丁基苯酞在脑血管病的药理作用及临床联合应用的研究进展

泥文娟[1], 李伟霞[2*], 王晓艳[2], 吴娅丽[2], 韩 冰[1], 贾金浩[1], 李 琨[1], 纪秋如[1], 唐进法[2*]

(1. 河南中医药大学, 河南 郑州 450046; 2. 河南中医药大学第一附属医院, 河南省中药临床应用、评价与转化工程研究中心, 河南省中药临床药学中医药重点实验室, 河南 郑州 450000)

摘要: 脑血管病具有发病率高、致残致死率高及复发率高等特点, 严重危害人类健康, 增加国民卫生经济负担。丁基苯酞是临床常用的治疗脑血管疾病的一类新药, 也是当归、川芎等中药中的主要活性成分之一。本文对丁基苯酞的药理作用进行了系统概述, 其具有抗血小板聚集、抗血栓形成、抑制神经细胞凋亡、抗氧化、抗脑缺血、减轻脑损伤、抗血管性痴呆等药理作用, 其临床常与依达拉奉、阿替普酶、法舒地尔、醒脑静注射液、复方丹参注射液等药物联合使用治疗脑卒中、血管性痴呆、脑血管痉挛等脑血管疾病, 并发挥较好的协同治疗作用, 可为丁基苯酞的临床合理应用提供支撑。

关键词: 丁基苯酞; 脑血管病; 药理作用; 临床联合应用

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Research progress on pharmacological effects and clinical combined application of 3-*n*-butylphthalide in cerebrovascular diseases

NI Wen-juan[1], LI Wei-xia[2*], WANG Xiao-yan[2], WU Ya-li[2], HAN Bing[1], JIA Jin-hao[1], LI Kun[1], JI Qiu-ru[1], TANG Jin-fa[2*]

(*1. Henan University of Chinese Medicine, Zhengzhou 450046, China; 2. Henan Province Engineering Research Center of Clinical Application, Evaluation and Transformation of Traditional Chinese Medicine, Henan Provincial Key Laboratory for Clinical Pharmacy of Traditional Chinese Medicine, the First Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou 450000, China*)

Abstract: Cerebrovascular diseases have the characteristics of high morbidity, high disability, high mortality and high recurrence rate, which seriously harm human health and increase the national health economic burden. 3-*n*-Butylphthalide (NBP) is a new drug commonly used in clinical treatment of cerebrovascular diseases, and it is also one of the main active components in traditional Chinese medicine such as *Angelica sinensis* and Chuanxiong. In this review, the pharmacological effects of NBP were systematically summarized. Studies have shown that NBP has pharmacological effects such as antiplatelet aggregation, anti-thrombosis, inhibiting neuronal apoptosis, anti-oxidation, anti-cerebral ischemia, anti-brain injury, and anti-vascular dementia. In clinical practice, it is often combined with edaravone, alteplase, fasudil, Xingnaojing injection, and compound Danshen injection to treat cerebral vascular diseases such as stroke, vascular dementia, and cerebral vasospasm, and plays a good synergistic effect. This summary could provide support for the rational clinical application of NBP, and also provide basis for the in-depth study of the interaction of its drug combination.

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*通讯作者 Tel: 86-371-66233612, E-mail: liweixia01@126.com; a0519@163.com

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Key words: 3-*n*-butylphthalide; cerebrovascular disease; pharmacological action; clinical combined application

脑血管病泛指脑部血管的各种疾病, 是各种原因导致的1个或多个脑血管病变引起的短暂性或永久性神经功能障碍。脑血管病属于中医“中风”病, 临床表现的主要特征为猝然昏仆而突然发生的口眼歪斜、半身不遂等, 具有高发病率、高致残率和高死亡率的特点[1], 在临床上常见的有脑卒中、血管性痴呆 (VD) 和脑血管痉挛等疾病[2,3]。脑血管病是导致我国人口死亡的主要疾病之一, 每5位死亡者中至少有1人死于脑卒中, 死亡人数约占全球脑血管病死亡的1/3[4], 已成为危害人类健康的重大疾病。丁基苯酞 (3-*n*-butylphthalide, NBP) 为简单苯酞类化合物, 是中药川芎、茶芎、佛手和当归等的主要药效成分[5,6], 研究表明[7-9], NBP具有抗血小板聚集、抗血栓形成、抑制神经细胞凋亡、抗自由基作用、改善脑组织微循环、保护线粒体、保护血脑屏障、抗脑缺血后炎症等药理作用, 临床上也常将NBP与其他药物联用共同治疗脑血管疾病。本综述首先对NBP在脑血管疾病中的药理作用进行概述, 然后对NBP联合用药治疗脑血管疾病的观察研究进行归纳, 系统概述NBP及其联合用药治疗脑血管病的研究现状, 为NBP的作用机制和临床应用等深入研究提供依据。

1 NBP的来源及结构式

NBP的化学名是3-丁基-1(3*H*)-异苯并呋喃酮, 化学式是$C_{12}H_{14}O_2$, 又称芹菜甲素, 是从芹菜种籽中分离出的有效成分, 是芹菜油中的化学成分之一, 为油状液体, 有芹菜香味。NBP的3位碳原子为手型碳原子, 有*S*-和*R*-对映异构体, 其化学结构式如图1。

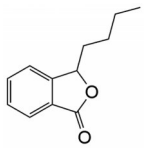

Figure 1 Chemical structure of 3-*n*-butylphthalide (NBP)

