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颅内动脉粥样硬化斑块形成与血管重构的关系*

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摘要 目的:研究颅内动脉粥样硬化斑块的形成与血管重构的关系。**方法:**选择 2017 年 3 月到 2017 年 10 月在上海市第一人民医院神经内科接受治疗的 47 例诊断为缺血性脑血管疾病的患者,所有患者发病 7 天内行头颅核磁共振以及高分辨率核磁共振检查。使用 vesselmass 软件测量斑块处血管及正常对照处的血管壁面积、流体面积,计算斑块负荷以及血管重构比(RR)。RR>1.05 为正向重构,0.95≤RR≤1.05 为中间重构,RR<0.95 为负向重构。分析大脑中动脉与基底动脉内斑块形成处血管重构情况。根据临床症状以及影像学检查,将斑块分为责任斑块与非责任斑块,比较两组斑块的负荷大小。**结果:**47 例患者中,共有 72 个斑块,其中责任斑块 47 个(占 65.28%),非责任斑块 25 个(占 34.72%)。位于大脑中动脉的斑块有 51 个(占 70.83%),位于基底动脉的有 21 个(占 29.17%)。大脑中动脉出现负向重构比例较基底动脉更高(47.06% vs. 19.05%, $P=0.027$),基底动脉出现正向重构比例较大脑中动脉更高(57.14% vs. 25.49%, $P=0.010$)。相比非责任斑块,责任斑块的斑块负荷更大(0.70 ± 0.08 vs. 0.65 ± 0.07 , $P=0.017$)。**结论:**颅内动脉在应对斑块形成后出现不同的血管重构模式,负荷更大的斑块更不稳定。

关键词:颅内动脉粥样硬化斑块;血管重构;斑块负荷;正向重构;负向重构

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The Relationship between Intracranial Atherosclerotic Plaque Formation and Vascular Remodeling*

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ABSTRACT Objective: To investigate the relationship between the formation of intracranial atherosclerotic plaques and vascular remodeling. **Methods:** 47 patients with cerebrovascular ischemic events who were treated in Shanghai General Hospital from March 2017 to October 2017 were analyzed. All patients underwent cranial magnetic resonance imaging and high-resolution magnetic resonance imaging examinations at 3.0 T in seven-days after symptom onset. Lumen area and outer wall area at the lesion and reference sites were measured by using Vesselmass software. Plaque burden and vascular remodeling ratio (RR) were calculated. Vascular remodeling was positive remodeling if $RR > 1.05$, intermediate remodeling if $0.95 \leq RR \leq 1.05$, and negative remodeling if $RR < 0.95$. The vascular remodeling of middle cerebral artery and basilar artery where plaques existed was analyzed. According to clinical symptoms and imaging examinations, the plaques were divided into culprit and non-culprit plaque, and plaque burdens of the two groups were compared. **Results:** There were 72 plaques in 47 patients, including 47 culprit plaques (65.28%), 25 non-culprit plaques (34.72%), 51 plaques existed in the middle cerebral artery (70.83%) and 21 plaques existed in the basilar artery (29.17%). The middle cerebral artery had a higher proportion to exhibit negative remodeling than basilar artery (47.06% vs. 19.05%, $P=0.027$) and basilar artery had a higher proportion to exhibit positive remodeling than the middle cerebral artery (57.14% vs. 25.49%, $P=0.010$). The plaque burden of culprit plaques was larger than non-culprit plaques (0.70 ± 0.08 vs. 0.65 ± 0.07 , $P=0.017$). **Conclusion:** The intracranial arteries exhibit different vascular remodeling in response to plaque formation, and the plaques with larger plaque burden are more unstable.

