·论著·

脑梗死急性期大鼠胃肠黏膜损伤的动态变化观察

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【摘要】 目的　观察脑梗死急性期大鼠胃肠黏膜的动态变化特点和与疾病进展的关系。**方法**　选择雄性 Wistar 大鼠 56 只，将大鼠按随机数字表法分为正常对照组、假手术组和脑梗死模型组。采用改良的 Longa 线栓法复制大脑中动脉闭塞（MCAO）模型。于制模后 24 h 和 4 d、7 d 观察各组大鼠血清胃泌素（GAS）水平；处死大鼠后留取各组大鼠胃窦及小肠组织切片后行苏木素－伊红（HE）染色，光镜下观察胃及小肠黏膜组织病理学改变；同时进行胃和小肠黏膜病理学评分，比较各组病理学评分的差异。**结果**　正常对照组和假手术组各时间点 GAS、胃和小肠黏膜病理学评分比较差异均无统计学意义（均 $P>0.05$）；脑梗死模型组 GAS 水平随时间延长逐渐降低，制模后 7 d 达最低水平，但脑梗死模型组 GAS 水平明显高于正常对照组和假手术组（ng/L：205.02±7.68 比 130.51±8.03、145.29±7.68，均 $P<0.05$）。脑梗死模型组胃和小肠黏膜病理学评分随时间延长呈先升高后降低的趋势，制模后 4 d 达到峰值，7 d 明显降低，但脑梗死模型组胃和小肠黏膜病理学评分均明显高于正常对照组和假手术组〔胃黏膜病理学评分（分）：82.50±2.95 比 21.38±1.57、36.10±3.41，小肠黏膜病理学评分（分）：62.00±2.78 比 18.25±1.39、25.55±1.75，均 $P<0.05$〕。光镜下可见正常对照组胃、肠黏膜形态完整，结构正常，绒毛排列整齐，无炎症细胞浸润；假手术组各时间点固有层可见炎症细胞浸润，绒毛轻度高低不平，间质增宽，偶见充血、水肿，未见明显溃疡；脑梗死模型组胃肠黏膜各层次欠清晰，腺体不规则排列，毛细血管扩张；部分组织可见充血、出血、水肿，炎症细胞浸润明显。**结论**　脑梗死急性期胃肠黏膜的损伤应与脑梗死本身的应激刺激和疾病进展有关，而不是 GAS 的异常分泌。

【关键词】 脑梗死急性期；　胃泌素；　胃肠黏膜损伤；　动态变化

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Observation on dynamic changes of gastrointestinal mucosal injury in rats with acute stage of cerebral infarction

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【Abstract】 Objective　To investigate the dynamic characteristic changes of gastrointestinal mucosa and its relationship with disease progression in rats with acute cerebral infarction. **Methods**　Fifty-six male Wistar rats were selected as the study subjects, and they were divided into three groups: normal control, sham operation and cerebral infarction model groups by random number table method. The middle cerebral artery occlusion (MCAO) model was prepared by the modified Longa thread embolic method. The levels of gastrin (GAS) were monitored in each group after modeling for 24 hours, 4 days and 7 days; after the rats were killed, the sections of gastric antrum and small intestine were taken and stained with hematoxylin-eosin (HE) staining method, the histopathological changes of gastric and small intestinal mucosa were observed under light microscope, in the mean time the gastric and small intestinal mucosal pathological scores were also performed, and the differences of pathological scores among the three groups were compared. **Results**　There were no statistical significant differences in GAS, gastrointestinal mucosa and small intestinal mucosal pathological scores between the normal control group and sham operation group at each time point (all $P > 0.05$); the GAS level in cerebral infarction model group was decreased gradually with time prolongation, reaching the lowest level 7 days after modeling, but the GAS level in cerebral infarction model group was significantly higher than that in normal group and shamoperation group (ng/L: 205.02±7.68 vs. 130.51±8.03, 145.29±7.68, both $P < 0.05$). The pathological scores of gastrointestinal mucosa and small intestinal mucosa in the cerebral infarction model group were increased first and then decreased with time prolongation, peaked on 4th day and decreased significantly on 7th day, the pathological scores of gastrointestinal mucosa and small intestinal mucosa in the cerebral infarction model group at each time point were significantly higher than those in the normal control group and sham-operated group (gastric mucosal pathological score: 82.50±2.95 vs. 21.38±1.57, 36.10±3.41; small intestinal mucosal pathological score: 62.00±2.78 vs. 18.25±1.39, 25.55±1.75, all $P < 0.05$). Under light microscopy, the normal control group showed complete normal morphological appearance, normal structure, orderly arrangement of villi and no infiltration of inflammatory cells; in shamoperation group, inflammatory cells infiltrated the lamina propria at each time point, and there were villi slightly uneven, enlarged stroma, congestion, edema occasionally seen and no obvious ulcer; in cerebral infarction model group, the various layers of gastrointestinal mucosal were not very clear, the glands were arranged irregularly and the

