·综 述·

小分子，大作为：酮体 D-β 羟基丁酸在医疗领域的应用与展望

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摘 要：人体两大供能模式主要是通过碳水化合物代谢或脂肪代谢。日常饮食下，身体会优先选择葡萄糖作为主要的能量来源。但近年来，科学家们发现在限制碳水化合物供给的条件下可以促进机体的脂肪代谢，该饮食模式可能会成为一种改善人类健康的全新的方式。其中，间歇性进食、生酮饮食等受到了广泛的关注，特别是在运动减肥、代谢疾病、脑部健康以及预防心血管疾病方面的效果十分明显。脂肪代谢中最为关键的产物是 D-β-羟基丁酸(酮体，D3HB)，是组成微生物内聚物聚-D-β-羟基丁酸(PHB)的单体。D3HB 是一个能够在不同细胞与组织器官中起到供能与保护作用的小分子物质。然而，仅靠饮食促发的营养性酮症会带来一定的副作用且需要经过非常长的适应期(3 个月以上)，因此，外源性 D3HB 酮体的补充逐渐成为一种更加新颖、便捷的方式，用于帮助人体快速进入营养性酮症并激发相应的功能作用。文中详细阐述了人体产生 D3HB 的过程与其代谢路径、D3HB 在人体内的作用效果以及外源性 D3HB 酮体在近年来的应用研究进展。

关键词：D-β-羟基丁酸；D3HB；PHB；酮体代谢；营养性酮症；外源性酮体；生物合成

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Applications and perspectives of ketone body D-β-hydroxybutyrate in the medical fields

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Abstract: Human body can obtain energy from either carbohydrate or fat digestion. Although glucose metabolism derived from carbohydrate-based diets has long been utilized for energy supply, it has been recently discovered that shifting from glucose to fatty acid metabolism may become a novel way for improving human health especially when carbohydrate is deprived. In recent years, intermittent fasting and ketogenic diets have received a lot of attention in respect to favoring fatty acid metabolism. In all cases, fatty acid metabolism produces D-β-hydroxybutyrate (D3HB), which is a natural ketone body, as well as, a monomer of microbial poly-D-β-hydroxybutyrate (PHB). D3HB can be utilized by different cells of the body as an alternative energy fuel or an intracellular signaling molecule with multiple downstream signaling pathways. Usually, the serum level of D3HB is increased during ketogenic diets, however, requires a very long period of adaptation (over 3-months) and exhibits unwanted adverse effects. Hence, exogenous ketone supplements using D3HB have become a more effective approach to induce and maintain nutritional ketosis for subsequent functional effects. This review describes how D3HB is produced and metabolized within the body, the functional roles played by D3HB, and a detailed summary of the different applications of exogenous ketones that have been explored to date in both nutritional and therapeutical context.

Keywords: D-β-hydroxybutyrate; D3HB; PHB; ketone metabolism; nutritional ketosis; exogenous ketones; biosynthesis

在日常饮食中，给人体提供能量的物质主要为碳水化合物和脂肪两大营养元素，绝大部分人都会通过碳水化合物代谢产生的葡萄糖为身体提供能量。当碳水化合物不足时[1]，身体才会更多地分解脂肪从而持续为身体供能。然而，近年来科学家们发现通过间歇性进食[2]、限时饮食[3]或生酮饮食[4]等方式能够使人体的代谢模式由葡萄糖代谢转化为脂肪代谢，这类饮食方式不仅能够长时间为身体供能，甚至可以改善人类健康。