Key words: Intracranial atherosclerotic plaque; Vascular remodeling; Plaque burden; Positive remodeling; Negative remodeling

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前言

颅内动脉粥样硬化疾病是导致缺血性卒中的主要病因^[1,2]。磁共振血管成像(magnetic resonance angiography, MRA)以及血

管造影(angiography)是临床上用来判断大动脉粥样硬化疾病的重要影像学检查。然而,在血管管腔出现狭窄前,动脉粥样硬化斑块早已形成且可以导致卒中事件的发生^[3,4]。有研究报道当斑块形成后,冠状动脉以及颈动脉可以出现正向重构向外扩张^[3,5,6]。

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此外,血管也可以出现负向重构向内缩窄^[7]。近年来,高分辨率核磁共振成像 (high-resolution magnetic resonance imaging, HR-MRI) 已被作为研究颅内大动脉粥样硬化斑块的重要手段^[8-11]。相比于血管造影,HR-MRI 可以更好地显示斑块以及血管壁情况^[6]。因此,本研究基于 HR-MRI 影像学检查,主要探讨了颅内动脉在出现斑块后血管重构情况,旨在为卒中患者的临床诊治以及预防提供更多的参考依据。

1 资料与方法

1.1 研究对象

本研究回顾性收集 2017 年 3 月至 10 月上海市第一人民医院收治的诊断急性缺血性脑卒中或短暂性脑缺血发作患者。所有患者均在发病 7 天内行头颅磁共振以及高分辨率核磁共振检查。入组标准:① 由颅内大动脉粥样硬化所引起的急性缺血性脑卒中或短暂性脑缺血发作患者;② HR-MRI 图像清晰,血管结构轮廓显示清楚;排除标准:① 其他原因所引起的缺血性脑血管事件,如心源性、烟雾病、动脉夹层等;② 血管完全闭塞无法测量,或图像不清晰。本研究方案得到上海市第一人民医院伦理委员会批准。

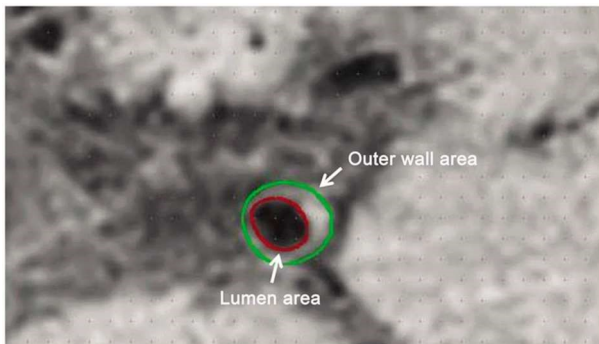


图 1 血管流体面积以及血管面积的测量

Fig.1 The measurement of lumen area and outer wall area

1.3 统计学方法

采用 SPSS 20.0(IBM SPSS statistics 20, Chicago, USA)处理数据,所有计量资料以($\bar{x} \pm s$)表示,计数资料以[例(%)]表示,采用 χ^2 检验比较大脑中动脉与基底动脉血管重构比例,采用 Mann-Whitney 检验比较责任斑块以及非责任斑块的斑块负荷、流体面积以及血管壁面积大小。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 患者基线数据以及斑块

本研究共入组 47 名患者,40 名(85.11%)诊断为急性缺血性脑卒中,7 名(14.89%)为短暂性脑缺血发作,平均年龄为 59.57 ± 12.22 。其中,男性 32 名(68.09%),总颅内斑块有 72 个,其中责任斑块有 47 个(65.28%),非责任斑块 25 个(34.72%)。位于大脑中动脉的斑块有 51 个(70.83%),位于基底动脉斑块有 21 个(29.17%),见表 1。

2.2 血管重构情况分析

大脑中动脉出现正向重构占 25.49%,中间重构占 27.45%,

1.2 检测方法

收集患者基线数据以及影像学资料。HR-MRI 检查:3.0T 成像系统,成像序列包括 T1 加权像(T1WI),T2 加权像(T2WI),T1 压脂序列以及增强序列。由 2 名经验丰富的神经影像医师对 HR-MRI 影像进行分析,结合病史区分责任斑块与非责任斑块:梗死患者责任斑块定义为梗死血管分布区唯一斑块或多个斑块时取最狭窄处斑块;短暂性脑缺血发作(Transient ischemic attacks, TIA)患者责任斑块定义为引起症状发作责任血管内的斑块;其余均为非责任斑块。大脑中动脉参考血管为对侧正常对应血管区域;基底动脉参考血管为斑块所在处近端以及远端正常血管处,取平均值^[12]。使用 OsiriX Lite 软件对斑块所在处以及参考血管进行重组,Vesselmass 软件测量血管的流体面积(lumen area, LA),血管面积(Outer wall area, OWA)(见图 1)。斑块负荷(plaque burden)=(OWA-LA)/OWA,血管重构比(remodeling ratio, RR)=OWA/OWA_{reference},RR > 1.05 定义为正向重构即血管向外扩张,0.95 ≤ RR ≤ 1.05 为中间重构即血管未向外侧扩张也未向内侧缩窄,RR < 0.95 为负向重构即血管向内缩窄^[13,14],见示意图 2。