2 NBP在脑血管病中的药理作用

2.1 抗血小板聚集与抗血栓形成 NBP有*DL*-NBP、*L*-NBP、*D*-NBP共3种构型, Xu等[10]利用大鼠体内抗血栓形成实验和体外抑制血小板聚集实验, 发现*DL*-NBP和*L*-NBP均具有明显抗血栓形成作用, *DL*-NBP、*L*-NBP、*D*-NBP均能抑制胶原 (Coll)、二磷酸腺苷 (ADP)、花生四烯酸 (AA) 诱导的血小板聚集, 且呈良好的剂量依赖关系; 同时, *DL*-NBP和*L*-NBP可剂量依赖性地升高血小板内环磷酸腺苷 (cAMP) 含量, *L*-NBP可剂量依赖性地显著抑制血小板5-羟色胺 (5-HT) 释放, 高浓度的*L*-NBP可抑制血栓素A2 (TXA2) 含量的升高。在这3种结构中, *L*-NBP抗血栓的作用最强, 与阿司匹林相似, 其机制可能与升高血小板内cAMP的含量及抑制5-HT释放有关。Ye等[11]研究发现, NBP能浓度依赖性地抑制ADP、凝血酶和Coll蛋白等多种激动剂诱导的血小板聚集, TXA2是由活化的血小板通过溶质磷脂酶A2 (cPLA2)、环氧合酶-1 (COX-1) 和血栓烷合酶依次转化AA而产生的, NBP抑制ADP刺激的血小板中cPLA2磷酸化, 而对cPLA2上游的信号分子p38和Src的磷酸化无影响; 同时, NBP对ADP诱导的血小板中cAMP含量的下降也无影响, 故NBP可能通过抑制cPLA2的磷酸化来抑制TXA2的合成发挥抗血栓作用。

2.2 抗炎 脑损伤与Toll样受体4 (TLR4) 调节的核因子*κ*B (NF-*κ*B) 炎症通路密切相关, Zhang等[12]发现NBP能显著降低大脑中动脉栓塞 (MCAO) 大鼠血清中肿瘤坏死因子-*α* (TNF-*α*)、白介素-1*β* (IL-1*β*)、IL-6和IL-18促炎因子的水平, 显著增加抗炎因子IL-10的水平; 显著降低MCAO大鼠大脑海马区和皮质区TLR4、髓样分化因子88 (MYD88)、IL-1*β*、IL-18、p-NF-*κ*B、磷酸化核因子*κ*B抑制物激酶*α* (p-IKK*α*) 和磷酸化核因子*κ*B抑制因子*α* (p-I*κ*B*α*) mRNA和蛋白的表达水平, 显著降低皮质和海马区TLR4阳性细胞, 提示NBP通过抑制TLR4/NF-*κ*B通路的激活来抑制炎症的发生。TNF-*α*是重要的炎症因子, 已被证明其可上调炎症反应中基质金属蛋白酶 (MMP) 的表达, 尤其是MMP-9, 研究报道[13]NBP显著抑制脑出血 (ICH) 模型大鼠脑组织中TNF-*α*和MMP-9的表达, 从而减少炎症反应。Cong等[14]以PC12细胞为研究对象, 建立缺糖缺氧/复氧 (OGD/R) 损伤模型, 发现NBP能显著下调模型组中TNF-*α*、IL-1*β*细胞因子及肿瘤坏死因子相关受体6 (TRAF6) 蛋白水平的表达; 同时设置NC抑制剂和miR-146b-5p抑制剂转染组, 证实NBP通过miR-146b-5p/TRAF6轴在OGD/R PC12细胞中减轻炎症反应。

2.3 抗氧化 超氧化物歧化酶 (SOD) 是一种重要的抗氧化酶, 具有清除自由基、减轻氧化损伤的作用, 丙二醛 (MDA) 是主要的氧化产物, 反映组织脂质过氧化, 二者的水平间接反映了氧化应激损害。活性氧 (ROS) 的产生是氧依赖呼吸的必然结果, 当自由基大量产生或SOD活性降低时, 自由基通过攻击生物膜中的多不饱和脂肪酸, 导致脂质过氧化和细胞功能障碍。Zhao等[15]研究发现, NBP能显著降低慢性脑缺血大鼠大脑皮层中SOD、MDA及海马区MDA的含量, 说明

NBP可减轻慢性脑缺血引起的脑组织氧化应激损伤。Huang等[16]研究发现NBP可剂量依赖性地升高MCAO模型大鼠SOD水平、血红素加氧酶-1 (HO-1) mRNA的表达、核因子E2相关因子2 (Nrf2)和HO-1蛋白表达, 剂量依赖性减少MDA水平, 提示NBP可通过上调Nrf2/HO-1通路发挥抗氧化作用进而保护神经。Chen等[17]发现NBP能显著增加OGD后PC12细胞中Nrf2、HO-1和腺苷酸活化蛋白激酶 (AMPK)的蛋白表达水平及SOD活性, 显著降低MDA和ROS水平, 提示NBP可增强抗氧化作用, 降低脂质过氧化。Sun等[18]研究发现NBP预处理能显著降低过氧化氢 (H_2O_2) 诱导后大鼠骨髓间充质干细胞 (rBMSCs)内ROS和MDA的水平, 显著增加SOD活性, 表明NBP可通过其抗氧化活性保护rBMSCs免受H_2O_2诱导的细胞死亡。