1 生酮概述

人体在长时间禁食、剧烈运动或特定饮食条件下会通过分解脂肪而产生酮体。脂肪酸在

肝脏细胞中进行 β 氧化形成乙酰辅酶 A (acetyl CoA)，乙酰辅酶 A 在 β-羟基-β-甲基戊二酰辅酶 A 合成酶 (3-hydroxy-3-methylglutaryl CoA synthase, HMGCS2) 的催化下形成乙酰乙酸，乙酰乙酸通过 β-羟基丁酸脱氢酶(β-hydroxybutyrate dehydrogenase, BDH1) 进一步形成 3-羟基丁酸 (D3HB)。肝脏细胞中产生的 D3HB 通过自由扩散的方式或细胞内膜上的单羧酸转运蛋白 (monocarboxylate transporter, MCT) 进入血液。血液中的 D3HB 被肝外组织上的 MCT 再次转运到细胞质中，随后在细胞线粒体内 BDH1 的催化下逆向转化为乙酰乙酸。乙酰乙酸在酮脂酰辅酶 A 转移酶 (succinyl-CoA: 3-ketoacid coenzyme A transferase, OXCT/SCOT) 催化下形成乙酰乙酰辅酶 A，又经过乙酰辅酶 A 疏解酶形成乙酰辅酶 A。随即，乙酰辅酶 A 进入三羧酸循环 (tricarboxylic acid cycle, TCA) 被进一步代谢生成 ATP (adenosine triphosphate) (图 1)[5]。

人体内产生的酮体包括 D3HB、乙酰乙酸和少量丙酮，其中 D3HB 在血液中的含量可占 70%以上[6]。D3HB 是一个具有高水溶性的小分子物质，能够快速穿过血脑屏障和毛细血管壁，抵达组织及器官并发挥功能。在正常饮食条件下，人体血液中的 D3HB 水平不超过 0.5 mmol/L，但在长时间饥饿条件下，血液中的 D3HB 可升至