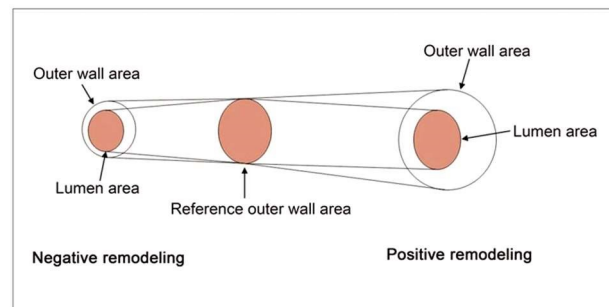


图 2 血管重构

Fig.2 Vascular remodeling

负向重构占 47.06%。基底动脉出现正向重构占 57.14%,中间重

表 1 入组患者基线数据以及斑块

Table 1 Baseline characteristics and plaques of patients

	Patients(%) n=47
Acute stroke	40 (85.11)
Transient ischemic attack	7 (14.89)
Culprit plaques	47 (65.28)
Non-culprit plaques	25 (34.72)
Middle cerebral artery plaques	51 (70.83)
Basilar artery plaques	21 (29.17)
Age, mean($\pm$ SD), y	59.57 $\pm$ 12.22
Male	32 (68.09)
Active smoker	24 (51.06)
Diabetes	13 (27.66)
Hypertension	34 (72.34)
Hyperlipidemia	20 (42.55)

构占 23.81%, 负向重构占 19.05%(见表 2)。基底动脉出现正向重构比例较大脑中动脉更高($P=0.010$), 大脑中动脉出现负相重

构比例较基底动脉更高($P=0.027$)。大脑中动脉以及基底动脉斑块的负荷无明显统计学差异($P>0.05$)。

表 2 大脑中动脉与基底动脉血管重构情况的比较

Table 2 Comparison of the vascular remodeling between middle cerebral artery and basilar artery

	Middle cerebral artery n=51	Basilar artery n=21
Negative remodeling	24 (47.06)	4 (19.05)
Intermediate remodeling	14 (27.45)	5 (23.81)
Positive remodeling	13 (25.49)	12 (57.14)

2.3 斑块负荷情况分析

与非责任斑块相比, 责任斑块流体面积更小 (0.05 ± 0.02 vs. 0.07 ± 0.04 , $P=0.009$), 斑块负荷更大(0.70 ± 0.08 vs. $0.65 \pm$

0.07 , $P=0.017$), 两者比较差异有显著的统计学意义(见表 3)。比较责任斑块与非责任斑块所在血管, 两者血管重构情况无明显统计学差异($P>0.05$)。

表 3 责任斑块与非责任斑块的斑块负荷比较

Table 3 Comparison of the plaque burden between culprit and non-culprit plaques

	Culprit plaques	Non-culprit plaques	P
Plaque burden	0.70 ± 0.08	0.65 ± 0.07	0.017
Lumen area (mm^2)	0.05 ± 0.02	0.07 ± 0.04	0.009
Outer wall area (mm^2)	0.18 ± 0.05	0.21 ± 0.09	0.161

3 讨论

动脉粥样硬化是导致缺血性心脑血管事件发生的重要病因。通常, 动脉粥样硬化斑块形成于大中动脉的血管壁上, 其发生主要与动脉内皮细胞受损、单核细胞及平滑肌细胞的迁移, 炎症因子如白介素-6、白介素-8 等表达上调有关^[15,16]。目前, 已有大量着重于斑块形成的机制研究, 但关于斑块形成对血管尤其是颅内血管的影响研究尚少。近年来, 有研究显示在斑块形成过程中, 血管壁也会随之发生改变, 当斑块形成后, 颅外动脉如冠状动脉、颈动脉会出现血管重构现象^[3]。血管重构是一个十分复杂的病理生理过程, 涉及到物理、生化以及遗传等多方面因素的影响, 其可以分为以下三种情况: ① 正向重构即血管向外扩张生长; ② 负向重构: 血管向内缩窄; ③ 中间重构: 血管既不向外扩张也不向内缩窄^[14]。疾病早期机体为了维持正常的血液供应, 血管会代偿性向外扩张, 此时血管的流体面积并不会出现明显狭窄, 但血管壁斑块可能已经形成, 因此尽管未见狭窄的管腔, 也仍有发生卒中事件的可能。由此可见, 仅通过磁共振血管成像以及颅内血管造影观察管腔狭窄并不能很好反映病情以及预测卒中事件的发生。基于此, 研究颅内血管对于斑块形成后出现的血管重构对临床诊治以及卒中预防有着重要的意义。