2.4 保护线粒体功能 Chen等[17]研究发现, OGD使PC12细胞的线粒体缩短、数量减少, 嵴粗糙破裂, 用NBP预处理后, 这些改变明显降低, 且OGD后的膜电位显著升高。此外, NBP还能显著增加OGD后ATP酶、线粒体呼吸链复合物 (MRCC) I、II和IV的活性及线粒体融合素基因-1 (Mfn1)和Mfn2的表达水平, 显著下调Drp1和Fis1的表达水平, 说明NBP通过增加线粒体的能量合成、调节线粒体融合和分裂的动态平衡, 减少了OGD引起的线粒体损伤。Li等[19]研究发现, NBP预处理显著降低OGD诱导的线粒体ROS的产生及线粒体膜电位下降和线粒体碎裂, 表明NBP可保持线粒体完整性, 最大限度减少功能损失, 保护人脐静脉内皮细胞 (HUVEC)免受OGD损伤。Yan等[20]采用改良线栓法制备MCAO模型大鼠, 然后提取各组大鼠脑组织中线粒体蛋白, 发现NBP能显著降低MCAO模型大鼠线粒体中细胞色素C氧化酶蛋白6A2 (COX6A2)、线粒体脱偶联蛋白3 (UCP3)的蛋白表达, 显著增加烟酰胺核苷酸转氢酶 (NNT)蛋白的表达, 从而减轻脑缺血再灌注损伤后的线粒体损伤。

2.5 抑制神经细胞的凋亡 大量的神经细胞凋亡可破坏神经系统, 从而导致神经功能的缺损甚至死亡。NBP是临床常用脑保护剂, 对脑梗死后的神经细胞有一定保护作用。Bu等[21]研究发现, NBP能显著降低脑梗死模型大鼠脑组织细胞凋亡率, 显著下调磷酸化c-Jun氨基末端激酶 (p-JNK)、磷酸化p38丝裂原活化蛋白激酶 (p-p38 MAPK)相对蛋白表达水平及B淋巴细胞瘤-2相关X蛋白 (Bax) mRNA水平, 显著上调B淋巴细胞瘤-2 (Bcl-2) mRNA水平, 其机制可能与抑制JNK/p38 MAPK信号通路激活有关。Zhang等[22]研究发现NBP能显著降低糖尿病大鼠海马内胶质纤维酸性蛋白 (GFAP)、分化抗原簇分子11b (CD11b)和半胱氨酸天冬氨酸蛋白酶-3 (caspase-3)阳性细胞的表达, 显著增加血管内皮生长因子 (VEGF)阳性细胞的表达, 通过上调糖尿病大鼠脑内VEGF的表达从而抑制caspase-3介导的神经细胞凋亡。窒息性心脏骤停会导致脑缺血再灌注损伤, Mai等[23]研究发现, NBP能改善心肺复苏模型大鼠的脑组织病理形态, 显著增加神经功能缺损评分和脑组织中Bcl-2、NF-κB蛋白的表达, 显著降低脑组织神经细胞凋亡率、TNF-α、IL-1β细胞因子及高迁移率族蛋白B1 (HMGB-1)、糖基化终产物受体 (RAGE)、NF-κB、caspase-3、Bax蛋白表达水平, 提示NBP预处理对心肺复苏后脑缺血再灌注损伤具有保护作用, 其机制可能是通过抑制HMGB-1/RAGE/NF-κB通路降低脑神经细胞凋亡来实现的。Wang等[24]研究发现NBP能抑制氯化钴诱导的神经母细胞瘤细胞株 (SK-N-SH)的凋亡率, 同时显著下调Bax蛋白的表达, 显著上调Bcl-2蛋白的表达。

2.6 抗脑缺血和脑损伤 Li等[25]研究发现NBP能显著降低tMCAO小鼠的神经功能缺损评分、脑梗死体积和微囊蛋白1 (caveolin-1)的表达, 显著增加脑血流流量, 改善脑水肿和血脑屏障通透性从而发挥抗脑缺血作用。Yang等[26]研究发现NBP能显著降低MCAO小鼠第1和第3天的神经功能缺陷和梗死体积及脑组织中IL-6、IL-1β、TNF-α、趋化因子配体3 (CCL3)和MMP-9等促炎因子的表达, 显著增加脑内皮细胞中紧密连接蛋白闭锁小带蛋白-1 (ZO-1)和紧密连接蛋白5 (claudin-5)的表达, 维持血脑屏障的完整性, 改善脑缺血引起的损伤。此外, 另有研究报道[27]NBP对急性和亚急性期缺血性脑卒中大动脉有血管舒张作用, 在亚急性期脑卒中后, NBP通过减少血栓和血管收缩而增加局部血流, 改善tMCAO大鼠的血管功能, 减少MCAO大鼠脑萎缩体积, 促进脑卒中后的恢复, 减轻脑损伤。Yu等[28]研究发现, NBP能改善MCAO大鼠神经功能缺损、减少脑梗死体积, 抑制NF-κB通路及下游产物细胞间黏附分子-1 (ICAM-1)的表达, 发挥抗脑缺血作用。Wei等[29]研究发现, 在小鼠iPS细胞来源的血管祖细胞中, NBP能显著增加新生血管标记物血小板源性生长因子受体α多肽 (PDGFRα)的表达和α平滑肌肌动蛋白 (αSMA)/血小板-内皮细胞黏附分子 (CD-31)双阳性细胞的百分率, 此外, NBP能显著增加脑卒中小鼠同侧皮层侧支直径、分支度II和V处的MCAO分支数量、缺血区和梗死周边区的动脉密度及绿色荧光蛋白 (GFP)/5-溴脱氧核苷尿嘧啶 (BrdU)双标记细胞, 显著上调VEGF、血管生成素1 (Ang-1)的蛋白表达水平, 显著下调神经元型一氧化氮合酶 (nNOS)的蛋白表达水平, 表明NBP通过增加再生因子的表达和动脉侧枝的发生, 改

