮抗剂 MRS 1754 可以抑制 NECA 的这种作用 [97]。$A_1^{-/-}$ 小鼠的胰岛素分泌增加，提示 A_1 受体参与胰岛功能的调节 [100]。多项研究已经分析了 A_{2B} 受体的作用，表明 A_{2B} 受体的激活可以调节葡萄糖稳态和肥胖 [101, 102]，提示该受体的激活可能是治疗 T2D 的潜在靶标。但除此之外，A_3 受体的作用仍然未知。总之，靶向 A_1 和 A_{2B} 受体可能被认为是治疗肥胖的方法，但是需要进一步的研究以便更深入了解 T2D 病理生理学过程的腺苷信号转导机制。

3.3 腺嘌呤核苷酸信号在细胞内的调控

有大量的文献总结了细胞内腺嘌呤核苷酸调节 AMPK 通路影响糖脂代谢的机制。我们在此总结 AMPK 之外的以下三种调节形式，如图 2 所示。

3.3.1 蛋白磷酸化

在体外实验中，AMP 不影响胰岛素与其受体 IR 的结合能力 [29]。但在胰岛素敏感组织肝脏和骨骼肌中，AMP 能够抑制胰岛素引起的 IR 自磷酸化，且该作用呈剂量依赖性，从而抑制 IR 酪氨酸激酶活性，削弱下游蛋白的磷酸化 [103]。另外，有证据表明 AMP 也削弱了肝脏和骨骼肌组织中胰岛素引起的 IR 下游重要的靶蛋白 —— 蛋白激酶 B (protein kinase B, AKT) 磷酸化。研究显示，在 *db/db* 糖尿病模型小鼠中，胰岛素引起的肌肉组织中 AKT 的磷酸化水平相比正常小鼠是下降的 [104]。降低 AKT 的活性能够减少 GLUT4 的移位、增加糖异生基因的表达、引起胰岛素抵抗 [104–106]。Xia 等研究显示，对于 IR，腺苷相比于 ATP 有可能是一个更好的配体 [103]。由于高浓度的腺苷与 ATP 竞争 IR 酪氨酸激酶的 ATP 结合位点，削弱了 IR 的自磷酸化水平，从而抑制了 IR 酪氨酸激酶的活性，导致胰岛素信号传递阻滞，最终降低了胰岛素引起的 AKT 磷酸化水平 [103]。在这一过程中，高浓度的腺苷起到了关键作用。而在细胞内，高浓度的腺苷通过与 ATP 的竞争，不仅仅影响了 IR 酪氨酸激酶活性，也有可能影响其他激酶甚至有可能包括 AKT 的活性。这个猜想目前并没有得到研究证实，为了证明腺苷的这种生理病理作用，关于腺苷和蛋白磷酸化的关系需要进一步的研究。

3.3.2 细胞的酸碱环境

细胞内的 pH 调控对于很多的生理过程有重要意义，例如细胞容积的调控、囊泡的转运、细胞代谢、细胞膜的极化、肌肉收缩以及细胞骨架的相互作用 [107–111]。而一些生长刺激因子，例如表皮生长因子、血小板源生长因子、胰岛素和抗利尿激素等刺激 Na^+-H^+ 交换体，都会引起胞内 pH 上升，这对于细

