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• 文献综述 •

核酸的吸收与代谢

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摘 要

肠细胞刷状缘表面广泛存在着钠离子依赖性的核苷转运蛋白，证明人体可利用外源性核酸，超过90%的核苷和核苷酸被吸收入肠上皮细胞之后，被体内各器官广泛存在的各种亚型的核苷转运蛋白转运入组织和细胞内，转运过程中，也存在着核苷的合成和分解。大约2～5%的饮食核苷酸进入了组织中的核酸池参与体内核酸的合成，吸收入体内的核苷和核苷酸还可参与细胞内众多的生化反应。体内核苷核苷酸的分解代谢主要发生在肝脏，分解产物主要由肾脏排出体外。本文就百余年来人们对核酸的消化、吸收和代谢研究作一综述。

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0 引言

自1980年的大量研究表明，肠细胞刷状缘表面存在着钠离子依赖性的核苷转运蛋白[1]，证明人体可利用外源性核酸。本文就百余年来人们对核酸的消化、吸收和代谢的研究现状作一综述。

1 核酸在体内的消化

食物中的核蛋白在胃内被胃酸水解成为核酸和蛋白质，核酸在肠道内的胰核酸酶的作用下被降解为单核苷酸、双核苷酸、三核苷酸以及多核苷酸的混合物，其中核糖核酸酶和脱氧核糖核酸酶分别特异的水解RNA和DNA。肠道中的多核苷酸酶或磷酸脂酶可以增强胰核酸酶降解核酸为单核苷酸的活性，释放出的核苷酸继而可被碱性磷酸酶和核苷酸酶水解为核苷，并可进一步为核苷酶所降解而成为嘌呤或嘧啶碱基(图1)[2,3]。

2 核酸的吸收和转运

利用Caco-2培养细胞进行摄入放射性同位素标记的核苷实验表明：高分化(培养15 d)和低分化(培养6 d)的Caco-2细胞均可摄入有放射标记的核苷，其中高分化程度的细胞比低分化组的细胞摄入速率和摄入量高，且在培养的最初3 h内，摄入速率与时间呈线形关系[4]。Bronk *et al*[5]对离体的空肠弯曲部灌肠时发现，灌注尿苷和尿嘧啶后，绒膜中的尿嘧啶浓度有显著升高；灌注胸苷、胞苷和胞嘧啶时，也发现浆膜中胸腺嘧啶、胞苷浓度分别升高，证明灌注的核苷可以被肠上皮摄入吸收。啮乳动物细胞的核苷转运载体主要分为两类[6-12]：一类是Na^+非依赖性的核苷转运载体(Na^+-independent nucleoside transporters)，可被不同浓度的硝基苯甲基肌苷6硫醇(nitro benzyl thioinosine, NBMPR)所阻断，主要介导核苷的平衡运输(equilibrative transport)，即易化扩散(facilitated diffusion)；另一类则是Na^+依赖性的核苷转运载体(Na^+-dependent nucleoside transporters)，其特性主要表现为对Na+的依赖性及对NBMPR阻抑的不反应性，可以逆浓度梯度将核苷转运入细胞内，故又称主动运输。在小肠的各部分中，小肠上段的核苷吸收能力最强[13]。