善脑卒中小鼠脑局部血流量和功能活动的恢复。

2.7 抗VD 慢性脑灌注不足 (CCH) 是导致VD的关键因素, 而双侧颈总动脉结扎 (BCCAO) 的动物模型常被用于研究低灌注导致的VD。Li等[30]分别建立BCCAO大鼠模型和OGD/R细胞模型, 通过体内外实验发现, NBP显著促进受体酪氨酸蛋白激酶 (Ret) 的上调, 进而上调胶质细胞源性神经营养因子 (GDNF)/胶质细胞系源性神经营养因子受体α1 (GFRα1), 激活下游效应通路, 尤其是蛋白激酶B (AKT) 和细胞外调节蛋白激酶1/2 (ERK1/2) 通路, 同时减少了海马神经元的凋亡。此外, NBP治疗可促进CCH大鼠脑血流量 (CBF) 的恢复, 降低缺氧诱导因子-1α (HIF-1α) 的水平, 改善其认知功能, 其机制可能与调节GDNF/GFRα1/Ret信号通路有关。Tian等[31]通过Morris水迷宫 (MWM) 实验、T迷宫实验及透射电镜, 发现NBP能明显改善VD大鼠的认知能力、海马神经元的丢失和自噬小体的形成。同时, NBP还能显著下调VD大鼠自噬特性蛋白Beclin 1和微管相关蛋白1轻链3II (LC3II) 的水平, 上调雷帕霉素靶蛋白 (mTOR) 磷酸化水平, 提示NBP的抗血管性痴呆作用可能依赖于mTOR。Niu等[32]研究发现NBP能显著改善VD大鼠MWM期间受损的学习和记忆能力, 明显减轻海马CA1区神经元的缺失, 显著增加突触素 (SYN)、生长相关蛋白43 (GAP43)、突触后密度蛋白95 (PSD95)、音猬因子 (Shh)、蛋白同源物修补1 (Ptch1)、七跨膜转导蛋白 (Smo) 和神经胶质瘤相关癌基因同源物1 (Gli1) 的蛋白和mRNA表达水平, 显著降低蛋白激酶R样内质网激酶 (PERK)、需肌醇酶1 (IRE1)、X盒结合蛋白1 (XBP1)、剪接型X盒结合蛋白1 (XBP1s)、活化转录因子6 (ATF6)、葡萄糖调节蛋白 (GRP78) 和caspase-12的蛋白和mRNA表达水平, 说明NBP可通过激活Shh/Ptch1通路, 抑制内质网应激 (ERS) 相关标志物的表达, 从而对CCH所致的认知障碍起到保护作用。NBP在脑血管病中的主要药理作用及机制见图2、表1[10-32]。

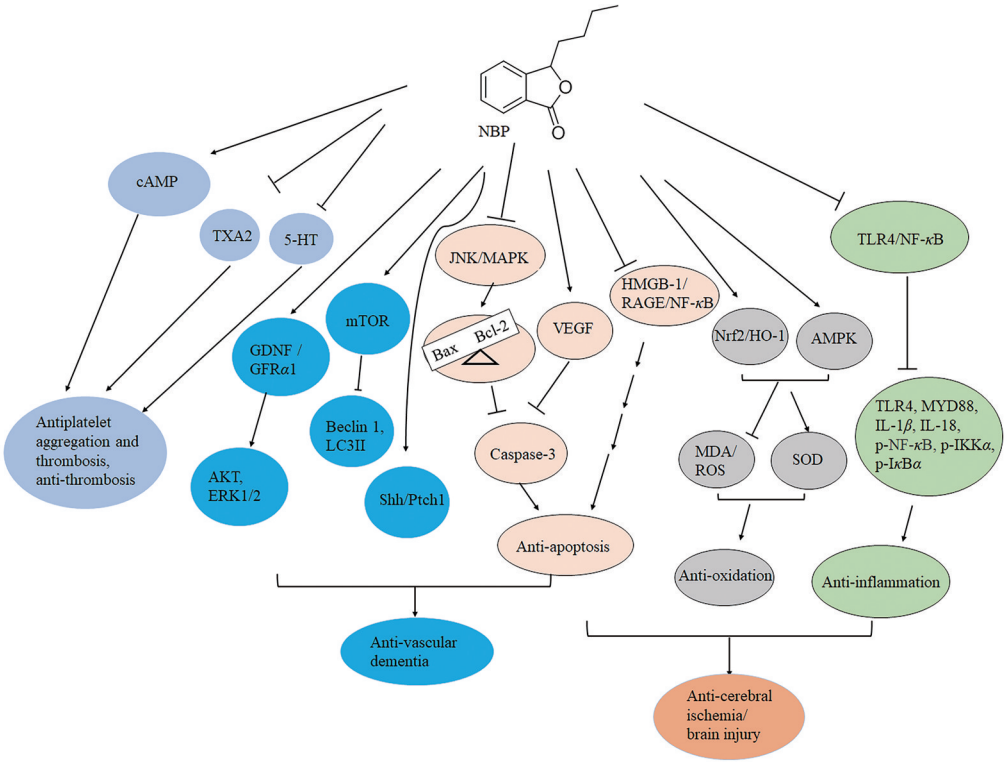

Figure 2 Pharmacological mechanism of NBP in the treatment of cerebrovascular diseases. cAMP: Cyclic adenosine monophosphate; TXA2: Thromboxane A2; 5-HT: 5-Hydroxytryptamine; JNK: c-Jun N-terminal kinase; MAPK: Mitogen-activated protein kinases; mTOR: Mammalian target of rapamycin; GDNF: Glial cell line-derived neurotrophic factor; GFRα1: GDNF family receptor alpha-1; AKT: Protein kinase B; ERK1/2: Extracellular regulated protein kinases 1/2; LC3II: Microtubule-associated protein1 light chain 3II; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2 associated X; VEGF: Vascular endothelial growth factor; HMGB-1: High mobility group box-1 protein; RAGE: Receptor for advanced glycation end; NF-κB: Nuclear factor kappa-B; Nrf2: NF-E2-related factor 2; HO-1: Heme oxygenase 1; AMPK: Adenosine 5-monophosphate (AMP)-activated protein kinase; MDA: Malondialdehyde; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TLR4: Toll-like receptor 4; MYD88: Myeloid differentiation factor 88; IL: Interleukin; p-IKKα: Phosphorylated inhibitor of kappa B kinase alpha; p-IκBα: Phosphorylated inhibitor kappa B alpha

