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# CaMK II在小鼠重症急性胰腺炎胰腺损伤中的作用

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**摘要:目的** 观察钙调素依赖蛋白激酶(CaMK II)在重症急性胰腺炎(SAP)小鼠胰腺组织中的表达情况,并探讨其抑制剂KN93对SAP胰腺损伤的保护作用和机制。**方法** 36只健康雄性C57小鼠随机分为假手术组、SAP组、KN93组、SAP组+KN93组,9只/组。于造模后24 h收集血清和胰腺组织;采用HE染色观察胰腺组织病理改变;Elisa检测血清脂肪酶、淀粉酶活性以及炎性因子变化情况;免疫印迹法检测CaMK II、p-CaMK II、p-NF-κB、MAPK、p-MAPK在小鼠胰腺组织中的表达变化。**结果** 与假手术组比较,SAP组p-CaMK II、p-NF-κB、p-MAPK表达水平升高($P$<0.05)。KN93干预后,SAP小鼠胰腺组织病理损伤减轻,血清脂肪酶、淀粉酶以及炎性因子(TNF-α、IL-6)水平降低($P$<0.05),同时NF-κB、ERK和MAPK蛋白磷酸化也降低($P$<0.05)。**结论** CaMK II蛋白在SAP疾病胰腺组织活性升高,CaMK II抑制剂KN93能有效减轻SAP小鼠胰腺损伤和炎症程度,其机制可能与ERK/MAPK信号通路有关。
**关键词:**重症急性胰腺炎;CaMK II;NF-κB;KN93

## Role of CaMK II in pancreatic injury in mice with severe acute pancreatitis

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**Abstract: Objective** To investigate the expression of $Ca^{2+}$/calmodulin-dependent protein kinase II (CaMK Ⅱ) in pancreatic tissues of mice with severe acute pancreatitis (SAP) and explore the protective effect of KN93, a CaMK Ⅱ inhibitor, against pancreatic injury in SAP and the possible mechanism. **Methods** Thirty-six healthy male C57 mice were randomly divided into sham operation group, SAP group, KN93 group and SAP+KN93 group ($n$=9). Serum and pancreatic tissue samples were collected 24 h after modeling. The pathological changes in the pancreatic tissues were observed using HE staining. Serum lipase and amylase activities and the levels of inflammatory factors were detected using ELISA. Western blotting was used to detect the expressions of CaMK Ⅱ, p-CaMK Ⅱ, p-NF-κB, MAPK and p-MAPK in mouse pancreas. **Results** Compared with those in sham operation group, the expressions of p-CaMK Ⅱ, p-NF-κB and p-MAPK were significantly increased in SAP group ($P$<0.05). KN93 treatment obviously alleviated pathological injuries of the pancreas in SAP mice, and significantly lowered serum levels of lipase, amylase and inflammatory factors (TNF-$\alpha$ and IL-6) and phosphorylation levels of NF-κB, ERK and MAPK proteins ($P$<0.05). **Conclusion** The activity of CaMK Ⅱ is significantly increased in the pancreatic tissue of SAP mice. KN93 can alleviate pancreatic injury and inflammation in SAP mice possibly through the ERK/MAPK signaling pathway.
**Keywords:** severe acute pancreatitis; CaMK Ⅱ; nuclear factor-κB; KN93

重症急性胰腺炎(SAP)是一种较高致死率的炎性疾病,亢进的炎症反应导致机体全身炎症反应综合征(SIRS)与多器官功能衰竭[1]。目前已经证实,胰腺腺泡细胞内钙离子浓度增高可以促进胰蛋白酶原激活和释放,加重组织损伤[2-4]。组织损伤因子的释放诱导NF-κB的表达水平升高进而调控IL-1β、TNF-α等炎症因子的水平的转录来参与SAP的局部炎症反应[5,6];局部炎症反应进一步可能发展为全身炎症反应,导致多器官功能衰竭[7]。因此,探索控制全身炎症进展的措施,对于SAP救治具有重要的现实意义。