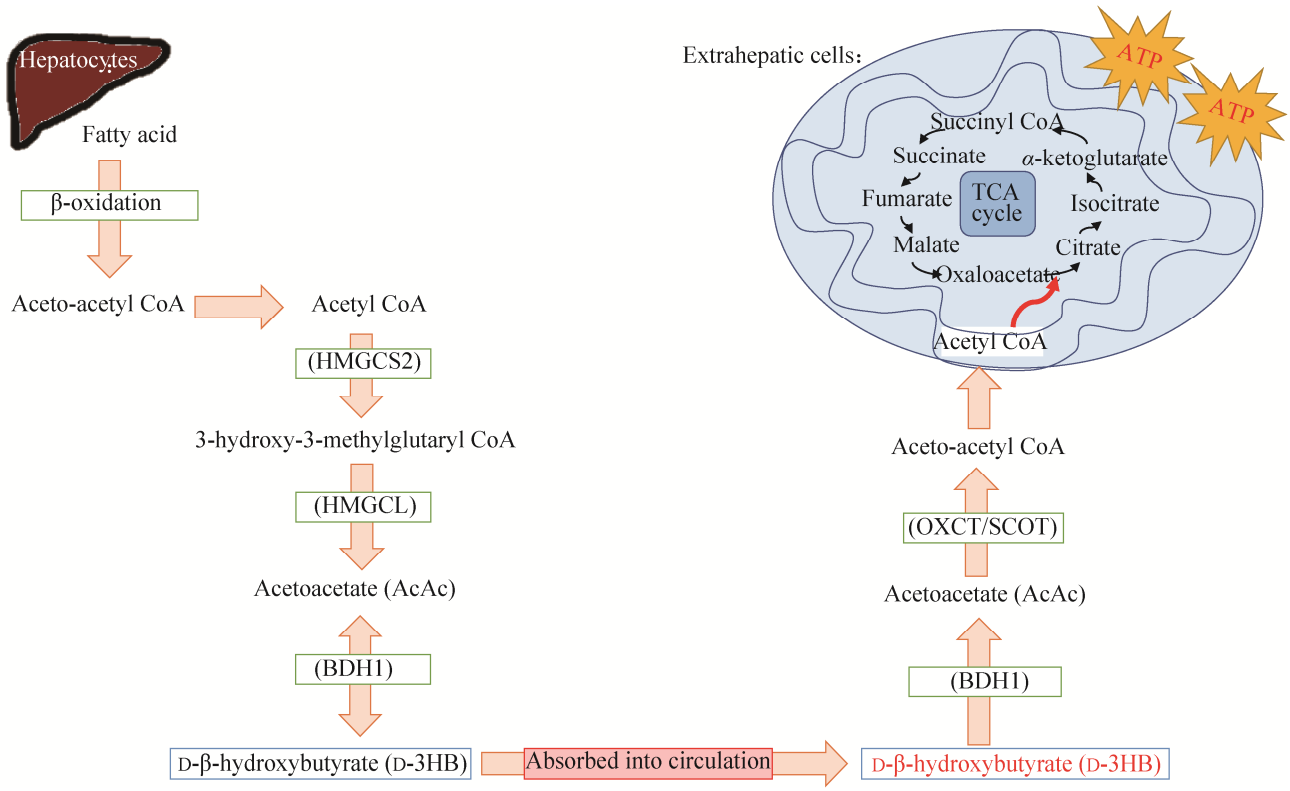

图 1　人体内源性 D3HB 的产生及代谢路径　D3HB 在肝脏细胞中通过脂肪酸的分解而产生，随后进入血液并被运输到肝外组织，在细胞线粒体内经代谢产生 ATP

Figure 1　Endogenous production and metabolism of D3HB. HMGCS2: 3-hydroxy-3-methylglutaryl CoA synthase 2; HMGCL: 3-hydroxy-3-methylglutaryl CoA lyase; BDH1: β-hydroxybutyrate dehydrogenase; OXCT/SCOT: succinyl-CoA: 3-ketoacid coenzyme A transferase; TCA: tricarboxylic acid.

4–6 mmol/L，甚至 10 mmol/L[7-8]。

近年来，生酮饮食逐渐成为一种能够帮助人们提高血清中 D3HB 水平的特殊膳食结构，并且在运动员[9]、健身人群[10]、军队[11]等群体中备受欢迎。生酮饮食主要是以一种高脂肪、低碳水的饮食结构来诱导肝脏优先代谢脂肪，并通过产生大量的 D3HB 为机体供能的饮食方式 (图 2)。研究显示，D3HB 在人体肌肉组织[12]、心脏[13]、肾脏[14]、脑部神经元[15]与神经胶质细胞[16]中的吸收利用尤为活跃 (图 3)。因此，许多科学家和医生们已经开始探索人体内源性 D3HB 可能会给不同代谢性与年龄相关性疾病带来的治疗作用[17-18]，同时还可帮助运动员、军队等提高运动能力以实现更加高效的训练[19]。