capillaries dilated, and in part of tissues, congestion, hemorrhage, edema and inflammatory cell infiltration were seen obviously. **Conclusion** The injury of gastrointestinal mucosa in acute stage of cerebral infarction should be related to the stress stimulation and disease progress of cerebral infarction itself, not due to the abnormal secretion of GAS.

【Key words】 Cerebral infarction acute phase; Gastrin; Gastrointestinal mucosal injury; Dynamic changes

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胃肠损伤是脑梗死急性期尤其是重症脑梗死患者常见的并发症之一[1-2]，临床可见恶心、呕吐、腹胀、腹泻、便秘、上消化道出血等症状[3]。脑梗死急性期胃肠损伤的发病机制至今尚不明确。胃肠黏膜损伤在脑梗死急性期是如何动态变化的？胃黏膜损伤何时达到高峰期？其影响因素又有哪些？这些问题仍有待验证。

目前相关研究显示，脑梗死急性期会引发应激反应[4]，在应激状态下胃酸分泌增加，胃肠黏膜屏障在酸性环境中极易受损，出现上皮细胞坏死、脱落、甚至黏膜出血糜烂等，从而引发应激性溃疡等各种胃肠道反应[5-6]。胃酸分泌的增加往往与胃泌素（GAS）过度分泌有关[7]。GAS的分泌多少是否是引起脑梗死急性期胃肠损伤的重要因素呢？本研究即以此为出发点，观察脑梗死急性期血清GAS分泌、胃肠黏膜损伤的动态变化与疾病进展的关系。

1 材料与方法

1.1 实验动物分组及模型制备：选择10周龄健康雄性清洁级Wistar大鼠56只，体质量180～220 g，购于山东中医药大学动物实验中心，动物合格证号：SCXK20120006。采用改良的Longa线栓法[8]复制大鼠大脑中动脉闭塞（MCAO）模型；假手术组仅穿线不结扎。将大鼠按随机数字法分为正常对照组（8只）、假手术组（24只）和脑梗死模型组（24只）。采用Langa法[8]对模型大鼠进行评分，评分2～3分为模型复制成功。

1.2 伦理学：本实验中动物处置方法符合动物伦理学标准（2018HC11LQ037）。

1.3 观察指标及方法

1.3.1 各组大鼠血清GAS水平测定：制模后7 d，腹腔麻醉各组大鼠，取下腔静脉血2 mL，离心取血清保存以备测各组GAS水平。

1.3.2 各组大鼠小肠组织病理学观察：于制模后4 d、7 d处死各组大鼠，取大鼠胃窦及小肠组织（胃窦距幽门口0.5 cm，小肠组织距屈氏韧带1.5cm），置于10%甲醛水溶液中固定，并脱水、透明、石蜡包埋、制备4 μm切片后进行苏木素－伊红（HE）染色，光镜下观察各组大鼠胃肠黏膜病理学改变，并进行胃肠黏膜病理学评分[9-10]。