钙调素依赖蛋白激酶(CaMK II)可以通过调控细胞膜及肌质网的钙通道来调节细胞质内的钙离子浓度,进而参与细胞的重要病理生理进程。研究表明,CaMK II蛋白与胰腺疾病的病理生理过程有密切的联系[8-9]。除了通过细胞内钙离子浓度参与机体病理生理过程外,CaMK II还可通过抑制NF-κB来参与调控疾病进程[10-11]。但是CaMK II蛋白在重症急性胰腺炎中的作用尚无深入研究。因此,本研究通过构建小鼠SAP模型,探索CaMK II在SAP疾病发生发展中的作用。此外我们还通过CAMK II特异性抑制剂KN93进行对CaMK II进行抑制,进一步明确其发挥作用的机制。

## 1 材料和方法

### 1.1 实验动物和主要试剂

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6~8周雄性SPF级C57小鼠36只(重庆恩斯维尔生物科技有限公司),体质量20~25 g。牛磺胆酸钠(Sigma)。小鼠血清淀粉酶、脂肪酶ELISA试剂盒(南京建成生物工程研究所),TNF-α、IL-6、IL-10ELISA试剂盒(上海茁彩生物科技有限公司)。全蛋白提取试剂盒(北京索莱宝公司)、Trizol试剂(Invitrogen)、BCA蛋白定量试剂盒(博士德)、抗CaMK II单克隆抗体(Abcam)。抗NF-κB单克隆抗体、抗p-NF-κB单克隆抗体、抗p-CaMK II单克隆抗体、抗ERK单克隆抗体、抗p-ERK单克隆抗体(CST)。抗GAPDH单克隆抗体(武汉Proteintech)。辣根过氧化物酶标记山羊抗兔IgG抗体(二抗)(Abcam)。山羊抗兔IgG抗体(二抗)(CST)。CaMK II蛋白抑制剂KN93(MedChem Express)。RT-PCR引物(广州锐博生物技术有限公司),异氟烷麻醉剂(深圳瑞沃德)。

### 1.2 动物分组及模型制备

SAP模型构造:将36只C57小鼠置于实验室IVC笼具适应1周,12 h昼夜交替光照,造模前禁食不禁水12 h,采用随机数字表法将小鼠分为4组:假手术组(Sham组)、抑制剂组(KN93组)、重症急性胰腺炎组(SAP组)、抑制剂和急性重症胰腺炎组(KN93+SAP组),9只/组。所有小鼠实验操作均采用异氟烷进行吸入性麻醉。Sham组小鼠麻醉后,开腹后翻动数次胰腺后关腹。SAP组小鼠麻醉后,开腹后十二指肠降段处确定胰胆管开口处,动脉夹夹闭胰胆管上端,用1 mL注射器经胰胆管逆行注射5%牛磺胆酸钠(1 mL/kg)诱导SAP。KN93组开腹后翻动数次胰腺以后关腹,同时尾静脉注射KN93(1 mg/kg)。KN93+SAP组开腹后经胰胆管逆行注射5%牛磺胆酸钠(1 mL/kg)诱导SAP并且同时尾静脉注射KN93(1 mg/kg)。实验过程均符合单位及国家相关实验动物管理和使用规定,遵循了国际兽医学编辑协会《关于动物伦理与福利的作者指南共识》。

### 1.3 标本采集

于建模后24 h分批进行取材,收集胰腺组织和血液。血液常温静置15 min后立刻离心(3000 r/min,15 min),收集上清液置于−80 ℃冰箱中冻存。胰腺组织分为两份,一份保存于−80 ℃冰箱用于蛋白质提取,另一份用4%甲醛固定后期用于相关检测。

### 1.4 病理评估

胰腺组织甲醛固定后进行脱水、包埋、切片、58 ℃烤片脱蜡,依次进行苏木素、伊红处理,自然晾干1 h后封片,于Leica DM300光学显微镜下仔细观察胰腺结构。由两个病理医师对胰腺病理进行独立评分,通过计算每张病理切片选取的10个视野的平均分得出最后评分。