本研究结果显示斑块形成后, 大脑中动脉更容易出现负向重构, 而基底动脉更容易出现正向重构, 这提示颅内动脉在应对斑块形成后存在不同的血管重构模式。更重要的是, 这也为我们在临床诊治过程中忽视的血管正向重构现象提供理论依据。先前已有研究报道, 基底动脉可以出现正向重构, 且正向重构后的血管更容易出现腔隙性脑梗死^[12]。在本研究中, 我们发现基底动脉相比于大脑中动脉出现正向重构比例更高, 而造

成这种不同血管重构模式的机制尚不明确, 原因可能是: ① 血流动力学因素影响: 血流动力学是引起血管重构的重要因素之一。在正常生理条件下, 血液流动带来的剪切力直接作用于血管的内皮细胞, 不同的剪切力会对内皮细胞产生不同的影响。在低剪切力情况下, 血管会发生重构^[17-19]。与前循环的动脉相比, 后循环血管的血液流速更慢, 因此前后循环动脉会产生不同大小的剪切力, 从而可能造成不同的血管重构^[20]。② 遗传因素: 目前多项研究报道, 基因在血管重构中也起着重要作用, 如神经元型一氧化氮合酶 (nNOS), 诱导型一氧化氮合酶(iNOS), toll 样受体-4(TLR4)以及肝细胞生长因子(HGF)等基因可以通过氧化应激、炎症反应等途径对血管进行调节^[21-24]。而前后循环动脉在这些基因表达上可能存在不同。③ 神经支配: 与前循环动脉相比, 后循环血管如椎动脉以及基底动脉有较少的交感神经支配, 从而导致后循环动脉的血管调节功能较差^[25,26]。④ 相比于其他动脉, 后循环血管更容易出现迂曲扩张, 其发生机制可能与基底动脉易出现正向重构相似^[27]。此外, 有研究报道, 椎基底动脉与冠状动脉有相同的基因支配, 因此可能会有相似的血管重构^[28]。如前所述, 冠状动脉在出现早期病变时, 血管会通过正向重构来维持组织的血液供应^[9], 这也为基底动脉易出现正向重构的机制提供了新的理论依据。

此外, 在我们的研究中也发现同一名患者血管壁上可能存在于多处不同的动脉粥样硬化斑块, 但并不是每一处斑块均会引起缺血性脑血管事件的发生。其中, 不稳定的动脉粥样硬化斑块才是导致心脑血管事件发生的主要原因。因此, 评估斑块的稳定性对预测卒中事件的发生十分重要。目前, 常规的影像学检查如血管造影以及磁共振血管成像所观察的血管腔狭窄并不能很好的反映病情, 且研究报道血管狭窄与斑块稳定性并无明显相关性^[29]。因此, 新的评估斑块稳定性的方法十分必要。目

前,超声造影术可以观察颈动脉斑块内新生血管的形成,从而用来评价斑块的稳定性^[30]。但颅内动脉斑块的稳定性尚缺少有效的评估方法。先前有研究指出除了斑块内的坏死核心的大小以及薄的纤维帽等因素,斑块的负荷也被认为与斑块的稳定性相关^[31,32]。几项临床研究也报道颈动脉内大负荷的斑块与缺血性卒中事件的发生密切相关^[33-35]。有较大的负荷的斑块更加不稳定^[29]。基于以上研究,我们通过应用高分辨率核磁共振成像技术分析责任斑块与非责任斑块的负荷大小,意在探索斑块负荷是否与斑块稳定性相关。研究结果显示相比于非责任斑块,责任斑块的斑块负荷更大,且有明显的显著性差异。这一结果进一步验证大负荷的斑块更不稳定,容易引起缺血性脑血管事件的发生,也进一步说明高分辨率核磁共振成像在判断斑块稳定性方面发挥重要的作用。