2 D3HB 在人体内的功能作用

事实上，酮体在很多年前已被用于复发性小儿癫痫疾病的治疗[20-21]。时至今日，人们发

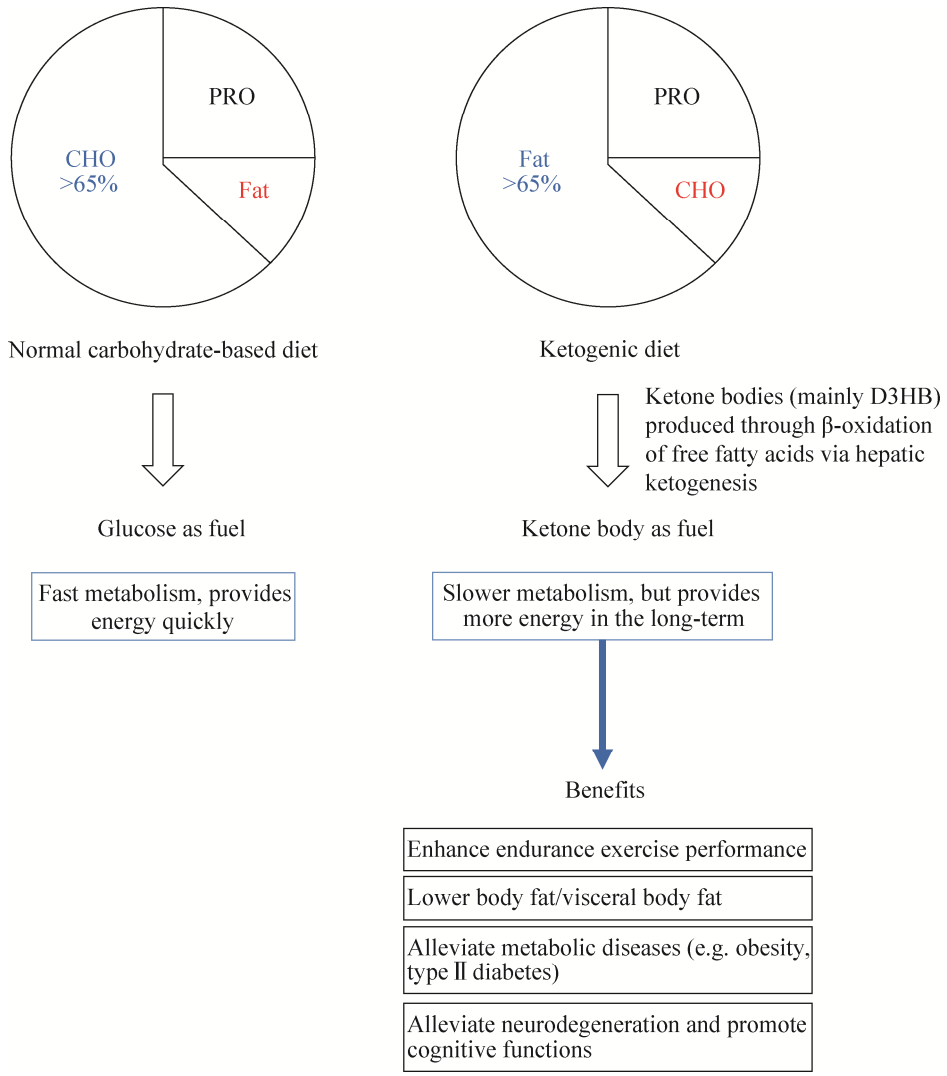

图 2　碳水和生酮饮食在供能模式上的差异(葡萄糖 vs D3HB 供能)以及酮体代谢对机体的优点

Figure 2　Carbohydrate-based & ketogenic diet in terms of energy metabolism and advantages of ketone metabolism. CHO: carbohydrate; PRO: protein.

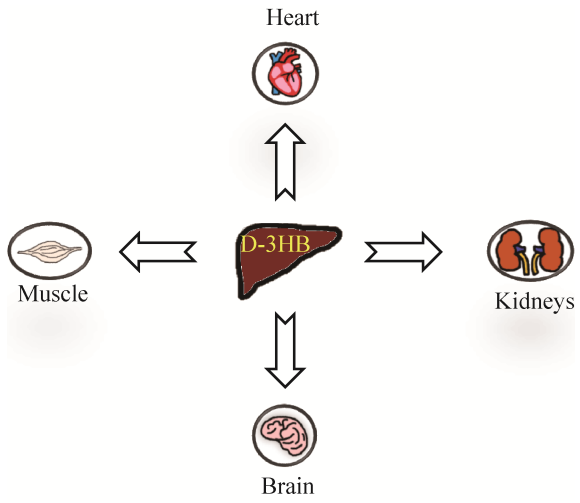

图 3 D3HB 在人体内的主要作用器官

Figure 3 Major downstream target organs of D3HB.

现 D3HB 在人体内的作用远远不仅限于此。在血清中 D3HB 含量被提高的状态下，人体会以酮体代谢供能为主并进入营养性酮症状态 (nutritional ketosis, NK)，即血清 D3HB 水平大于 0.5 mmol/L[22]。研究发现，D3HB 能够带来诸多好处，其中包括：提高运动耐力表现[23]、改善身体组成成分[24]、降低有害低密度胆固醇[25]、调节代谢相关的荷尔蒙[26]、控制食欲[27]和维持肠道健康[28]。在喂食生酮饮食的小鼠中发现其升高的 D3HB 水平对老年性肌肉萎缩起到了抑制作用[29]。