### 1.5 酶联免疫吸附测定(ELISA)

严格依照ELISA试剂盒说明书测定血清中淀粉酶、脂肪酶、IL-6、IL-10与肿瘤坏死因子α的浓度。

### 1.6 免疫蛋白印迹

依照全蛋白提取试剂盒说明书进行小鼠胰腺组织的蛋白质提取,并用BCA法测定胰腺总蛋白水平。蛋白样品经电泳、转膜、封闭后与CaMK II(1∶4000)单克隆抗体、p-CaMK II(1∶1000)、NF-κB(1∶1000)单克隆抗体、p-NF-κB(1∶1000)单克隆抗体、ERK(1∶1000)单克隆抗体、p-ERK(1∶1000)单克隆抗体、GAPDH(1∶10000)单克隆抗体、反应,于4 ℃环境下孵育12 h。次日用新配TBST洗涤3次后与二抗(1∶2000)孵育1 h,TBST洗涤曝光,以GAPDH为内参,使用ImageJ采集图像、计算灰度值。

### 1.7 免疫组织化学

采用免疫组织化学方法检测胰腺组织中NF-κB的表达。根据标准步骤对包埋的胰腺组织进行切片后58 ℃烤片3 h,透明剂脱蜡10 min、pH=9的柠檬酸钠抗原修复液煮沸10 min,山羊血清封闭过夜,次日滴加兔抗小鼠NF-κB(1∶1000)抗体在4 ℃下孵育12 h。新配PBS溶液温和冲洗切片后滴加生物素标记的山羊抗兔免疫球蛋白G(1∶200),37 ℃孵箱孵育1 h。一次进行DAB染色,分化,反蓝后封片,在Leica DM300光学显微镜下观察阳性染色并采集图像。

### 1.8 RT-PCR

RT-PCR测定胰腺组织CaMK II mRNA的表达水平。采用TRIzol法提取胰腺组织总RNA,并用分光光度仪检测总RNA的含量和纯度,$A_{260}/A_{280}$比值在1.9~2.0的样本符合要求。依照一步法RT-PCR对CaMK II mRNA的表达水平进行检测。

### 1.9 统计学方法

采用GraphPad prism9.2和SPSS 26.0进行数据统计。定量数据以均数±标准差表示,组间比较采用单因素ANOVA方差分析,两两比较采用LSD-$t$检验。$P<0.05$为差异具有统计学意义。

**表1** RT-PCR引物序列

Tab.1 Primer sequences for RT-PCR

| Gene | Primer sequences |
|---|---|
| GAPDH | |
| REVERSE | AGGTCGGTGTGAACGGATTTG |
| REVERSE | TGTAGACCATGTAGTTGAGGTCA |
| CaMKII | |
| FORWARD | CGTTTCACCGACGAGTACCAG |
| REVERSE | GCGTACAATGTTGGAATGCTTC |

## 2 结果

### 2.1 SAP小鼠模型成功构建

HE染色结果显示，SAP小鼠的胰腺结构可见明显的破坏，出现大片坏死，组织水肿，小叶结构消失，炎症细胞浸润（图1A、B）。相比Sham组，SAP组促炎因子IL-6、TNF-α表达水平升高（$P<0.01$，图1C），同时SAP组小鼠血清脂肪酶和淀粉酶也升高（$P<0.01$，图1D），小鼠的SAP模型成功构建。