Table 1 Main pharmacological effects and mechanisms of NBP in cerebrovascular diseases. MMP-9: Matrix metalloprotein-9; COX6A2: Cytochrome c oxidase subunit 6A2; UCP3: Uncoupling protein 3; NNT: Nicotinamide nucleotide transhydrogenase; ICAM-1: Intercellular adhesion molecule-1; TNF-α: Tumor necrosis factor-α; CCL3: Chemokine ligand 3; ZO-1: Zonula occludens protein 1; PDGFRα: Platelet-derived growth factor; Ang-1: Angiopoietin-1; TRAF6: Tumor-necrosis factor receptor-associated factor 6; MRCC: Mitochondrial respiratory chain complex; cPLA2: Cytoplasmic phospholipase A2; rBMSCs: Rat marrow mesenchymal stem cells; HUVEC: Human umbilical vascular endothelial cells

Action object	Drug concentration/dose	Pharmacological action	Function/mechanism
Rat	3, 10, 30, 100 μmol·L^{-1}; 5, 10, 20 mg·kg^{-1}	Antiplatelet aggregation and anti-thrombosis[10]	Increase cAMP content in platelets, inhibit TXA2 content and platelet 5-HT release
	4.5 mg·kg^{-1}	Anti-inflammatory[12]	Reduce the levels of pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-18, increase the levels of anti-inflammatory cytokines IL-10, and inhibit the activation of TLR4/NF-κB pathway
	25 mg·kg^{-1}	Anti-inflammatory[13]	Inhibition of TNF-α and MMP-9 expression
	30, 120 mg·kg^{-1}	Anti-oxidation[15]	Reducing the contents of SOD and MDA
	20, 40, 80 mg·kg^{-1}	Anti-oxidation[16]	Increase SOD level, HO-1 mRNA expression, Nrf2 and HO-1 protein expression, decrease MDA level and activate Nrf2/HO-1 pathway
	80 mg·kg^{-1}	Protecting mitochondrial function[20]	Reduce COX6A2, UCP3 protein expression and increase NNT protein expression
	4.5 mg·kg^{-1}	Inhibition of neuronal apoptosis[21]	Inhibition of JNK/p38 MAPK signaling pathway activation
	80 mg·kg^{-1}	Inhibition of neuronal apoptosis[22]	Up-regulation of VEGF expression and inhibition of caspase-3-mediated neuronal apoptosis in diabetic rats
	0.25, 0.50, 0.75 mg	Inhibition of neuronal apoptosis[23]	Inhibition of HMGB-1/RAGE/NF-κB pathway activation
	90 mg·kg^{-1}	Anti-brain injury[27]	Reducing thrombosis and vasoconstriction increases local blood flow and reduces infarct volume
	80 mg·kg^{-1}	Anti-cerebral ischemia[28]	Inhibition of the expression of NF-κB pathway and downstream product ICAM-1
	60 mg·kg^{-1}	Anti-vascular dementia[31]	Down-regulation of Beclin 1 and LC3II and up-regulation of mTOR phosphorylation
	30, 60, 120 mg·kg^{-1}	Anti-vascular dementia[32]	Activation of Shh/Ptch1 signaling pathway
Rat and hippocampal neurons	5 mg·kg^{-1}, 60 mol·L^{-1}	Anti-vascular dementia[30]	Activation of GDNF/GFRα1/Ret signaling pathway
Mouse	40 mg·kg^{-1}	Anti-cerebral ischemia[25]	Reduce neurological deficit score, infarct volume and cavolin-1 expression, increase cerebral blood flow, improve cerebral edema and blood-brain barrier permeability
	60 mg·kg^{-1}	Anti-brain injury[26]	Decrease the expression of IL-6, IL-1β, TNF-α, CCL3 and MMP-9, increase the expression of ZO-1 and claudin-5, and maintain the integrity of blood-brain barrier
Mice and vascular progenitors	80 mg·kg^{-1}, 10 μmol·L^{-1}	Anti-cerebral ischemia[29]	By increasing the expression of PDGFRα, VEGF, Ang-1 and other regeneration factors and the occurrence of arterial collateral branches, the recovery of local blood flow and functional activities in cerebral apoplexy rats was improved
PC12 cells	10 μmol·L^{-1}	Anti-inflammatory[14]	Reduced expression of TNF-α, IL-1β cytokines and TRAF6 protein levels
	0.01, 0.1, 10, 100 μmol·L^{-1}	Anti-oxidation[17]	Increased Nrf2, HO-1 and AMPK protein expression and SOD activity, decreased MDA and ROS levels
	0.01, 0.1, 10, 100 μmol·L^{-1}	Protecting mitochondrial function[17]	Reduced expression of Drp1 and Fis1, increased activity of ATPase, MRCC I, II and IV, and increased expression of Mfn1 and Mfn2
rBMSCs	0.1, 1, 10, 100 mol·L^{-1}	Anti-oxidation[18]	Reducing ROS and MDA levels and increasing SOD activity
HUVEC	0.01, 0.1, 1, 10, 100 μmol·L^{-1}	Protecting mitochondrial function[19]	Reducing mitochondrial ROS production, mitochondrial membrane potential decline and mitochondrial fragmentation
SK-N-SH cells	1, 10 μmol·L^{-1}	Inhibition of neuronal apoptosis[24]	Significantly down-regulated Bax protein and significantly up-regulated Bcl-2 protein
Human	30, 100, 300 μmol·L^{-1}	Anti-thrombosis[11]	Inhibition of TXA2 synthesis by inhibiting cPLA2 phosphorylation