近期的研究中发现，D3HB 还可以作为小信号分子抑制细胞内的组蛋白去乙酰基酶 (histone deacetylase, HDAC) 并调控下游基因[30]、抑制细胞中的 Nod-like receptor pyrin-domain containing 3 (NLRP3) 炎性小体引发抗炎和抗癌等作用[31-33]、激活 G 蛋白偶联受体 109A (G-protein-coupled receptor, GPCR109A) 从而改善动脉粥样硬化[34]。最新研究显示，D3HB 除了作为 HDAC 抑制剂调控基因表达外，还能够直接对蛋白起到修饰作用[35]，其中最主要的修饰作用是在组蛋白赖氨酸位置 (histone 3 lysine 9 or 14, H3K9 or H3K14) 上的 β-羟基丁酰化 (β-hydroxybutyrylation, Kbhb) 修饰作用[36]。Wu 等[37]发现在 H3K9 的 β-羟基丁酰化修饰后成功抑制了糖尿病小鼠的血管内壁损伤。

2.1 运动领域

大量的研究已经证明人体在 NK 状态下能够更有效地减重和减脂，尤其以内脏脂肪的降低为主要表现形式[38]。同时，D3HB 能够很好地被骨骼肌利用并提高骨骼肌线粒体的供能效率[12]。Vargas 等[24]证明男性运动员在为期 8 周的生酮饮食中达到了很好的减重减脂的效果，并维持了良好的抗阻力运动能力。Chang 等[23]发现在长时间有氧运动中，长跑运动员的最高脂肪氧化速率可达到 1.5 g/min。总之，内源性 D3HB 水平的升高能够在运动中减少人体对糖原的利用，更多地消耗脂肪来维持运动表现；并且，在运动中储存的糖原与 D3HB 结合有利于运动后的肌肉恢复[39]。

2.2 肥胖症及代谢性疾病

肥胖症是一种极为普遍且复杂的代谢病症，并容易引发其他继发性疾病。根据世界卫生组织的最新数据，全球在 2016 年有超过 19 亿成年人的体重属于超重范围 (body mass index, BMI > 25)，其中有大约 6.5 亿人属于肥胖症 (BMI > 30)[40]。严重的患者往往需要去医院接受系统的治疗以避免危及健康。随着 D3HB 的研究进展越来越多，许多课题组陆续发现 D3HB 可以帮助肥胖人群达到更好的减重减脂效果，其作用机制一方面在于其能调节体内代谢相关的荷尔蒙 (胃饥饿素、瘦素、胰淀素、肠抑胃肽)，从而提升饱腹感、帮助控制食欲[26-27]；另一方面 D3HB 在降低有害低密度胆固醇、增加高密度胆固醇上的功效[25,41]，使肥胖人群的血脂指标更加健康。

再者，研究发现 D3HB 可以激活肥胖小鼠体内的褐色脂肪组织 (brown adipose tissue,

BAT) 从而提高肥胖小鼠的基础代谢，促进能量消耗[42]。美国国立卫生研究院的 Veech 教授曾在喂食生酮饮食的小鼠中证明了小鼠 BAT 中的线粒体蛋白 (mitochondrial uncoupling protein, UCP1) 表达明显增高，继而增加了 BAT 线粒体氧化磷酸化以及生热反应[43]。与之相似，人体内同样含有大量能够帮助人体调节能量代谢、维持体温及能量平衡的 BAT[44]。因此，D3HB 在 BAT 上的作用可能会为预防与治疗肥胖症带来新的可能。

2.3 肠道健康

近年来，部分课题组发现 D3HB 能够辅助肠道细胞分化[45]、改善肠道菌群[46]、促进肠道干细胞自主更新从而维持肠道平衡[28]。Wang 等[45]还发现当肝脏中促进 D3HB 生成的限速酶 (HMGCS2) 表达增高时同样可以促肠道细胞分化，反之则起抑制作用。此外，另一课题组发现生酮小鼠肠道内的双歧杆菌数量减少并降低了肠道内辅助 T 细胞 (helper T17 cells, Th17) 的数量，抑制促炎症因子的释放[46]。

3 提升内源性 D3HB 的困难

尽管饮食干预能够使人体进入营养性酮症，其适应期却是一个十分漫长且不容易坚持的过程。有研究发现，过于严格的生酮饮食也可能导致不良副作用[47-50]。因此，为了避免严苛的饮食干预同时帮助人体快速提升血清 D3HB 水平，外源性 D3HB 补充提供了一种更加便捷的方式给身体提供能量、提高线粒体供能效率、保护体内不同的细胞及器官并预防代谢性与神经变性疾病。