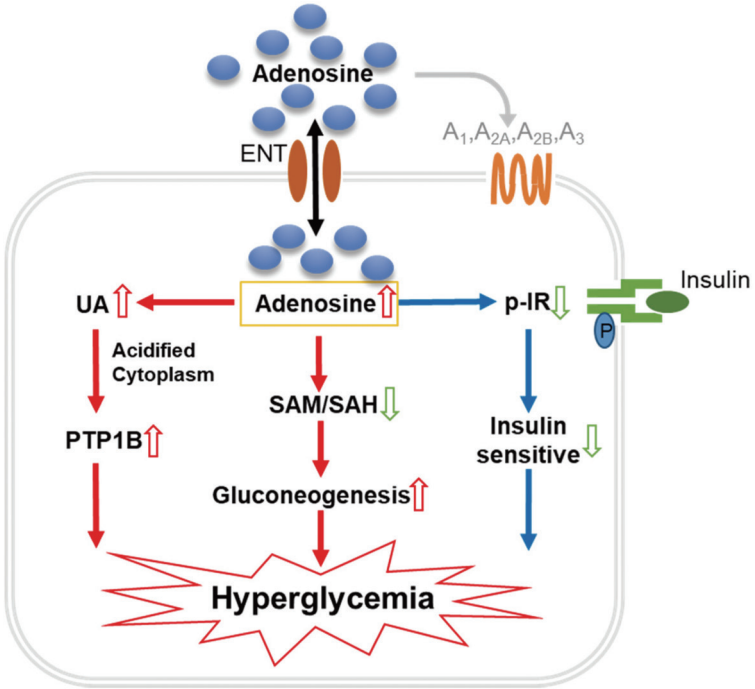

图 2. 腺苷独立于嘌呤受体通路的三种作用通路

Fig. 2. Three functions pathways of adenosine independent of adenosine receptors. The adenosine enters the target cell and triggers three pathways independent of adenosine receptors. Cellular adenosine directly causes cytoplasmic acidification and activates the insulin negative regulatory pathway of PTP1B; adenosine reduces the ratio of S-adenosyl methionine (SAM) to S adenosine homocysteine (SAH) and influences methylation at different levels; adenosine significantly attenuates the insulin-stimulated insulin receptor (IR) autophosphorylation in the liver. These efforts have led to hyperglycemia. UA, uric acid; ENT, equilibrative nucleoside transporter.

胞的激活，生长以及增殖有重要意义[112–116]。胞内pH的变化也可以通过调节酶的活性影响生理活动。腺嘌呤核苷酸代谢产物次黄嘌呤、黄嘌呤以及尿酸能抑制Na^+/K^+-ATPase的活性，引起肝脏胞内ATP的累积[35]。胞内ATP的升高引起了体系pH的下降[35]。降低胞内pH，促使PTP1B活性的上升，抑制胰岛素敏感性，导致血糖的快速上升[35]。这种作用依赖于ENT对腺苷的转运[35]。

3.3.3 甲基化

外源AMP导致肝脏腺苷水平呈剂量依赖性升高[117]。腺苷一方面通过ADK与ADA代谢为AMP和次黄嘌呤核苷，另一方面，可能通过SAH水解酶的可逆反应生成SAH。SAH是所有甲基化反应的有力抑制剂，而细胞内的SAM/SAH比值被认为是细胞甲基化潜能的重要标志[118]。S-腺苷甲硫氨酸(S-adenosyl methionine, SAM)和SAH的浓度与糖尿病有关[119, 120]。在糖尿病患者中，SAM浓度降低，SAM/SAH比值降低[119]。与非糖尿病患者相比，T2D患者的红细胞或血浆SAH浓度也显著增加[121]。除此之外，Cuyas等发现抗糖尿病药物二甲双胍可通过调节SAM/SAH比值来提高甲基化能力[122]。表观遗传修饰，包括DNA、RNA以及组蛋白甲基化，已被确定为环境与基因组相互作用的一种机制。有证据表明，DNA甲基化的改变可能导致T1D和T2D发病率的增加[123]。Shen等研究显示，RNA m6A甲基化改变与T2D相关[124]。T2D患者和糖尿病大鼠的RNA甲基化水平显著降低[124]。T2D患者脂肪量与肥胖相关(fat mass and obesity associated, FTO)基因的mRNA表达水平明显升高，而FTO的RNA甲基化水平与表达变化相反[124]。在*db/db*小鼠和HFD喂养的小鼠肝脏中，H3组蛋白赖氨酸9甲基化的水平显著降低[125]。H3K9甲基化水平降低与糖尿病并发症相关[126]。研究显示，腺苷降低甲基化潜力，减少了组蛋白H3组蛋白赖氨酸9甲基化，促进糖异生相关基因叉头框蛋白O1、磷酸烯醇丙酮酸羧化激酶和葡萄糖-6-磷酸酶表达，提高糖异生水平[127]。SAM是多种甲基转移酶的甲基供体底物，而SAH是所有甲基化反应的强力抑制剂。腺

苷通过改变 SAM/SAH 比值对 DNA、RNA 和组蛋白甲基化产生潜在影响，从而影响糖尿病的发展。

4 高血糖形成因素与腺嘌呤核苷酸代谢的联系

目前认为炎症、氧化损伤及应激是高血糖产生的三个主要因素，但是均不足以解释所有问题。我们认为异常腺嘌呤核苷酸代谢才是高血糖产生最直接的影响因素。在此总结炎症、氧化损伤、应激这些公认的高血糖产生因素与异常上升的腺嘌呤核苷酸代谢物的联系。如图 3 所示，炎症、氧化损伤、应激均导致腺嘌呤核苷酸代谢产物增加，从而引起胰岛素敏感性下降，最终导致高血糖产生。