根据对NBMPR的敏感性不同，又可将Na^+非依赖性的核苷转运载体分为"NBMPR敏感转运系统(equilibrative NBMPR-sensitive system, ES)"和"NBMPR不敏感转运系统(equilibrative-insensitive system, EI)"两类[14-19]。ES对nmol/L浓度的NBMPR即具有敏感性，而EI对浓度高达1 μmol/L的NBMPR仍不敏感。ES和EI两种转运系统都能以嘌呤或嘧啶核苷作为转运底物。ES系统在多种组织中均有表达，而EI系统只存在于小肠、白细胞、骨骼肌以及信血管组织细胞中[20-22]。对于人类和大鼠，ES和EI又分别被命名为hENT1, hENT2; rENT1, rENT2[23-29]。根据不同的转运底物，正常组织中的Na^+依赖性的核苷转运载体可被分为3种亚型[30-32]：Cif(selective for purine nucleosides and uridine)、Cit(selective for pyrimidine nucleosides and adenosine)和Cib(broadly specific for purine and pyrimidine nucleosides)，他们被统一归为CNT家族[33]。目前已经分别鉴定了编码这三个亚型载体蛋白的cDNA克隆：一个cDNA克隆是从大鼠的空肠组织中分离出来的，主要编码特异转运嘧啶核苷的核苷载体蛋白(concentrative nucleoside transporter)，该蛋白被命名为CNT1，属于cit亚型，刚被发现时只证实存在于空肠和肾脏中，现在已知大鼠脑中多个部位均有CNT1 mRNA的表达，并且利用反转录PCR技术从大鼠的肝脏中也分离出了与CNT1高度同源的mRNA，证实CNT1也存在于哺乳动物的肝脏中，人编码CNT1蛋白的基因定位于15号染色体长臂的2区[34-42]；另一个cDNA克隆编码蛋白CNT2最初是从大鼠的肝脏中被分离出来的，其编码的转运载体可转运嘌呤以及与嘌呤类似的核苷和尿苷，对嘌呤核苷的亲和力很高，可以归为cif亚型，由其所在的位置推测其功能可能在于保持肝细胞中核苷的浓度，使其不至于随胆汁而流失。已经证实大鼠体内的CNT2广泛存在于肝脏、空肠、脾脏、心脏和肌肉组织中，并且应用CNT2特异的引物对大鼠脑组织的mRNA进行反转录PCR扩增，证实CNT2如同CNT1一样，在脑的多个部位均有mRNA的表达；人类的CNT2广泛存在于心脏、肝脏、骨骼肌、肾脏、肠道、胰腺、胎盘、脑和肺脏中，其基因定位于人的15号染色体长臂1区[37,43-48]。对CNT2与CNT1进行的同源性分析表明，二者有64%的氨基酸序列同源，并且二者的结构非常相似，其主要不同的区域存在于N-和C-末端的结构域，在CNT2的N末端存在有供ATP/GTP结合的模块(motif)，而在CNT1则不存在，这两种载体蛋白在结构上的相似性证明他们同属于一个基因家族[43]。1992年Pajor *et al*[49]从兔肾脏中分离出了SNST1蛋白(Na^+/nucleoside cotransporter, SNST1)，他是一种可广泛转运嘌呤和嘧啶两种核苷的核苷载体，关于SNST1的转录产物只在肾脏和心脏中被观察到。但由于SNST1和CNT家族已发现的蛋白没有任何同源性序列，并且由于在肾脏和心脏中没有观察到cib类型的转运活性，因此Ritzel *et al*[31]推测SNST1可能不属于CNT家族。2001年Ritzel *et al*[30]为了寻找新的CNT家族成员，利用BLAST检索Genbank的EST库，获得了一个具有245个氨基酸开放阅读框的合成cDNA片段，既而应用5'-RACE技术

从分化的 HL-60 细胞中获得了一个新的具有 691 个氨基酸开放阅读框的全成 cDNA 序列，并且应用反转录 PCR 技术从分化的 HL-60 细胞和乳腺中获得了具有完整的编码序列的 cDNA，并将其编码的蛋白命名为 CNT3，人的 CNT3 与 CNT1 和 CNT2 相比，分别有 48 % 和 47 % 的同源性。经过基因重组证实，在非洲爪蟾卵母细胞中表达的人类 CNT3 蛋白可广泛转运嘌呤和嘧啶两种核苷，表明其应属于 cib 家族。多组织杂交分析表明人类的 CNT3 蛋白在乳腺、小肠、肝脏、胰腺、骨髓、气管、肺脏、胎盘、睾丸以及脑和心脏组织中均有表达，其编码基因定位于 9 号染色体长臂 2 区[30,31]。核苷的转运蛋白在不同的组织、细胞中的存在和表达如表 1 所示，他们在各自组织、细胞中的存在可能与吸收和重吸收核苷的功能有关。

表 1　核苷转运系统在各组织中的表达

系统分类	亚型	主要特征	表达此蛋白的组织
Na^+ 非依赖性核苷转运载体	ES	对 NBMPR 敏感	各组织均有表达
	EI	对 NBMPR 不敏感	小肠、白细胞、骨骼肌、心血管组织细胞
Na^+ 依赖性核苷转运载体	Cit	特异转运嘧啶核苷	空肠、肾脏、脑和肝脏
	Cif	特异转运嘌呤核苷	肝脏、肠道、脾脏、心脏、肾脏、胰腺、脑、胎盘、肺脏和骨骼肌
	Cib	广泛转运嘌呤和嘧啶两种核苷	乳腺、小肠、肝脏、胰腺、骨髓、气管、肺脏、胎盘、睾丸以及脑和心脏组织骨肌、心脏