4 外源 D3HB 的不同存在形式及应用研究

外源性 D3HB 补充可分为酮盐 (KS)、酮酯 [(*R*)-hydroxybutyl-(*R*)-hydroxybutyrate (KME)、1,3-butanediol diacetoacetate (BD-$AcAc_2$) 或 bis hexanoyl-(*R*)-1,3-butanediol (BH-BD)] 、D3HB 前体 (1,3-丁二醇) 以及纯酸形式的 D3HB。目前，绝大部分是由化学合成法制造的[51-52]，其中也有少部分通过生物基制作 D3HB 的方法 (lab-scale)[53]。酮酯和 1,3-丁二醇都属于 D3HB 的前体，需要在体内降解后释放 D3HB[54]。

近年来全球已有大量的研究表明通过体外摄入 D3HB 盐或酯都能够引发不同的生理效应 (表 1)，例如：提高运动耐力[55]、帮助减肥[56]、促进运动后的肌肉修复[39,57-58]、预防或治疗脑部相关疾病[59-60]、代谢疾病[61]、心血管疾病[34,62-65]、慢性肾病[14,66]、抑制肿瘤细胞滋生[67-68]甚至减缓细胞衰老[69-71]。

4.1 酮盐 (KS)

酮盐是目前全球市面上最普遍的酮体补充剂，主要以 D3HB 钠、钙、钾或镁盐的形式存在。研究表明，酮盐的摄入可以将血酮升至大约 1–1.5 mmol/L 并提高脂肪酸氧化的效率，但是并未对改善高强度运动表现起到明显的效果[72]。Kackley 等[73]在近期发现酮盐与其他作用物质的复配产品对提升高强度运动起到了一定的作用。从成分角度分析，大部分酮盐都是混旋手性而 L-3HB 并非人体内自然产生的物质，而以 D/L 形式存在的酮盐其中 L-手性的量若高于 D-手性，则容易导致原本促发酮症所需的时间被延长[74]。

4.2 酮酯 (KE)

酯类酮体补充剂和盐类最大的区别在于酮酯的吸收率和提升血酮的能力比酮盐更快[54,75]。英国牛津大学的 Clarke 教授在 2014 年发明了全球第一款纯酮酯——KME，并已经取得了美国食品药品监督局的 GRAS 证明[76]。该团队也做了非常多的研究证明酮酯在提高运动能力[77]、

表 1 外源性酮体在运动、代谢疾病等医学领域的最新应用研究及效果

Table 1 Most recently explored applications of exogenous ketone body in exercise, metabolic and age-related diseases

No.	Functional area	Types of exogenous ketones used			References
		Ketone salts	Ketone esters	1,3-butanediol	
1	Exercise performance	😐 Increased fat oxidation	☺ Significant improvement in endurance	😐 Minimal benefits	[55,72,77,84]
2	Weight loss & anti-obesity treatment	☺ Appetite control, modulation of appetite-regulating hormones, activates BAT to help maintain energy balance & increase resting energy expenditure		*	[41,97-99]
3	Muscle recovery	☺ Glycogen-sparing effect during exercise Enhances post-exercise glucose uptake and increases muscle glycogen content		*	[57-58,100]
4	Prevent overtraining symptoms	*	☺ Lowers GDF15 which is a key factor that increases when overtraining symptoms develop	*	[101]
5	Neurodegenerative & psychiatric diseases (ALZ, PARK, PTSD)	☺ Improves cognition and alleviates symptoms related to various neurodegenerative & psychiatric disorders		*	[31,78,80,102]
6	Metabolic deficiencies (MADD, FAO)	😐 Observed gastrointestinal side effects	☺ May better alleviate symptoms	*	[61,88-89]
7	Cardiovascular health (Heart failure, stroke, atherosclerosis)	☺ Increases cardiac output in heart failure patients Alleviates atherosclerosis		*	[64-65,103]
8	Chronic kidney disease (DKD)	*	*	☺ Inhibition of renal mTORC1 hyperactivation and minimizes renal tubular damage	[66]
9	Anti-aging	☺ Prevents cellular senescence	*	*	[70-71,82]

☺: very effective; 😐: not very effective; *: haven't been explored. BAT: brown adipose tissue; ALZ: Alzheimer's disease; PARK: Parkinson's disease; PTSD: post-traumatic stress disorder; MADD: multi-acyl CoA dehydrogenase deficiency; FAO: fatty acid oxidation disorders; ATH: atherosclerosis; DKD: diabetic kidney disease; mTORC1: mechanistic target of rapamycin complex 1.