综上所述,颅内动脉在应对斑块形成后会有不同的血管重构模式,基底动脉更易出现正向重构,因此,尽管临床上通过影像学并未观察基底动脉的管腔出现明显狭窄,也并不能代表血管壁无病变,需要进一步通过高分辨率核磁共振血管壁成像检查来评估患者病情。斑块的负荷可以用作评估以及预测卒中事件发生的重要参考指标。本研究对颅内血管应对斑块形成后所引起的改变提供新的理论支持,也为进行精准的卒中诊治及预防具有重要的指导作用。

参 考 文 献(References)

- [1] Torres N, Guevara-Cruz M, Velázquez-Villegas LA. Nutrition and Atherosclerosis[J]. Arch Med Res, 2015, 46(5): 408-426
- [2] Hurtubise J, McLellan K, Durr K, et al. The Different Facets of Dyslipidemia and Hypertension in Atherosclerosis [J]. Curr Atheroscler Rep, 2016, 18(12): 82
- [3] Astor BC, Sharrett AR, Coresh J, et al. Remodeling of carotid arteries detected with MR imaging: atherosclerosis risk in communities carotid MRI study[J]. Radiology, 2010, 256(3): 879-886
- [4] Cao Y, Sun Y, Zhou B, et al. Atherosclerotic plaque burden of middle cerebral artery and extracranial carotid artery characterized by MRI in patients with acute ischemic stroke in China: association and clinical relevance[J]. Neurol Res, 2017, 39(4): 344-350
- [5] Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human atherosclerotic coronary arteries [J]. N Engl J Med, 1987, 316(22): 1371-1375
- [6] Babiarz LS, Astor B, Mohamed MA, et al. Comparison of gadolinium-enhanced cardiovascular magnetic resonance angiography with high-resolution black blood cardiovascular magnetic resonance for assessing carotid artery stenosis [J]. J Cardiovasc Magn Reson, 2007, 9(1): 63-70
- [7] Fearon WF, Felix R, Hirohata A, et al. The effect of negative remodeling on fractional flow reserve after cardiac transplantation [J]. Int J Cardiol, 2017, 15(241): 283-287
- [8] Wang E, Shao S, Li S, et al. A High-Resolution MRI Study of the Relationship Between Plaque Enhancement and Ischemic Stroke Events in Patients With Intracranial Atherosclerotic Stenosis [J]. Front Neurol, 2019, 8(9): 1154
- [9] Huang J, Jiao S, Zhao X, et al. Characteristics of patients with enhancing intracranial atherosclerosis and a association between plaque enhancement and recent cerebrovascular ischemic events: a high-resolution magnetic resonance imaging study [J]. Acta Radiol, 2019, 16[Epub ahead of print]
- [10] Lu M, Cui Y, Peng P, et al. Shape and Location of Carotid Atherosclerotic Plaque and Intraplaque Hemorrhage: A High-resolution Magnetic Resonance Imaging Study [J]. J Atheroscler Thromb, 2019, 9
- [11] 洪波. 高分辨率核磁共振管壁成像技术带来颅内血管疾病诊疗的革命性进展[J]. 中国脑血管病杂志, 2017, 7(14): 337-339
- [12] Feng C, Hua T, Xu Y, et al. Arterial remodeling of basilar atherosclerosis in isolated pontine infarction [J]. Neurol Sci, 2015, 36(4): 547-551
- [13] Guo R, Zhang X, Zhu X, et al. Morphologic characteristics of severe basilar artery atherosclerotic stenosis on 3D high-resolution MRI[J]. BMC Neurol, 2018, 18(1): 206
- [14] Qiao Y, Anwar Z, Intrapirromkul J, et al. Patterns and Implications of Intracranial Arterial Remodeling in Stroke Patients [J]. Stroke, 2016, 47(2): 434-440
- [15] Tabas I, García-Cardeña G, Owens GK. Recent insights into the cellular biology of atherosclerosis[J]. Nature, 2015, 209(1): 13-22
- [16] Camare C, Pucelle M, Negre-Salvayre A, et al. Angiogenesis in the atherosclerotic plaque[J]. Redox Biol, 2017, 12: 18-34
- [17] Hayashi K, Kakoi D, Makino A, et al. Remodeling of the arterial wall: Response to restoration of normal blood flow after flow reduction[J]. Biorheology, 2018, 54(2-4): 95-108
- [18] Stone PH, Coskun AU, Kinlay S, et al. Regions of low endothelial shear stress are the sites where coronary plaque progresses and vascular remodelling occurs in humans: an in vivo serial study [J]. Eur Heart J, 2007, 28(6): 705-710
- [19] Hayashi K, Makino A, Kakoi D, et al. Remodeling of arterial wall: Response to changes in both blood flow and blood pressure [J]. J Mech Behav Biomed Mater, 2018, 77: 475-484
- [20] Buijs PC, Krabbe-Hartkamp MJ, Bakker CJ, et al. Effect of age on cerebral blood flow: measurement with ungated two-dimensional phase-contrast MR angiography in 250 adults [J]. Radiology, 1998, 209(3): 667-674
- [21] Arnold C, Feldner A, Zappe M, et al. Genetic ablation of NFAT5/TonEBP in smooth muscle cells impairs flow- and pressure-induced arterial remodeling in mice [J]. FASEB J, 2018, 1[Epub ahead of print]
- [22] Hollestelle SC, De Vries MR, Van Keulen JK, et al. Toll-like receptor 4 is involved in outward arterial remodeling [J]. Circulation, 2004, 109(3): 393-398
- [23] Rudic RD, Bucci M, Fulton D, et al. Temporal events underlying arterial remodeling after chronic flow reduction in mice: correlation of structural changes with a deficit in basal nitric oxide synthesis[J]. Circ Res, 2000, 86(11): 1160-1166
- [24] Chen J, Zhang H, Zhang R, et al. Transfer of human hepatocyte growth factor reduces inflammation and prevents pulmonary arterial remodeling in monocrotaline-induced[J]. Int J Clin Exp Pathol, 2014, 7(12): 8763-8669
- [25] Beausang-Linder M, Bill A. Cerebral circulation in acute arterial hypertension--protective effects of sympathetic nervous activity[J]. Acta Physiol Scand, 1981, 111(2): 193-199