1.4 统计学分析：使用SPSS 21.0统计软件处理数据，符合正态分布的计量数据以均数 ± 标准差（$\bar{x}\pm s$）表示，各组间数值资料比较需在方差齐性的前提下采用方差分析，两两比较采用q检验；分类资料以只表示，采用χ^2检验。$P<0.05$为差异有统计学意义。

2 结 果

2.1 各组大鼠血清GAS水平的比较（表1）：正常对照组和假手术组不同时间点血清GAS水平比较差异均无统计学意义（均$P>0.05$）；脑梗死模型组血清GAS水平随时间延长逐渐降低，制模后7 d达最低水平，且脑梗死组各时间点血清GAS水平均较正常对照组和假手术组显著升高（均$P<0.01$）。

表1 不同处理方法各组大鼠血清GAS水平比较（$\bar{x}\pm s$）

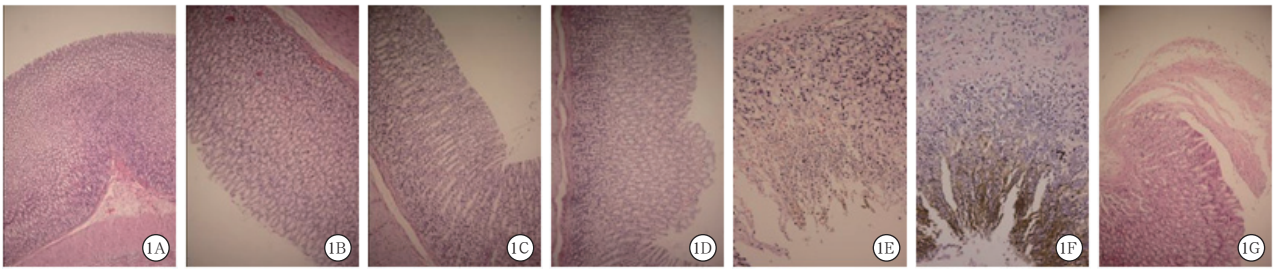
组别	动物数（只）	GAS（ng/L）		
		制模后24 h	制模后4 d	制模后7 d
正常对照组	8	130.51± 8.03	130.51± 8.03	130.51±8.03
假手术组	24	140.12±11.83	140.93±13.48	145.29±7.68
脑梗死模型组	24	298.97±17.69 ^{ab}	216.28±19.42 ^{abc}	205.02±7.68 ^{abcd}

注：与正常对照组比较，$^aP<0.01$；与假手术组比较，$^bP<0.01$；与本组制模后24 h比较，$^cP<0.05$；与本组制模后4 d比较，$^dP<0.05$

2.2 胃肠黏膜病理学观察

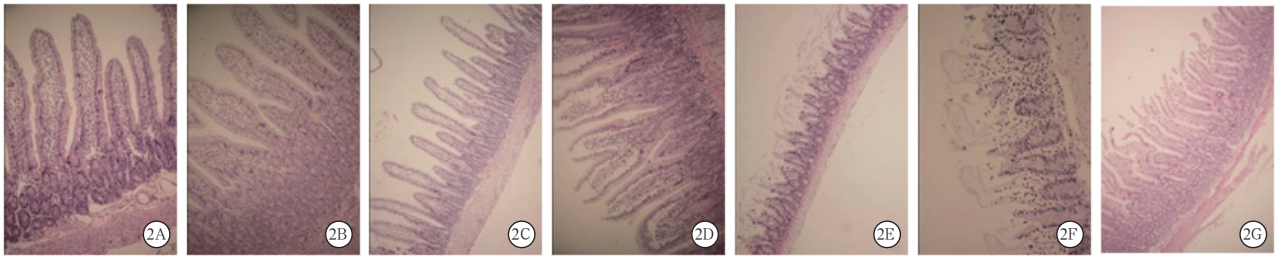
2.2.1 不同处理方法各组大鼠胃黏膜的动态变化比较（图1）：正常对照组胃黏膜各层次清晰，腺体排列整齐，结构完整，未见炎症细胞浸润；假手术组各时间点胃黏膜层次欠清晰，腺体排列不规整，黏膜层偶可见充血、水肿，可见少量炎症细胞浸润；脑梗死模型组制模后24 h胃黏膜各层次欠清晰，腺体排列不规则，可见部分细胞变性、坏死，部分区域呈现充血、出血及水肿，炎症细胞浸润明显，制模后4 d黏膜腺体排列不规则较制模后24 h加重，固有层可见大片状变性、坏死，周围腺上皮细胞增生，黏膜组织明显充血、水肿，炎症细胞浸润明显，制模后7 d黏膜腺体排列不规则较制模后4 d有所减轻，黏膜组织充血及水肿亦较制模后4 d减轻，偶可见糜烂。