3 NBP在脑血管病中的联合用药

3.1 NBP联合用药治疗缺血性脑卒中 Zhang等[33]将急性缺血性脑卒中 (AIS) 患者分成对照组 (常规治疗措施+阿托伐他汀钙+阿司匹林肠溶片) 和治疗组 (常规治疗措施+阿托伐他汀钙+阿司匹林肠溶片+NBP软胶囊), 连续治疗4周后, 发现治疗组患者的临床治疗

总有效率、日常生活活动能力量表 (BI) 评分、前动脉血流及后动脉血流均显著高于对照组, 神经功能缺损评分 (NIHSS) 显著低于对照组。内皮祖细胞 (EPCs) 被认为是在外周血循环中的未成熟内皮细胞, 参与缺血区血管新生, 促进缺血区侧支循环的建立, Xiong 等[34]将 96 例 AIS 患者均分成对照组 (银杏叶提取物注射液+阿司匹林肠溶片) 和观察组 (NBP+银杏叶提取物注射液+阿司匹林肠溶片), 发现观察组血清中高密度脂蛋白胆固醇 (HDL-C) 水平、EPCs 数量、迁移能力及总有效率 (89.58%) 显著高于对照组, 血清总胆固醇 (TC)、甘油三酯 (TG)、低密度脂蛋白胆固醇 (LDL-C) 水平显著低于对照组, 由此得出 NBP 联合用药治疗急性缺血性脑卒中的临床疗效更好, 可能是通过增加 EPCs 数量, 增强其向损伤区域的迁移能力, 从而促进血管新生。Qian 等[35]将 165 名 AIS 患者以 2∶1 的比例随机分配到两个治疗组, 分别为人尿激肽原酶 (HUK) 联合 NBP 组和依达拉奉 (Eda) 联合 NBP 组, 结果发现 HUK 联合组 12 个月的 MRS 评分显著低于 Eda 联合组; 此外, HUK 联合组治疗的独立率为 79.1%, 显著高于 Eda 联合组 (45.3%), 故 HUK 与 NBP 联合使用可增强 AIS 患者长期独立率和治疗效果, 且临床疗效优于 Eda 与 NBP 联合。另研究发现[36], NBP 联合阿替普酶可显著降低急性前循环脑梗死患者治疗后第 1、7 和 30 天的 NIHSS 评分, 其有效率和术后恢复率显著高于单独给予尿激酶溶栓治疗的患者。NBP 联合双抗血小板 (阿司匹林肠溶片+硫酸氢氯吡格雷片) 治疗老年急性脑梗死患者的有效率可达到 92.5%, 与给予双抗血小板治疗的患者相比, 其有效率、日常生活能力量表 (ADL) 评分和血浆 3-巯基丙酮酸硫转移酶 (3-MST) 水平显著增加, NIHSS 评分和血浆 β-淀粉样蛋白 (Aβ42) 水平显著降低[37]。NBP 联合复方丹参注射液治疗急性缺血性脑卒中患者, 其总有效率为 93.10%, 显著高于对照组 (给予 NBP 的急性缺血性脑卒中患者), 与对照组相比, 联合给药能显著降低神经功能评分以及血清中 IL-6、IL-β、TNF-α 和超敏 C 反应蛋白 (hs-CRP) 水平, 显著增加 IL-8 水平, 同时减少不良反应的发生[38]。Xiong 等[39]研究发现 NBP 联合阿司匹林、阿替普酶等常规治疗可显著降低 AIS 患者 NIHSS 评分和血浆中 MMP-9 水平, 升高 VEGF 水平, 从而改善脑卒中的预后。综上, NBP 联合用药治疗脑卒中有利于改善患者的生活能力和神经功能, 临床疗效显著, 且安全性较高。

3.2 NBP 联合用药治疗出血性脑卒中 Wang[40]将 NBP 与纳洛酮联用治疗脑出血患者, 与 NBP 单用患者相比, 联用组患者血清中同型半胱氨酸 (Hcy)、hs-CRP、HIF 显著降低, 有效率显著提高。NBP 联合 Eda 能显著增加高血压脑出血患者的脑血管平均流速、平均流量、一氧化氮 (NO) 水平和有效率, 显著降低脑血管周围阻力、动态阻力、氧化型低密度脂蛋白胆固醇 (ox-LDL)、内皮素 1、ICAM-1、血管细胞黏附分子 1 (VCAM-1)、血小板衍生因子 (PDGF)、TNF-α、IL-6、降钙素基因相关肽 (CGRP) 和沉默信息调节因子 2 同源体 1 (SIRT1) 水平, 说明 NBP 联合 Eda 临床疗效显著[41]。NBP 联合尼莫地平能明显改善脑出血患者的外周阻力、平均血流量及平均血流速度, 显著降低血肿体积, 显著增加认知评分、生活能力评分, 从而提高患者的生理能力[42]。