- gen and fibronectin in neural cell adhesion and migration [J]. *Developmental Biology*, 1981, 87: 259-266
- [15] 龚海鹏,钟映晖,公衍道,等.多聚赖氨酸改性壳聚糖对神经细胞的作用[J].*生物物理学报*, 2000, 16(03): 553-561
- [16] I-Chi Lee, Yu-Chieh Wu, En-Ming, et al. Biomimetic niche for neural stem cell differentiation using poly-L-lysine/hyaluronic acid multilayer films [J]. *Journal of biomaterials applications*, 2015, 29(10): 1418-1427
- [17] Matsumura K, Nakajima N, Sugai H, et al. Self-degradation of tissue adhesive based on oxidized dextran and poly-L-lysine [J]. *Carbohydrate Polymers*, 2014, 113: 32-38
- [18] 常翔,方淑环,张玉,等.新生小鼠海马神经元培养及形态学观察的优化方法[J].*重庆医学*, 2014, 43(22): 2910-2912
- [19] 阳小飞,梅颖,余意,等.印防己毒素在不同类型突触分泌中的作用[J].*中南民族大学学报(自然科学版)*, 2016, 35(03): 80-84
- [20] 阳小飞,余意,刘孟雪,等.稳定表达绿色荧光蛋白的 HEK293T 细胞的构建[J].*中南民族大学学报(自然科学版)*, 2017, 36(02): 38-41
- [21] 刘新颖. 2005 成年大鼠海马神经细胞的体外培养[D]. 西北农林科技大学, 2005
- [22] Wei L, Wen-Bin L I, Chen Z J, et al. Protective effects of IGF-1 on cortical nerve cells of neonatal rats under oxidative stress [J]. *Zhongguo Dang Dai Er Ke Za Zhi*, 2014, 16(2): 203-207
- [23] Liu X, Wang G, Pu H, et al. Abnormal intracellular calcium homeostasis associated with vulnerability in the nerve cells from heroin-dependent rat[J]. *Brain Research*, 2014, 1572: 40-49
- [24] Qi Y, Ge J Y, Wang Y N, et al. Co-expression of activin receptor-interacting protein 1 and 2 in mouse nerve cells [J]. *Neuroscience Letters*, 2013, 542: 53-58
- [25] Tissir F, Goffinet A M. Shaping the nervous system: role of the core planar cell polarity genes[J]. *Nature Reviews Neuroscience*, 2013, 14(8): 525-535
- [26] Fan H L, Yin S G, Lou P, et al. Expressions of P-JNK in nerve cell apoptosis of A2AR knockout newborn mice after hypoxia/ischemia brain damage[J]. *Chinese journal of applied physiology*, 2013, 29(2): 187
- [27] 黄卫东,费舟,章翔,等.体外培养大鼠脑皮层神经元机械性损伤模型的建立[J].*第四军医大学学报*, 2004, 25(04): 307-309
- [28] 王明明,梅颖,阳小飞.铝离子对神经细胞突触生长的影响[J].*绿色科技*, 2017, (08): 229-231
- [29] Song S H, Augustine G J. Synapsin Isoforms and Synaptic Vesicle Trafficking[J]. *Molecules & Cells*, 2015, 38(11): 936-940
- [30] 王平,陈秀.胎鼠海马神经细胞无血清原代培养法及鉴定[J].*临床合理用药杂志*, 2018, 11(04): 29-30+32
- [31] Schulte C, Ripamonti M, Maffioli E, et al. Scale Invariant Disordered Nanotopography Promotes Hippocampal Neuron Development and Maturation with Involvement of Mechanotransductive Pathways [J]. *Frontiers in Cellular Neuroscience*, 2016, 10: 267
- [32] Zhang Q Y, Zhang Y Y, Xie J, et al. Stiff substrates enhance cultured neuronal network activity[J]. *Scientific Reports*, 2014, 4: 6215