有研究表明饮食核酸至少可促进上述转运载体的表达[51]。Leleiko *et al*[52] 对成年大鼠饲喂无嘌呤和无嘧啶的饮食可导致小肠和结肠中的总 RNA 和蛋白质的显著下降，这提示饮食核苷酸可能会影响肠道中编码酶相关基因的表达，表明饮食成分可能存在着某种调控体内蛋白质合成的机制。Valdes *et al*[53,54] 应用 Western Blot 方法测定了经过 48 h 禁食的大鼠空肠刷状缘中 CNT 表达情况及其活性，发现 CNT 类转运蛋白中，与嘧啶亲和力较强的 CNT1 对小肠内营养素的充足与否十分敏感，进一步应用无核酸饮食进行添加核苷酸和不添加核苷酸的分组饲养，发现核苷酸的充足与否可显著调节大鼠体内空肠中的核苷转运载体的数量，主要是 CNT1 的数量。目前，对动物的研究已经揭示，核苷是被吸收的主要形式[2,55]，超过 90 % 的核苷和碱基被吸收入肠道上皮细胞[56,57]。

3　吸收后核酸的分布、代谢及排泄

被吸收的核苷在从肠上皮细胞转运入血的过程中，也存在着核苷的合成和分解。如 Bronk *et al*[58] 在对大鼠空肠进行不同浓度的胸苷灌注时，注意到在浆膜中胸苷的浓度较低，取而代之的是胸腺嘧啶，并且尿嘧啶浓度升高；在灌注尿苷时也可观察到浆膜中尿嘧啶浓度的升高，表明在转运过程中存在对吸收了的核苷的分解和转化过程；在 Caco-2 细胞培养中发现在运输过程中，嘌呤核苷的代谢比较完全，并存在不同嘌呤核苷的互变现象，但在培养物中加入放射标记的胞嘧啶和尿嘧啶时，便可发现有嘧啶核苷被转运。大多数被转运的代谢产物都可较容易地参与补救合成而被重新利用[4]。饮食核苷酸的 2～5 % 进入了组织中的核酸池参与体内核酸的合成，这些组织主要是小肠、肝脏和骨骼肌[56,58]。Gross *et al*[59,60] 也证实口服碱基和核苷后，在代谢旺盛的组织中，其长的利用和储留增加且分解代谢下降，其原因主要与因于快速增生组织中黄嘌呤氧化酶活性下降[53]。于守洋 *et al*[61] 曾以碱基被同位素标记过的核酸食物饲喂实验动物，2～4 h 后测定不同组织器官中放射性同位素的含量，结果表明 RNA 和 DNA 在 4 h 内全部被吸收，8 h 后有约 40 % 经呼吸和尿液排泄，余者在体内的分布为：胃肠道占近 50 %，骨骼肌占约 40 %（图 2），DNA 的 70 % 以二氧化碳的形式由呼吸排出，其余的分布于胃肠道、骨骼、肝脏、脾脏、肾脏、心脏、肺脏和睾丸等组织细胞中。