3.3 NBP 联合用药治疗 VD VD 为斑片状智能损害, 主要发病于老年群体, 病发后会增加患者致残率, 是危害中老年患者身体健康的主要疾病之一。Qiao[43]以 83 例 VD 患者作为研究对象, 将其分成对照组 (抗凝、活血化瘀和扩张血管等常规治疗) 和观察组 (NBP+常规治疗), 连续治疗 90 天后, 与对照组患者相比, 观察组患者的简易精神状态检查表 (MMSE) 评分、ADL 评分及血清中 SOD 活性显著增加, MDA 含量和临床痴呆评定量表 (CDR) 评分显著下降, 推测 NBP 联合抗凝、活血化瘀和扩张血管等常规方法治疗 VD 的作用机制可能与其改善脑组织代谢水平、发挥抗氧化作用、降低自由基对神经元的损伤相关。Dong 等[44]将 86 例 VD 患者随机分为对照组 (NBP 软胶囊) 和观察组 (NBP 软胶囊联合舒血宁注射液), 治疗 30 天后, 发现观察组有效率、SOD 水平、MMSE、痴呆简易筛查量表 (BSSD) 和 ADL 量表评分显著高于对照组, MDA、IL-1β、TNF-α、C 反应蛋白 (CRP) 水平显著低于对照组, 说明 NBP 软胶囊联合舒血宁注射液能降低 VD 患者氧化应激及炎症反应, 改善患者认知功能与生活质量, 安全性高。NBP 氯化钠注射液联合美金刚能显著降低 VD 患者 CDR 评分及氧化应激指标脂质过氧化物 (LPO) 和 MDA 的水平, 显著增加 MMSE、BI 评分、SOD 水平及脑血流动力学指标舒张期峰值速度 (V_{min})、搏动指数 (PI) 和屏气指数 (BHI) 水平, 说明 NBP 联合美金刚治疗可有效缓解 VD 患者认知功能障碍, 降低氧化应激损害, 恢复脑血流动力学, 提高临床疗效, 且临床较为安全[45,46]。

3.4 NBP 联合用药治疗脑血管痉挛 Sun 等[47]将脑动脉瘤栓塞术后脑血管痉挛患者随机均分成对照组 (抗感染、镇静止咳等常规治疗) 和试验组 (在对照组的基础下给与 NBP 和法舒地尔), 治疗后与对照组相比, 试验组能显著降低血清 caspase-3、MMP-9 和 MMP-2 的水平及总药物不良反应的发生率, 说明 NBP 注射液联合法舒地尔注射液治疗脑动脉瘤栓塞术后脑血管痉挛的临床疗效确切。Lei 等[48]将 NBP 与尼莫地平和醒脑静注射液联合用于动脉瘤性蛛网膜下腔出血脑血管痉挛

患者, 发现与给予NBP与尼莫地平的患者比较, 能显著降低治疗后3和7天血清神经特异性烯醇酶 (NSE)、CRP、脂肪酸结合蛋白 (FABP)、ICAM-1、TNF-α、IL-1β、TXB2的水平和大脑中动脉血流速度, 显著增加NO水平, 说明NBP注射液联合醒脑静注射液可提高动脉瘤性蛛网膜下腔出血脑血管痉挛的临床疗效。

3.5 NBP联合用药治疗迟发性脑病 迟发性脑病是与急性一氧化碳 (CO) 中毒相关的最严重的并发症, NBP能显著增加脑局部血流量, 改善特定神经细胞的记忆功能, 在治疗CO中毒迟发性脑病 (DEACMP) 中发挥了重要作用[49,50], 在临床上常与其他药物联合治疗DEACMP。Xiang等[51]将184名DEACMP患者随机分成对照组 (接受高压氧疗法) 和试验组 (接受NBP和高压氧疗法), 治疗8周后以总缓解率 (RR) 用于评估临床疗效、MMSE用于评估认知功能、NIHSS用于评估神经功能, 结果发现, 与高压氧相比, 联合用药能显著增加RR值和MMSE评分, 显著降低NIHSS评分, 因此得出NBP和高压氧联合应用可显著改善DEACMP患者的认知功能障碍, 具有很好的临床疗效。Zhang等[52]将171例DEACMP患者分成联合治疗组 (NBP+地塞米松5 mg·d^{-1}+高压氧治疗) 和对照组 (高压氧治疗为单药治疗), 在治疗后1、3个月及1年, 采用MMSE、蒙特利尔认知评估 (MoCA) 量表和ADL评分评估患者的认知和运动变化, 结果发现联合治疗组治疗后1、3个月和1年的MMSE、MoCA和ADL评分均显著高于对照组, 此外NBP和地塞米松的添加并没有显著增加不良事件发生率。Kang等[53]使用醒脑静注射液联合NBP治疗DEACMP患者, 发现其治疗总有效率、MMSE评分、SOD水平明显高于单独使用NBP患者, MDA水平显著低于单独使用NBP患者, 表明醒脑静注射液与NBP联合治疗DEACMP患者可改善其精神状态, 快速增加SOD活性, 降低MDA含量, 有效修复脑组织损伤。NBP联合用药在脑血管病中的主要临床应用及临床药理作用见表2[33-48,51-53]。