4.1 腺嘌呤核苷酸代谢、免疫以及高血糖三者之间的关联

4.1.1 高血糖和免疫

T1D 和 T2D 本质上是慢性炎症，都涉及胰岛炎症，而全身低级别炎症是肥胖和 T2D 的特征。目前认为先天免疫系统的长期激活会损害胰岛素的分泌和作用，炎症也会导致糖尿病的大血管和微血管并发症。与 T1D 不同，慢性低度炎症过程在代谢综合征、肥胖引起的胰岛素抵抗和 T2D 的发病机理中起着更重要的作用 [128]。虽然炎症与胰岛素抵抗和 T2D 相关性被很多研究所证实，炎症相关的信号通路可以调控胰岛素信号，但这些研究结果仍有一些矛盾。TLR4 的敲除只能部分改善肥胖诱导的胰岛素抵抗；在 TNF 受体敲除的 *ob/ob* 肥胖模型小鼠中，Uysal 等同样只观察到了胰岛素抵抗的部分改善 [129]；而 IL-6 基因敲除小鼠在高脂喂养状况下同样表现出胰岛素抵抗 [130]。另外，许多 T2D 患者也并没有表现出明显的炎症反应 [131]。对 T2D 患者使用肿瘤坏死因子 -α (tumor necrosis factor-α, TNF-α) 抗体也不能明显改善高血糖或提高胰岛素敏感性 [132–134]。目前还没有针对先天免疫介质的糖尿病治疗方法获得批准。以上这些都对炎症是糖尿病最直接源头的观点提出了质疑。

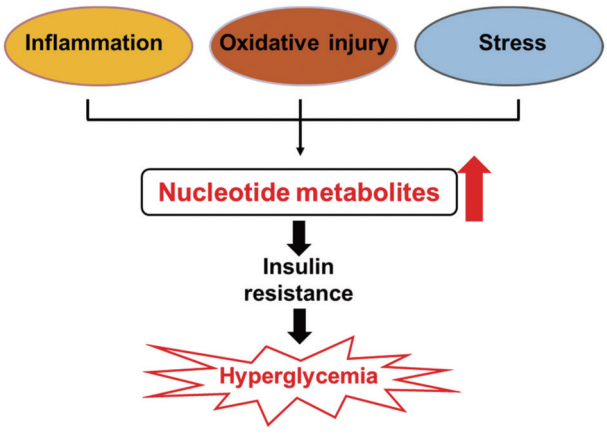

图 3. 异常核苷酸代谢在高血糖形成过程的影响

Fig. 3. The influence of abnormal nucleotide metabolism on the formation of hyperglycemia. Inflammation, oxidative injury and stress increase levels of nucleotide metabolites. Abnormal nucleotide metabolism triggers a loss of insulin sensitivity, leading to hyperglycemia.

4.1.2 异常的腺嘌呤核苷酸代谢介导免疫反应

在 T2D 患者中，P2X7 与炎性介质 (例如 C 反应蛋白、TNF-α 和 IL-1β) 的增加，以及 IL-10 的降低有关 [135]。此外，在代谢紊乱的患者以及循环中低密度脂蛋白 (low density lipoprotein, LDL) 升高的患者身上提取的巨噬细胞、T 细胞和 B 细胞中，P2X7 表达上调 [40]。炎症部位受伤的细胞可被动释放足以激活 P2X7 受体的 ATP。有报道称，不同受体识别模式的激动剂触发人单核细胞内源性 ATP 释放，刺激 P2X7 受体 [136]。在糖尿病的发展过程中，炎症可能先导致腺嘌呤核苷酸的异常代谢，然后影响糖代谢 (图 3)。腺苷及其受体参与调节 T1D 中 β 细胞和免疫细胞之间的相互作用。在 HFD 处理过的 $A_{2B}^{-/-}$ 小鼠脂肪组织，TNF-α 和单核细胞趋化蛋白 -1 (monocyte chemotactic protein 1, MCP-1) 的水平显著提高。经典活化巨噬细胞具有促炎作用，并促进肥胖症诱导的胰岛素抵抗的发展，而选择性活化巨噬细胞的促炎能力较弱，并且可以对抗胰岛素抵抗 [137]。体外研究表明，A_{2B} 受体对选择性活化巨噬细胞激活有刺激作用 [138, 139]。此外，在 A_{2B} 受体基因敲除小鼠脂肪组织的基质血管成分中，选择性活化巨噬细胞的标记物水平降低 [138]。Figler 等研究显示，激活 A_{2B} 受体后，糖尿病小鼠巨噬细胞和内皮细胞中 IL-6 的产生增加，并且 T2D 患者 A_{2B} 受体基因 SNP 与炎症标志物 (如 IL-6 和 CRP) 显著相关 [140]。在体外，用伴刀豆球蛋白 A (Con A) 激活并随后用选择性 A_{2A} 激动剂 (GS21680) 处理来自患者和健康受试者的外周血单核细胞，结果降低了 T2D 患者中的 $CD8^+$ T 细胞和总淋巴细胞中的凋亡比例 [55]。Ghaemi Oskouie 等研究显示，NOD 小鼠的树突状细胞表达高水平的 ADA[141]。相反，NOD $ADA^{-/-}$ 小鼠树突状细胞无法有效触发自身免疫性糖尿病，提示 ADA 在树突状细胞介导的 T 细胞活化中的重要