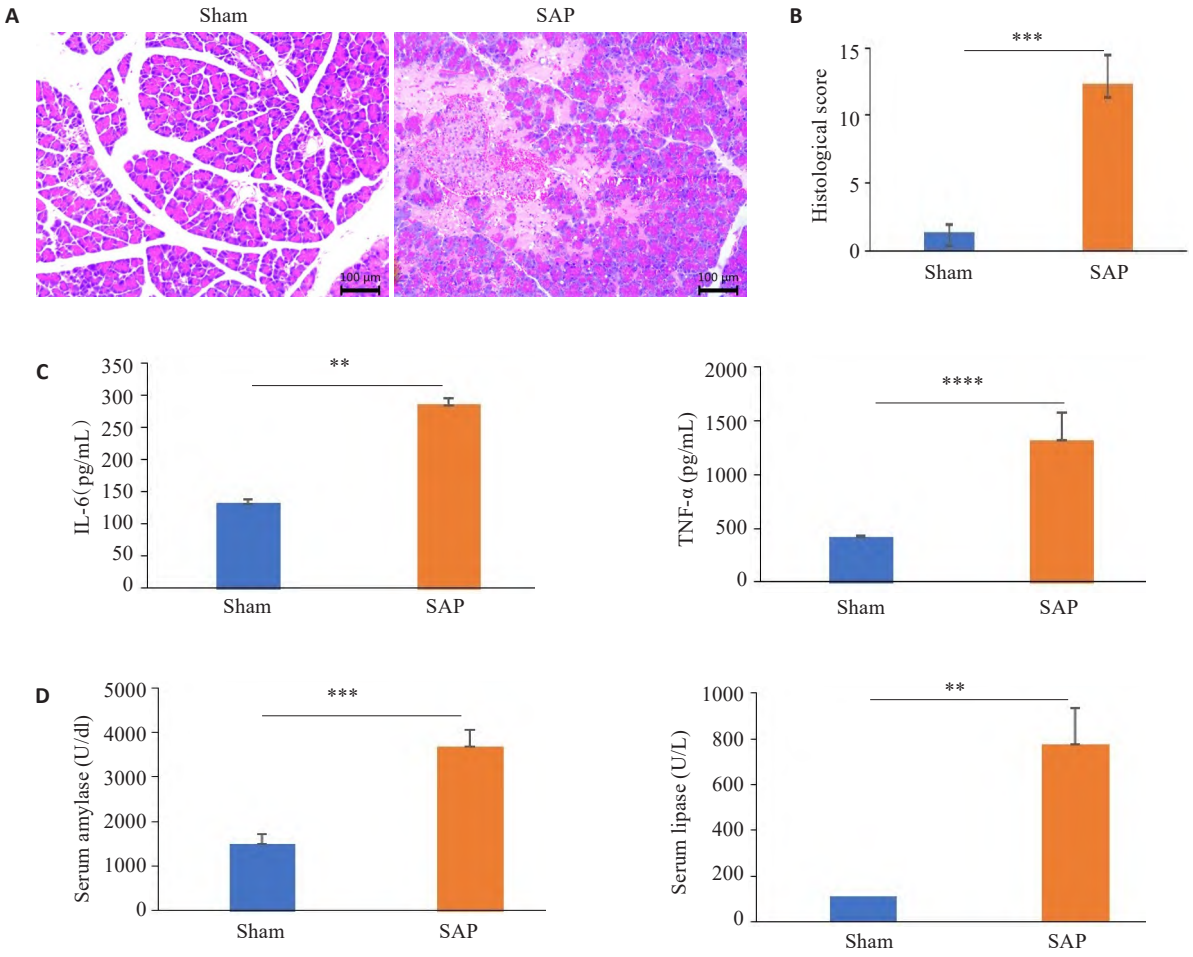


**图1 SAP对于胰腺组织和炎症的影响**

Fig.1 Pathology of the pancreatic tissue and inflammatory response in SAP mice. **A**: HE staining of the pancreatic tissue (scale bar=100 μm). **B**: Pathological score of the pancreatic tissue. **C**: Serum IL-6 and TNF-α levels. **D**: Serum lipase and amylase activity. **$P<0.01$, ***$P<0.001$, ****$P<0.0001$.

### 2.2 CaMK II蛋白在SAP组胰腺组织中活性升高

RT-PCR和Western blot结果显示，SAP组小鼠胰腺组织总CaMK II（T-CaMK II）表达水平相较于Sham组没有明显变化（$P>0.05$，图2A、B）。但是，SAP组小鼠p-CaMK II的蛋白表达量比假手术组升高（$P<0.001$，图2B）。

### 2.3 抑制CaMK II可有效减轻SAP小鼠的胰腺损伤

注射KN93以后，KN93+SAP组的小鼠的胰腺损伤减轻（图3A）。相比于SAP组的小鼠，KN93+SAP组的小鼠的血清淀粉酶和脂肪酶降低（$P<0.05$，图3B、C）。ELISA实验结果显示，血清IL-6、TNF-α的水平降低，抑炎因子IL-10水平升高（$P<0.05$，图3E~G）。