Table 2 The main clinical application and clinical pharmacological effects of NBP in cerebrovascular diseases. HUK: Human urinary kallidinogenase; BI: Barthel index; NIHSS: National institute of health stroke scale; EPCs: Endothelial progenitor cells; HDL-C: High-density lipoprotein cholesterol; TC: Serum total cholesterol; TG: Triglyceride; LDL-C: Low-density lipoprotein cholesterol; MRS: Modified rankin scale; ADL: Activities of daily living; 3-MST: 3-Mercaptopyruvate sulfurtransferase; Aβ42: Amyloid beta 42; hs-CRP: High sensitive C reaction protein; Hcy: Homocysteine; HIF: Hypoxia-inducible factor; NO: Nitric oxide; ox-LDL: Oxidized low-density lipoprotein; ET-1: Endothelin-1; ICAM-1: Intercellular adhesion molecules-1; VCAM-1: Vascular endothelial cell adhesion molecule-1; PDGF: Platelet-derived growth factor; CGRP: Calcitonin gene related peptide; SIRT1: Silent information regulator 1; CDR: Clinical dementia rating; MMSE: Mini-mental state examination; BSSD: Brief screening scale for dementia; CRP: C-reactive protein; V_{min}: Peak diastolic velocity; PI: Pulsatility index; BHI: Breath-holding index; NSE: Neuro-specific endolase; FABP: Fatty acid-binding protein; sICAM-1: Soluble intercellular adhesion molecule-1; TXB2: Thromboxane B2; MoCA: Montreal cognitive assessment

Cerebrovascular disease	Number of cases (*n*)	Age stage	Dosage per day	Time of administration /day	Combined drug	Clinical pharmacological effect
Cerebral ischemic stroke	128	41−86	0.8 g	28	Atorvastatin calcium, aspirin enteric-coated tablets, etc.[33]	Increase the total effective rate, BI score, anterior and posterior arterial blood flow, and decrease NIHSS
	96	40−80	200 mg	84	Extract of ginkgo biloba leaves injection and aspirin enteric-coated tablet[34]	Increase the number of EPCs, migration ability, total effective rate and serum HDL-C level, and decrease serum TC, TG and LDL-C levels
	165	18−85	200 mg	12	HUK[35]	Reduce MRS score, enhance long-term independence and therapeutic effect
	80	53−74	25 mg	14	Alteplase[36]	Reduce NIHSS score, enhance effective rate and postoperative recovery rate
	122	45−70	200 mL (14 days), 0.6 g (14 days)	28	Aspirin enteric-coated tablets and clopidogrel bisulfate tablets[37]	Increase effective rate, ADL score and plasma 3-MST level, decrease NIHSS score and plasma white Aβ42 level
	58	−	25 mg	14	Compound Danshen injection[38]	Reduce neurological function score, serum IL-6, IL-β, TNF-α and hs-CRP levels, and increase IL-8 levels
	70	40−80	25 mL (14 days), 0.6 g (20 days)	34	Aspirin, alteplase, etc.[39]	Reducing NIHSS and plasma MMP-9 level and increasing VEGF level can improve prognosis after stroke

Continued

Cerebrovascular disease	Number of cases (*n*)	Age stage	Dosage per day	Time of administration /day	Combined drug	Clinical pharmacological effect
Hemorrhagic stroke	120	56−78	25 mg	14	Naloxone[40]	Reduce the levels of Hcy, hs-CRP and HIF in serum and improve the effective rate
	100	−	0.6 g	28	Edaravone[41]	Increase NO level and effective rate, decrease ox-LDL, ET-1, ICAM-1, VCAM-1, PDGF, TNF-α, IL-6, CGRP and SIRT1 levels
	88	40−65	0.6 g	70	Nimodipine[42]	Improve peripheral resistance, mean blood flow and mean blood flow velocity, reduce hematoma volume, increase cognitive score and life ability score
Vascular dementia	83	48−74	0.6 g	90	Anticoagulation, promoting blood circulation to remove blood stasis and vasodilating drugs[43]	Increase MMSE score, ADL score and SOD activity in serum, decrease MDA content and CDR score
	86	50−75	0.6 g	30	Shuxuening injection[44]	Increase the effective rate, SOD level, MMSE, BSSD and ADL scale scores, and decrease the levels of MDA, IL-1β, TNF-α and CRP
	200	48−79	50 mg	28	Memantine[45,46]	Reduced CDR score, LOP and MDA levels, increased MMSE, BI score, SOD levels and cerebral hemodynamic parameters V_{min}, PI and BHI
	129	64−78	0.6 g	60		
Cerebral vasospasm	92	30−70	100 mL	14	Fasudil[47]	Reduce the levels of caspase-3, MMP-9 and MMP-2 in serum and the incidence of total adverse drug reactions
	58	33−72	100 mL	7	Refreshing static injection[48]	Reduce the serum levels of NSE, CRP, FABP, sICAM-1, TNF-α, IL-1β and TXB2, and increase the middle cerebral artery blood flow velocity and NO level
Delayed encephalopathy	215	−	0.6 g	56	Hyperbaric oxygen[51]	Increase RR and MMSE score, decrease NIHSS score
	171	−	200 mL	14	Dexamethasone and hyperbaric oxygen[52]	Increase MMSE, MoCA and ADL scores
	72	22−66	0.6 g	56	Refreshing static injection[53]	Increase total effective rate, MMSE score and SOD level, decrease MDA level

4 总结与展望

NBP治疗脑血管疾病的药理作用主要集中在抗血小板聚集、抗血栓形成、抑制神经细胞凋亡、抗氧化、保护线粒体功能、抗炎、抗脑缺血、减轻脑损伤和抗VD等方面, 在临床上常与Eda、阿替普酶、法舒地尔、醒脑静注射液、复方丹参注射液等药物联合使用治疗脑血管病, 并表现出良好的协同作用, 可为NBP的临床合理用药提供支撑, 但目前对NBP与其联合药物的相互作用机制研究较少, 提示学者可关注NBP与上述高频联合用药的相互作用机制研究。

作者贡献: 泥文娟负责文章撰写; 王晓艳和吴娅丽负责梳理文章框架; 韩冰、贾金浩、李琨和纪秋如负责文献查阅与整理; 李伟霞和唐进法负责总体构思和文章修改。

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