作用 [141]。

4.2 氧化应激、高血糖以及腺嘌呤核苷酸代谢

高血糖可上调慢性炎症标志物，并导致 ROS 生成增加，最终导致血管功能障碍。相反，氧化应激和炎症的增加会导致胰岛素抵抗和胰岛素分泌受损。氧化应激导致肌肉和脂肪细胞葡萄糖摄取受损，减少细胞胰岛素分泌 [142, 143]。Furukawa 等研究显示，NADPH 氧化酶抑制剂可降低全身氧化应激，改善小鼠葡萄糖代谢 [144]。Meigs 等研究显示，胰岛素抵抗患病率和氧化应激标记物尿 8- 异构前列腺素 F2α (8-epi-PGF2α) 的浓度之间存在正相关关系 [145]。这些结果表明，在非糖尿病患者和糖尿病风险高的亚群 (如肥胖或空腹血糖受损) 中，胰岛素抵抗与氧化应激有关。

但是大多数抗氧化剂并不能逆转糖尿病引起的高血糖，这些药物只能作为胰岛素治疗的佐剂 [146]。例如，酶 Q10 是一种内源性脂溶性抗氧化剂，可以改善糖尿病引起的氧化应激变化，但是不能改善糖尿病大鼠的血糖 [147]。槲皮素是一种生物类黄酮，可直接清除自由基，抑制生物分子氧化，改变体内外的抗氧化途径 [148]。但槲皮素治疗后糖尿病大鼠血糖升高，症状反而加重 [149]。牛磺酸有抗氧化性能 [150]。膳食添加牛磺酸可以改善糖尿病前白内障晶状体的丙二醛水平、GSSG/GSH 和 NAD^+/NADH 比值，但不能改善葡萄糖利用和降低 ATP 水平 [151]。这些证据表明氧化应激虽然和糖脂代谢相关，但可能并不是糖尿病的发病机制。研究表明，异常核苷酸代谢发生和氧化应激有关。在 ROS 存在的情况下，由于外核苷酶活性降低，细胞外核苷酸延迟分解代谢 [152]。严重的氧化应激可以降低细胞内的 ATP 水平 [152, 153]。在 HLMVEC 和胎儿肺成纤维细胞中，低氧处理也会诱导 ATP 释放 [154, 155]。用 FFA 处理胰岛细胞后，细胞内 ROS、脂质过氧化产物丙二醛和一氧化氮水平显著升高，ATP/ADP 比值也改变 [156]。

4.3 应激高血糖与腺嘌呤核苷酸代谢的联系

应激高血糖是公认的正常代谢应激反应 [157]。应激高血糖与多种疾病有关，包括心肌梗死 [158–160]、卒中 [161, 162] 和创伤 [163–165]。目前认为这种急速血糖上升现象的产生与激素上升有关。但是在细胞受损 (炎症、缺氧、急性损伤) 的条件下，ATP 从细胞快速释放到胞外，造成胞外 ATP、ADP 或 AMP 以及水解产生的腺苷水平急速上升 [166]。在细胞快速死亡与再生的组织中，如慢性炎症和肿瘤，大量细胞的应激与凋亡导致胞外 ATP 和腺苷长期升高 [167]。应激性高血糖的产生，往往伴随着高浓度的胞外腺嘌呤核苷酸，结合文献中报道的高浓度腺嘌呤核苷酸处理能提高正常小鼠血糖的现象 [29]，我们推测应激性高血糖也有可能是由于胞外腺嘌呤核苷酸增多造成的。