### 2.4 抑制CaMK II后NF-κB蛋白降低，SAP的炎症缓解

免疫组化染色结果显示，SAP组胰腺组织的NF-κB表达水平相比于Sham组升高；CaMK II被抑制后，SAP组胰腺组织NF-κB的蛋白含量下降（图4A）。Western blot结果显示，SAP组的NF-κB磷酸化水平相比于Sham组明显增高（图4B）；但CaMK II蛋白被抑制后，蛋白ERK的磷酸化水平降低，NF-κB的活性也被抑制（图4B、C）。

## 3 讨论

本研究发现CaMK II蛋白在SAP小鼠的胰腺组织中活性明显升高，抑制CaMK II可以有效抑制SAP的胰腺损伤和降低全身炎症反应，表明CaMK II参与SAP的进展。CaMK II在SAP当中的作用在既往研究中还未

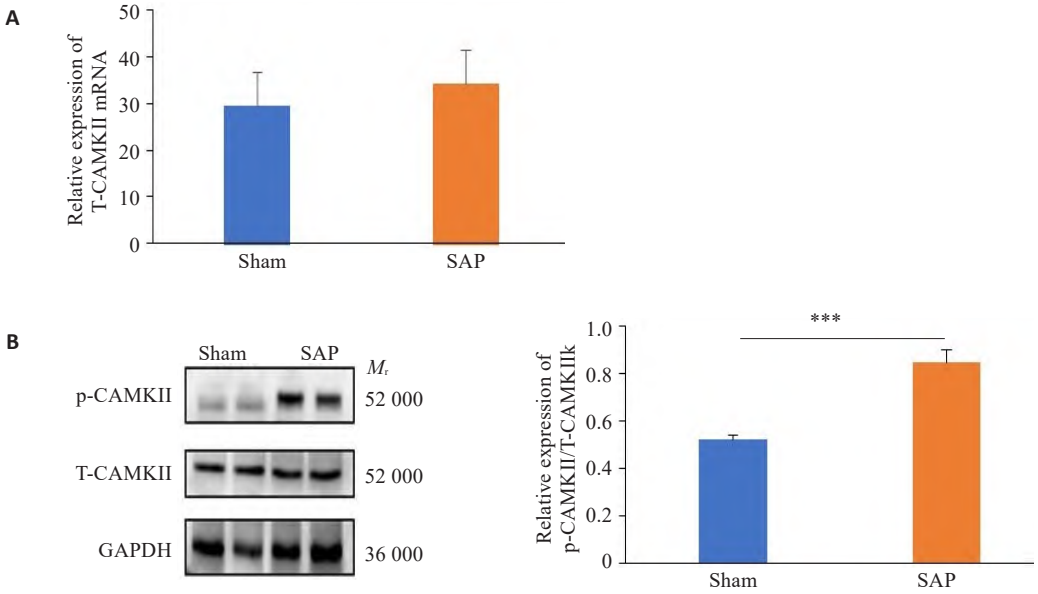


**图2 胰腺组织中p-CaMK II蛋白和CaMK II mRNA的表达情况**

Fig.2 Expression of p-CaMK II and T-CaMK II proteins (**A**) and CaMKⅡ mRNA (**B**) in pancreatic tissue of SAP mice. ***$P$<0.001.