2.2.2 不同处理方法各组大鼠小肠黏膜的动态变化比较（图2）：正常对照组肠黏膜形态完整，结构正



注：A 为正常对照组；B 为假手术组制模后 24 h；C 为假手术组制模后 4 d；D 为假手术组制模后 7 d；E 为脑梗死模型组制模后 24 h；F 为脑梗死模型组制模后 4 d；G 为脑梗死模型组制模后 7 d

图 1　不同处理方法各组大鼠胃黏膜病理学变化观察（HE 染色　低倍放大）



注：A 为正常对照组；B 为假手术组制模后 24 h；C 为假手术组制模后 4 d；D 为假手术组制模后 7 d；E 为脑梗死模型组制模后 24 h；F 为脑梗死模型组制模后 4 d；G 为脑梗死模型组制模后 7 d

图 2　不同处理方法各组大鼠小肠黏膜病理学变化观察（HE 染色　低倍放大）

表 2　不同处理方法各组大鼠胃黏膜和小肠黏膜病理学评分比较（$\bar{x} \pm s$）

组别	动物数（只）	胃黏膜病理学评分（分）			小肠黏膜病理学评分（分）		
		制模后 24 h	制模后 4 d	制模后 7 d	制模后 24 h	制模后 4 d	制模后 7 d
正常对照组	8	21.38±1.57	21.38±1.57	21.38±1.57	18.25±1.39	18.25±1.39	18.25±1.39
假手术组	24	31.13±2.46	36.00±3.24	36.10±3.41	24.75±1.63	26.25±1.49	25.55±1.75
脑梗死模型组	24	80.50±3.58 ^{ab}	96.50±4.73 ^{abc}	82.50±2.95 ^{abcd}	64.00±2.54 ^{ab}	86.00±3.43 ^{abc}	62.00±2.78 ^{abcd}

注：与正常对照组比较，$^{a}P<0.01$；与假手术组比较，$^{b}P<0.01$；与本组制模后 24 h 比较，$^{c}P<0.05$；与本组制模后 4 d 比较，$^{d}P<0.05$

常，绒毛排列整齐，无炎症细胞浸润；假手术组各时间点固有层可见炎症细胞浸润，绒毛轻度高低不平，间质增宽，偶见充血、水肿，未见明显溃疡；脑梗死模型组制模后 24 h 肠黏膜水肿、充血、萎缩，部分脱落、出血，绒毛间质增宽，可见少量炎症细胞浸润；制模后 4 d 肠黏膜水肿、充血，血管扩张明显，固有膜损害，绒毛间质较前增宽明显，黏膜大面积脱落，出血，炎症细胞浸润明显，制模后 7 d 肠黏膜充血、水肿较制模后 4 d 减轻，绒毛排列尚整齐，可见充血及出血点，偶可见黏膜脱落。

2.3　不同处理方法各组大鼠胃和小肠黏膜病理学评分比较（表 2）：正常对照组和假手术组各时间点胃和小肠黏膜病理学评分比较差异均无统计学意义（均 $P>0.05$）；脑梗死模型组胃和小肠黏膜病理学评分随时间延长呈先升高后降低的趋势，制模后 4 d 达到峰值，7 d 达最低水平，且脑梗死模型组各时间点胃和小肠黏膜病理学评分均明显高于正常对照组及假手术组（均 $P<0.05$）。