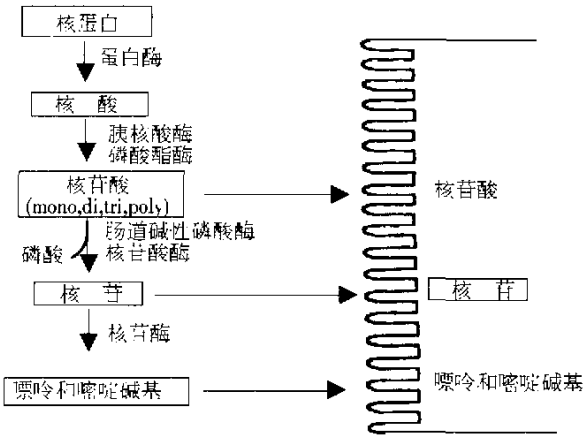

图 1　膳食核酸的消化和吸收以及相关产物

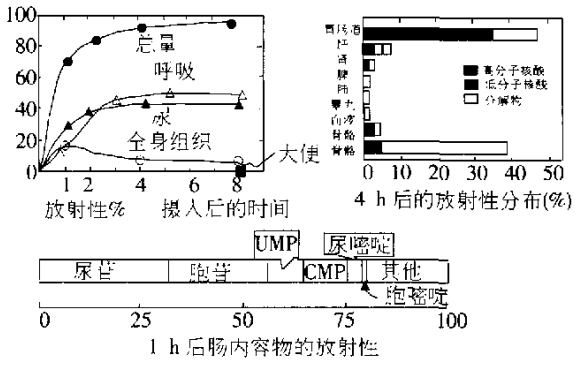

图 2　标记过的 RNA 经口摄入后的体内分布

对Wistar大鼠进行的实验表明，无核苷酸饮食组的大鼠1 wk后肝脏中的ATP、ADP、GTP、GDP以及RNA的浓度均显著下降，表明膳食核苷酸至少部分的被肝脏利用来维持细胞中的核苷酸池，无核酸饮食影响了肝中的核苷酸代谢和RNA合成，肝中的核苷酸代谢可受膳食中的核苷酸所调节[62]。机体内源性合成核苷的主要部位是肝脏，肝脏核酸补救合成酶活性较高，底物足够时，主要通过补救途径合成核酸[63,64]。摄入外源性核酸，可增加补救途径核酸生成量并反馈抑制从头合成途径而起节能作用并减轻肝脏的负担。体内核苷酸的从头合成与补救合成的关系如图3所示，存在着一个反馈调节的机制[65]。

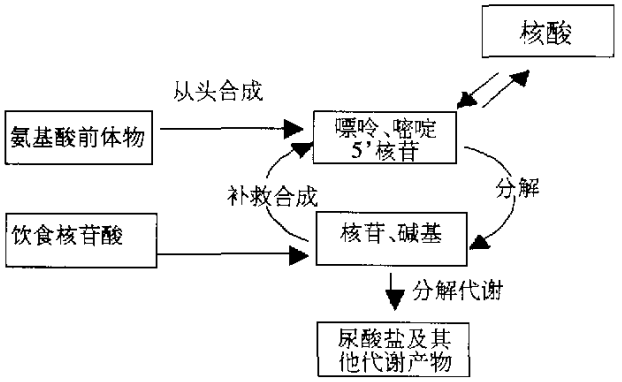

图3 体内核苷酸的从头合成与补救合成关系

吸收入体内的核苷和核苷酸参与了众多的细胞内的生化反应，如作为核酸合成的前体物质[62]，作为能量载体分子参与高能反应以及脂类、糖类和蛋白质的合成，同时也作为多种反应的辅酶，如NAD和FAD。体内嘌呤核苷酸的分解代谢主要在肝脏、小肠及肾脏中进行，黄嘌呤氧化酶在这些脏器中的活性较强，嘌呤碱在体内经过一系列转化最终变成黄嘌呤，在黄嘌呤氧化酶的作用下生成尿酸；嘧啶碱的降解主要在肝脏中进行，胸腺嘧啶降解成β-氨基异丁酸，而胞嘧啶最终生成NH_3、CO_2及β-丙氨酸，可直接随尿排出或进一步分解[3]。此外，研究发现在小肠中嘌呤和嘧啶的分解酶要优于合成酶，并且在消化道的近端其嘌呤分解酶的水平更高[66]，这在人体内是除了肾脏排泄尿酸的另一条途径。取自人结肠癌细胞的Caco-2(human colon carcinoma cell lines, Caco-2)在培养物中达到融汇状态时仍可自发地进行分化，因此经常被作为研究肠道分化、转运功能的体外模型[67,68]。在正常培养条件下，加入核苷酸补充物并没有显著影响Caco-2细胞的生长，但当在无谷氨酰胺或去除谷氨酰胺和非必需氨基酸(non-essential amino acid, NEAA)的培养基中生长时，加入核苷酸混合物(AMP、CMP、GMP、IMP和UMP各10 mg/L的等量混合物)时，则会抑制细胞死亡，并促进Caco-2细胞的生长；而对于正常细胞系IEC-6(normal rat intestinal epithelial crypt cells)在正常的培养条件下，加入核苷酸混合物便会使细胞数量显著增加，表明核苷酸补充物可改变人和大鼠肠上皮培养细胞的增生和分化状态[69,70]。

总之，饮食中补充核苷酸可被人体吸收利用，并且对于骨髓细胞、白细胞、小肠上皮细胞这些核酸从头合成能力非常弱的组织来说，其意义更为重要。此外，开展对核苷酸吸收代谢的研究也对药理学研究，如对抗肿瘤药物等核酸类似物作用机制的探讨也提供了非常有意义的参考。

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