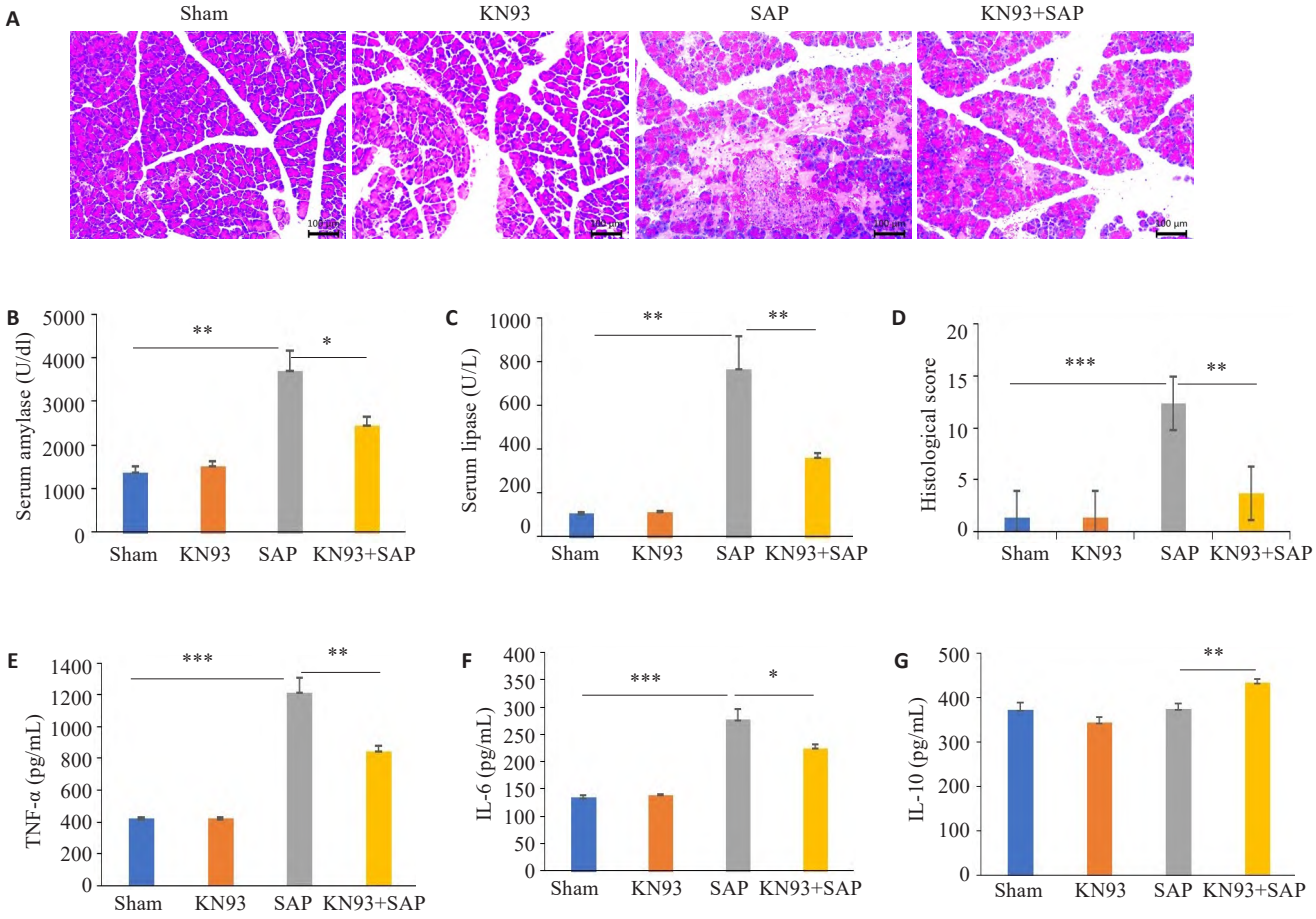


**图3 各组小鼠的组织病理学检查及血清淀粉酶脂肪酶炎症因子水平**

Fig.3 Histopathological examination of the pancreas, serum amylase and lipase activities and serum levels of inflammatory factor levels in each group. **A**: HE staining of the pancreatic tissue (scale bar=100 μm). **B**, **C**: Serum amylase and lipase activities. **D**: Pathological score of the pancreas; **E**: Serum TNF-α levels. **F**: Serum IL-6 levels. **G**: Serum IL-10 levels. *$P$<0.05, **$P$<0.01, ***$P$<0.001.