5 糖尿病药物的治疗机制与腺嘌呤核苷酸代谢的联系

5.1 二甲双胍与腺嘌呤核苷酸代谢

多年来，二甲双胍一直是糖尿病的主要治疗药物 [168]。二甲双胍被认为通过抑制肝葡萄糖生成而发挥其主要的抗糖尿病作用。学者普遍认为二甲双胍通过调节 AMPK 作用而产生影响。二甲双胍抑制线粒体呼吸链复合物 1，通过 AMPK 影响能量代谢 [169]。尽管这一观点在缺乏肝 AMPK 的小鼠实验中受到了质疑 [170]，仅能解释肝胰岛素敏感性的变化 [169]。注射 AMP 不会提高细胞内 AMP 水平，反而导致细胞内 AMP/ATP 比值下降，从而降低活性形式的磷酸化 AMPK 水平 [29]。二甲双胍可以恢复 FFA 造成的胰岛细胞 ATP/ADP 比值失衡 [156]，提示二甲双胍可能通过调节核苷酸代谢来影响糖脂代谢。研究显示，二甲双胍通过影响果糖 -1,6- 二磷酸酶 (fructose-1,6-bisphosphatase 1, FBP1) 调节糖异生 [171]。FBP1 活性由变构抑制剂 AMP 和果糖 -2,6- 二磷酸协同调节 [171]。AMP 通过与独特的变构位点结合而非竞争性抑制，而果糖 -2,6- 二磷酸与果糖 -1,6- 二磷酸竞争结合至活性位点 [171]，提示二甲双胍可能通过调节 AMP 浓度作用 FBP1。最新的研究显示，二甲双胍可降低肝脏 ATP 的含量，同时作为一个被细胞吸收而又不被分解的碱性物质，升高肝脏细胞的 pH，导致胰岛素信号传递的关键负调节因子 PTP1B 的肝脏活性降低，从而改善胰岛素抵抗 [35]。

5.2 格列本脲和DPP-4抑制剂与腺嘌呤核苷酸代谢

格列本脲是第二代磺脲类药物，在 T2D 的治疗中可以通过提高胰岛素的分泌和胰岛素敏感性来控制血糖 [172, 173]。一般认为，促进胰岛素的分泌是格列本脲的主要作用 [174]，而提高胰岛素敏感性的作用是通过代谢的调控或直接作用于外周器官 [175]。格列本脲是 ATP 敏感性钾离子通道，可抑制钾离子的外流引起细胞膜的去极化和钙离子的内流，从而增加胰岛素的分泌 [176, 177]。同时，格列本脲被发

现是囊性纤维化跨膜传导调节因子 (cystic fibrosis transmembrane conductance regulator, CFTR) 和体积调节性阴离子通道 (volume regulated anion channel, VRAC) 的抑制剂 [178, 179]。CFTR 和 VRAC 同时也是细胞向胞外释放 ATP 的重要通道。研究显示，格列本脲可以抑制 CFTR 和 VRAC，从而抑制油酸引起的腺嘌呤核苷酸释放 [30]，提示格列本脲的作用可能部分来自对胞外嘌呤核苷酸浓度的降低。另一个药物 DPP-4 抑制剂于 2006 年被引入治疗 T2D[180]。DPP-4 又称腺苷脱氨酶结合蛋白 (adenosine deaminase binding protein, CD26)，是一种多功能的细胞表面糖蛋白，可与 ADA 相互作用，在血浆中循环 [181, 182]。高 ADA 活性在胰岛素敏感组织降低腺苷水平，增加细胞葡萄糖摄取 [183]。DPP-4 结合 ADA 已被证明可改变细胞外腺苷浓度，DPP-4 抑制剂通过阻止 DPP-4 和 ADA 的双分子配合物的形成提高腺苷水平 [184]。我们猜想 DPP-4 抑制剂可能作用于 ADA，发挥了调节胞外腺嘌呤核苷酸的作用。

6 结论

腺嘌呤核苷酸及其代谢产物在糖脂代谢调节中起到关键的作用。积累的证据已经指出脂代谢紊乱可能首先导致腺嘌呤核苷酸代谢异常，然后通过异常的腺嘌呤核苷酸信号引起糖代谢紊乱。腺嘌呤核苷酸调控机制的阐明会加深我们对肥胖诱导胰岛素和高血糖的分子机制的认识，并为开发胰岛素抵抗及代谢相关疾病的药物提供新的靶点。

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