3　讨　论

本研究结果显示，正常对照组及假手术各时间点胃肠黏膜损伤不明显，且未发现有时间动态变化性。而脑梗死模型组胃肠组织损伤程度较正常对照组及假手术组明显加重，胃肠黏膜上皮细胞大量脱落、凋亡、黏膜层糜烂，重者甚至累及黏膜下层。上述现象的发生，单纯应用“应激性胃肠黏膜损伤学说[11]”来解释略显牵强。毕竟引起应激反应发生的因素较多，单纯脑梗死疾病本身可引起应激反应，同样实验过程中假手术组的制模手术本身也可引起应激反应。但为何可引起应激反应的假手术组没有出现明显胃肠黏膜损伤呢？一方面有可能胃肠损伤的发生与应激刺激程度有关，假手术组手术创伤刺激尚不能激活机体应激反应系统，或者说轻度应激刺激不能让机体发生失代偿，不足以激活机体胃肠系统产生明显损伤。另一方面，胃肠损伤的发生或许与应激方式或者说是应激特点有关。颅脑的缺血变化或许跟各种手术、感染等引起的应激刺激

不同，颅脑缺血对机体来讲是一种特殊的应激刺激，且能引发机体胃肠系统的重大变化。此外脑与胃肠之间必定通过一条或多条反馈途径相互影响。颅脑组织的缺血损伤可反射性引起胃肠黏膜的变化，从而进一步证实了脑与胃肠在病理上的密切相关性。

本研究也表明，脑梗死急性期，胃肠黏膜即开始出现充血、水肿、糜烂等损伤，制模后 4 d 时胃肠损伤达到最高峰，7 d 时胃肠黏膜损伤较前反而减轻。结合脑梗死病情发展轨迹，以及胃肠黏膜损伤的时间变化性发现，胃肠黏膜损伤的高峰低谷与脑梗死整体的病情变化时间基本一致。随着脑血管闭塞的发生，颅脑缺血缺氧，同时脑水肿持续加重，颅内压亦同时增高，第 4 天往往是颅脑水肿的高峰期，同时也是脑梗死病情变化的分水岭[12-14]。第 4 天以后，脑梗死病情趋于稳定并好转，脑水肿亦会减轻改善，中枢神经系统再次恢复了对胃肠系统的有力调节，胃肠黏膜局部的缺血缺氧改善，其胃肠黏膜损伤亦会进行修复。由此推测，脑梗死急性期胃肠黏膜的损伤与脑梗死本身的病情发展密切相关。

研究显示，应激性胃肠黏膜病变是脑梗死急性期胃肠损伤的常见病理学表现[15-16]，其中胃酸过度释放是引发胃肠道应激损伤的重要因素[17]。应激刺激下，GAS 水平异常增高，胃蛋白酶原被大量激活，胃酸分泌增多[18]，胃肠环境的 pH 值降低明显，黏膜内 H^+ 明显增多，其弥散反渗，并刺激肥大细胞使组织胺释放增多，局部微循环障碍，胃肠黏膜毛细血管通透性明显增高[19]，导致胃肠黏膜出血、水肿甚至局部糜烂，出现应激性溃疡。并推测 GAS 的过度分泌可导致胃酸增多，从而造成胃肠黏膜损伤[20]。

本实验结果证实，脑梗死急性期 GAS 分泌异常增多，制模后 24 h GAS 分泌最多，随着时间延长 GAS 的分泌亦呈下降趋势。而胃肠黏膜组织的损伤程度与 GAS 分泌高低并不呈完全对应关系。胃肠黏膜的损伤以制模后 4 d 最为严重，随后逐渐减轻。由此推测急性脑梗死胃肠黏膜损伤的重要因素并不是 GAS 过度分泌，可能与脑梗死本身的应激刺激和疾病进展密切相关，毕竟脑梗死后脑水肿高峰期主要发生于第 3～4 天，与胃肠黏膜损伤的高峰期相吻合。脑与胃肠之间必然存在相应的反馈与负反馈机制，具体调节机制还有待进一步探索。

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