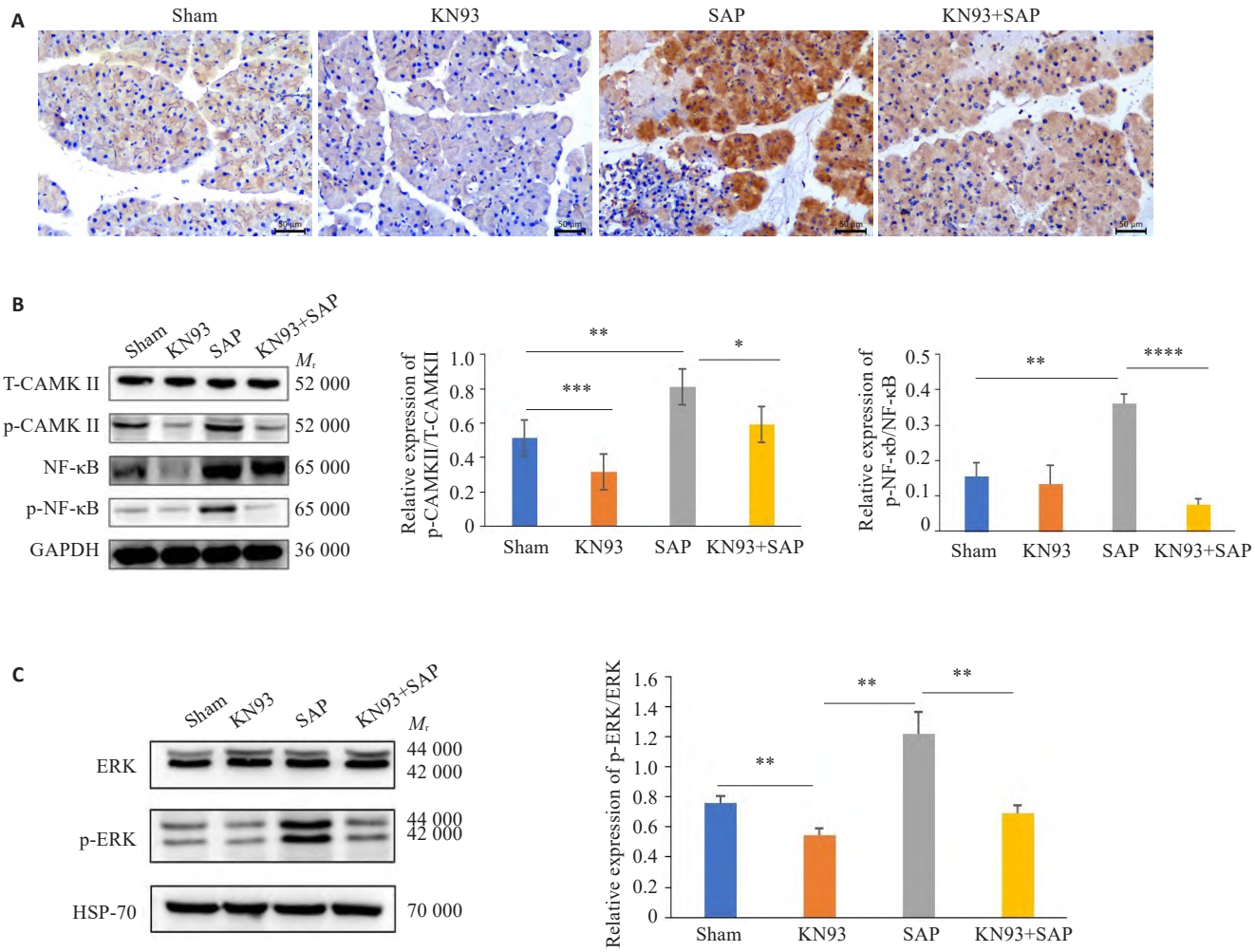


**图4 胰腺组织中p-NF-κB、p-CaMK II和p-ERK的表达水平**

Fig.4 Expression of p-NF-κB, p-CaMK II and CaMK II in the pancreas in each group. **A**: Immunohistochemical staining of NF-κB in the pancreas (scale bar=50 μm). **B**: Expression levels of p-CAMK/CaMK II and p-NF-κB/NF-κB proteins in the pancreatic tissue. **C**: Expression levels of p-ERK/ERK protein in the pancreatic tissue. **P*<0.05, ***P*<0.01, ****P*<0.001, *****P*<0.0001.