改善认知[78-80]、治疗或抑制神经性损伤[81]以及抗衰老[82]方面的相关作用。Cox 等[55]发现专业运动员饮用 KME 0.5 h 后的 D3HB 水平可以提升至 3–5 mmol/L，并且有效地增强了骑行选手的耐力表现。

4.3 1,3-丁二醇 (BD)

除了已知的酮盐和酮酯外，1,3-丁二醇也是一种常见的酮体前体，并同样在肝脏中降解形成 D3HB。Kesl 等[83]对比了不同外源性酮体补充剂在快速提高血液中 D3HB 水平上的效果。

试验中所有外源酮体种类都达到了类似的生酮效果，然而 1,3-丁二醇相比酮酯的效果较为欠佳。再者，Scott 等[84]通过有氧运动试验发现饮用了复配 1,3-丁二醇-碳水饮料的跑者血液中的 D3HB 水平相比碳水对照组也提高了至少一倍；同时在运动中产生的乳酸有所减少且运动后的葡萄糖水平高于对照组。虽然在最后的 5 km 计时冲刺中并没有和对照组显现出很大差异，但通过乳酸和葡萄糖水平的变化可以认为饮用了 1,3-丁二醇的跑者在运动过程中更依赖于脂肪代谢所产生的酮体供能。

4.4 最新一代酮体补充剂：酮酸 (D3HB)

化学合成的酮盐与酮酯不管是从工艺角度还是生酮效果(主要针对盐类)都存在一定的劣势以及副作用，因此，纯酸形式的 D3HB 可能会开拓出更加新颖且具有疗效的临床治疗方法。Wu 等[85]在 5XFAD 转基因阿尔茨海默小鼠体内注入 1.5 mmol/kg D3HB 后发现，小鼠海马体内的 beta 淀粉样蛋白沉淀和小神经胶质细胞活性有明显降低，减少了 Aβ 毒性，并提高了小鼠的认知与记忆功能。Kraeuter 等[86]在药物促发 (MK-801-induced) 的精神分裂症小鼠中发现短时间或长期注入高剂量的 D3HB (10–20 mmol/kg) 成功缓解了实验小鼠的精神分裂症状，其中包括抑制过度自主活动、提高社交能力、改善受损的惊跳反射弱刺激抑制 (pre-pulse inhibition) 和恢复感觉运动门控 (sensorimotor gating) 功能。

5 未来与展望

生酮饮食目前在国内正受到科学家与医生们的广泛关注，也有越来越多的课题组发现 D3HB 或可被用于各种不同疾病的治疗，甚至包括一些极罕见的遗传性病症或严重的代谢疾病[61,87-88]。市面上现有的类似 D3HB 产品主要为含有钠、钙、钾、镁的酮盐，或是经过化学合成法制造的酮酯。酮盐的制造工艺相对简单、价格便宜，但容易导致肠胃副作用[89]，同时，D3HB 钠盐易于导致人体摄入过多的钠，并引发高血压[90]。相对而言，酮酯在人体内的安全性和耐受性远远大于酮盐[91-93]，但其需要经过肝脏代谢后才能降解成酸被吸收。然而，纯酸形式的 D3HB 目前在市场上的供应极少，大部分为化学合成，而现有唯一的纯 D3HB 酮酸也仅作为标样销售因此价格十分昂贵。

陈国强等[94]在 2002 年发明了一种利用重组大肠杆菌发酵制作 D3HB 的方法；而在 2021 年，麦得发公司首次开发出了一种全新的通过生物合成法大量生产纯酸形式的 D3HB 的制作工艺[95]，并已实现百公斤级规模化生产。由于纯酸形式的 D3HB 自身的新颖性，其在人体内的药代动力学数据、剂量-效果关系 (dose-response)、人体对外源性 D3HB 的耐受性是目前仍需要进一步研究和探索的主要方向。