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- [26] Edvinsson L, Owman C, Sjoberg NO. Autonomic nerves, mast cells, and amine receptors in human brain vessels [J]. *Brain Res*, 1976, 115(3): 377-393
- [27] Gutierrez J, Sacco RL, Wright CB. Dolichoectasia-an evolving arterial disease[J]. *Nat Rev Neurol*, 2011, 7(1): 41-50
- [28] Tanaka M, Sakaguchi M, Miwa K, et al. Basilar artery diameter is an independent predictor of incident cardiovascular events [J]. *Arterioscler Thromb Vasc Biol*, 2013, 33(9): 2240-2244
- [29] Kim JM, Jung KH, Sohn CH, et al. Middle cerebral artery plaque and prediction of the infarction pattern [J]. *Arch Neurol*, 2012, 69(11): 1470-1475
- [30] 陈建梅,王秋霜,黄党生,等.超声造影技术评价颈动脉粥样硬化斑块稳定性的临床研究 [J]. *现代生物医学进展*, 2017, 17(2): 280-282, 330
- [31] Oberoi R, Vlacil AK, Schuett J, et al. Anti-tumor necrosis factor- α therapy increases plaque burden in a mouse model of experimental atherosclerosis[J]. *Atherosclerosis*, 2018, 277: 80-89
- [32] Rodriguez-Granillo GA, Campisi R, Reynoso E, et al. Atherosclerotic plaque burden evaluated from neck to groin: effect of gender and cardiovascular risk factors[J]. *Int J Cardiovasc Imaging*, 2018, 13
- [33] Zhao X, Underhill HR, Zhao Q, et al. Discriminating carotid atherosclerotic lesion severity by luminal stenosis and plaque burden: a comparison utilizing high-resolution magnetic resonance imaging at 3.0 Tesla[J]. *Stroke*, 2011, 42(2): 347-353
- [34] Zhao H, Zhao X, Liu X, et al. Association of carotid atherosclerotic plaque features with acute ischemic stroke: a magnetic resonance imaging study[J]. *Eur J Radiol*, 2013, 82(9): 465-470
- [35] Sun R, Wang L, Guan C, et al. Carotid Atherosclerotic Plaque Features in Patients with Acute Ischemic Stroke [J]. *World Neurosurg*, 2018, 112: 223-228