有明确探索,因此探明其在SAP发生发展过程中的作用及相关的机制有助于进一步认识SAP的发病机制及寻找可能的治疗靶点。CaMK II为一种多聚体蛋白,受到刺激后,自身Thr286或Thr287位点发生磷酸化,Thr286位点自磷酸化后促进酶亚基相互磷酸化,亚基磷酸化后具有捕捉钙调蛋白能力,进而促进全酶活化发挥作用[12-13]。CaMK II在许多疾病进展中起着重要作用。研究显示,当CaMK II抑制剂和吡喹酮同时使用后,血吸虫病的治疗效果明显改善[14];在心脏中,CaMK II被发现可以通过蛋白质精氨酸甲基转移酶1来调节心脏的收缩功能[15]。不仅如此,CaMK II在胰腺疾病中也发挥着重要的作用。在高糖刺激下,CaMK II蛋白可以发生自身磷酸化[16]来诱导ERK的激活[17],最终促进胰岛素的分泌[18,19]。CaMK II还被发现与炎症密切相关[20]。但是CaMK II在SAP发生发展过程中的作用机制还不清楚。

本实验发现在SAP小鼠中CaMK II的磷酸化水平明显增高,当CaMK II的活性被KN93抑制后,SAP小鼠的胰腺损伤明显减轻,全身炎症明显改善,与CaMK II在其他疾病中的作用一致。进一步提示CaMK II可能参与促进SAP小鼠的全身炎症的发生发展。有研究表明在人大脑微血管内皮细胞中,CaMK II可以通过ERK/NF-κB信号通路促进TNF-α诱导的金属蛋白酶9的表达[20]。在未分化的小鼠骨髓单核细胞中,KN93可以通过抑制细胞外信号调节激酶(ERK)和Akt的表达来抑制NF-κB的表达[21]。而NF-κB作为促炎细胞因子分泌的关键调节因子,是胰腺炎早期的重要分子[22]。大量激活的胰蛋白酶原造成组织损伤,细胞破裂[23]。组织细胞破裂释放大量组织因子,诱导NF-κB从无活性形式转变为活性形式[23]。一方面,NF-κB多聚体的IκB激酶解离[24],NF-κB发挥作用促进TNF-α的转录[25]。另一方面,NF-κB的激活导致胰腺中性粒细胞大幅度增加[26],大量促炎因子和黏附分子流入胰腺,加重胰腺炎症反

应。组织损伤后中性粒细胞由胰腺局部扩散至肝脏、肺等组织器官，进一步导致全身炎症反应。本研究发现，使用KN93抑制CaMK II后，NF-κB的表达出现了明显的降低，同时血清中的促炎因子IL-6/TNF-α明显降低，抗炎因子IL-10明显升高，表明CaMK II可能通过增加NF-κB的表达参与SAP进展。本实验在SAP进展早期进行KN93干预，降低CaMK II的活性从而减少 NF-κB的表达，进一步减少IL-6、TNF-α的转录。

在神经系统炎症中，CaMK II可以通过负向调控ERK/MAPK信号通路来降低NF-κB的表达，减轻神经炎症水平[27]。在急性胰腺炎中ERK/MAPK信号通路已经被证实发挥重要作用[28,29]，其机制是通过上调NF-κB来参与SAP的胰腺进展。急性胰腺炎中，黄芩素抑制ERK/MAPK信号通路和NF -κB表达水平来降低急性胰腺炎的炎症水平[30]。氧化苦参碱可以通过降低ERK/MAPK途径蛋白的表达水平来降低NF-κB的表达，减轻急性胰腺炎的胰腺损伤和炎症水平[31]。川穹素可以通过抑制ERK/MAPK信号通路来减轻急性胰腺炎的胰腺损伤，同时也能在体外使用AR42J细胞观察到当ERK/MAPK通路被抑制后，细胞的炎症因子也出现了明显的下调[32]。本研究发现当CaMK II的活性被抑制后，ERK（细胞外信号调节激酶）蛋白的磷酸化水平明显降低，提示CaMK II通过抑制ERK/MAPK信号通路来降低IL-6、TNF-α的表达水平。

综上所述，抑制CaMK II可能通过抑制ERK/MAPK信号途径来减少NF -κB的蛋白水平，最终缓解SAP的炎症程度。但是CaMK II与ERK之间具体的机制还有待进一步的研究去探索和发现。CaMK II可能是治疗SAP炎症反应的一个新的靶点。

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