然而值得关注的是，近年来已经有不少课题组利用纯酸形式的 D3HB 在动物模型中开展了针对不同疾病的探究 (表 2)。其中，Fischer 等[96]甚至运用了阳离子交换树脂或草酸沉淀法将 D3HB 钙盐中的钙离子成分剔除从而得到 D/L-3HB 酮酸，并给一名 12 岁的 MADD (multi Acyl-CoA dehydrogenase deficiency) 患者进行过为期 5 d 的治疗。虽然 D/L-3HB 未能将血酮提升至理想的治疗水平，其中的因素可能来源于酮盐的混旋结构 (L-3HB 在血液中停留时间长但其作用和代谢还有待研究)，因此为 D3HB 的未来应用发展提供了更多可能。总而言之，D3HB 作为一种人体可以通过自然代谢所产生的小分子物质或许有望给运动及医学领域带来更大的突破与应用；而随着外源性酮体补充剂的普及与发展，可能会为改善人类健康提供一个比饮食干预更加有效且便捷的平台。

表 2 D3HB 纯酸形式的应用研究进展

Table 2 Novel applications using D3HB in its acid form

No.	Functional area	Experimental model	Dose/ concentration	Main findings	Reference
1	Alzheimer's disease	5XFAD mice	156.0 mg/(kg·d) (osmotic pump)	↑ Cognitive function ↓ amyloid-β (Aβ) deposition and neuroinflammation ↑ Mitochondrial respiratory function ↓ Aβ toxicity and reactive oxygen species	[85]
2	Alzheimer's disease & atherosclerosis	$ApoE^{-/-}$ mice	156.0 mg/(kg·d) (s.c.)	Anti-inflammatory effects of D3HB alters pathology of both conditions	[104]
3	Schizophrenia	MK-801-induced SCZ mice	208.0 mg/(kg·d) 1.0 g/(kg·d) 2.1 g/(kg·d)	Both acute injection of highest dose and chronic injection of lower dose for 3 weeks inhibited the MK-801-induced SCZ symptoms	[86]
4	Glioma treatment	Rat C6 glioma cells (*in vitro*)	1.0 mmol/L 10.0 mmol/L 25.0 mmol/L	Cells incubated with mid- or high doses of D3HB demonstrated inhibition of NLRP3 inflammasome via activating GPR109A, which in turn inhibits the migration of C6 glioma cells, activation of caspase-1, and IL-1β release	[68]
5	Prevents diabetic vascular injuries	Diabetic rats	160.0 mg/kg 200.0 mg/kg 240.0 mg/kg	D3HB promotes β-hydroxybutyrylation on lysine residues of histone 3 (H3K9bhb) and results in increased gene expression of vascular endothelial growth factor (VEGF)	[37]
6	Anti-depression	Mice	100.0–300.0 mg/kg (i.p.)	Alleviates depressive behaviors of mice after chronic administration for 11 days; lower doses combined with fluoxetine exerts better anti-depressive effect and alleviate symptoms	[105]
7	Prevention of liver ischemic reperfusion injury (IRI)	Mice	1.0 g/kg (i.p.)	Following 12 h fast or intraperitoneal injection of D3HB, mice had reduced inflammation and enhanced FOXO expression in which contributed to protection of the liver from IRI	[106]
8	Multi-acyl CoA dehydrogenase deficiency (MADD)	Patient case-study (age 12)	D/L-3HB 0.8–2.0 g/kg	D/L-3HB acid may be used as an adjunct to sodium-D/L-3HB salt as a potential novel way of treating MADD	[96]

5XFAD: transgenic mice model of Alzheimer's disease; GPR109A: G-protein-coupled receptor 109A; NLRP3: nod-like receptor pyrin-domain containing 3 inflammasome; IL-1β: interleukin-1β; HDAC: histone deacetylase; IRI: ischemic reperfusion injury; FOXO: transcription factor; i.p.: intraperitoneal; s.c.: subcutaneous.

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