网络首发时间：2025-11-06 10:12:46　网络首发地址：https://link.cnki.net/urlid/34.1065.R.20251105.1734.011

视前区正中核注射前列腺素E_2对雌性小鼠体温的影响及其机制

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摘要　目的　研究视前区正中核(MnPO)微量注射前列腺素E_2(PGE_2)对雌性小鼠体核温度的影响,并阐明其作用机制。**方法**　采用立体定位术在雌性小鼠MnPO植入微量注射套管。此后采用多通道温度信号采集系统同步监测MnPO注射不同试剂前后小鼠的直肠温度和棕色脂肪(BAT)温度。为观察MnPO微量注射PGE_2的体温调节作用,将12只雌性C57BL/6小鼠随机分为生理盐水组(n=6)和PGE_2组(n=6),分别注射0.1 μL生理盐水和PGE_2(2.8 mmol/L)。为了确定E系列前列腺素受体(EP)1、EP3、EP4是否介导PGE_2的体温调节作用,将15只雌性C57BL/6小鼠均分为3组,每组5只。往各组小鼠的MnPO分别先后注射0.1 μL PGE_2(2.8 mmol/L),待体温回复至基线水平后,再分别注射EP1、EP3或EP4拮抗剂(ant)(20 mmol/L) + PGE2(2.8 mmol/L)混合液。**结果**　与基础水平比较,MnPO微量注射PGE_2后,雌性小鼠的直肠温度(P<0.01)和BAT温度(P<0.001)均明显升高。与生理盐水组比较,PGE_2组小鼠直肠温度(P<0.001)和BAT温度(P<0.000 1)的上升幅度明显更大。此外,往MnPO注射PGE_2后,小鼠BAT温度的上升幅度明显大于直肠温度的上升幅度(P<0.001)。与注射PGE_2后比较,小鼠MnPO注射EP3 ant + PGE_2后直肠温度的上升幅度(P<0.001)和BAT温度的上升幅度(P<0.001)均更小;而小鼠MnPO注射EP1 ant + PGE_2和EP4 ant + PGE_2后小鼠直肠温度的上升幅度(P>0.05)和BAT温度的上升幅度,均差异无统计学意义(P>0.05)。**结论**　MnPO注射PGE_2可经EP3受体明显升高雌性小鼠的BAT温度和体核温度。

关键词　雌性小鼠;发热;棕色脂肪组织;前列腺素E_2;视前区正中核;EP3受体
中图分类号　R 714;R 339.6
文献标志码　A　**文章编号**　1000-1492(2026)02-0250-08
doi:10.19405/j.cnki.issn1000-1492.2026.02.009

2025-10-21 接收
基金项目:国家自然科学基金项目(编号:32100926);四川省老年医学临床医学研究中心开放课题项目(编号:24LHLNYX1-25);四川青年创新科研课题计划项目(编号:Q22010)
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发热可导致流产等不良妊娠结局和胎儿出生缺陷的风险明显升高[1]。但是孕期使用解热镇痛类药物会增加胎儿神经和生殖系统发育障碍的风险[2-4]。这些发现促使学者们深入研究雌性哺乳动物发热的中枢机制,以寻求新的妊娠期退热方法。既往研究[5]显示脂多糖等致热源进入机体后可通过

expression, mutation, or knockdown on key proteins (SMAD2, SMAD3, SMAD4) in the transforming growth factor-β (TGF-β)/Small mothers against decapentaplegic (SMAD) signaling pathway was examined by Western blot. ***Results*** Compared to *SKI* overexpression alone, the introduction of *SKI* mutations significantly promoted S-phase progression, enhanced proliferation and migration, and inhibited apoptosis. Mechanistically, *SKI* mutations suppressed the phosphorylation of SMAD2 and SMAD3 proteins, thereby inhibiting the transcriptional activity of the TGF-β signaling pathway. Conversely, *SKI* knockedown produced the opposite effects. ***Conclusion*** *SKI* gene mutation acts as a gain-of-function genetic alteration, exerting an oncogenic role in cholangiocarcinoma cells. The primary mechanism involves the inhibition of the TGF-β/SMAD signaling pathway, which in turn promotes proliferation and cell cycle progression, and suppresses apoptosis in QBC939 and RBE cells, ultimately driving tumor progression.

Key words　cholangiocarcinoma; cholangiocarcinoma cells; *SKI*; cell cycle; proliferation; apoptosis; migration
Fund program　National Natural Science Foundation of China (No. 82002573)
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多种途径诱导终末致热介质前列腺素E_2(prostaglandin E_2,PGE_2)合成并释放到参与体温调节的脑区,引起体核温度上升。但是目前尚不清楚PGE_2介导雌性哺乳动物发热反应的靶点核团及其神经机制。视前区是体温调节的中枢,其亚核视前区正中核(median preoptic nucleus,MnPO)是参与雌性哺乳动物体温调节的重要核团[6]。该核团神经元可经下行神经通路及交感神经调控棕色脂肪组织(brown adipose tissue,BAT)产热,参与体温内稳态的形成[7]。此外,该核团分布有PGE_2的E系列前列腺素受体(E-series prostaglandin receptor, EP)1、EP3和EP4[8-9]。据此推测,PGE_2可能通过作用于MnPO引起雌性小鼠体温升高。然而目前尚无相关报道。因此,该研究以成年雌性小鼠为实验对象,采用脑立体定位、核团微量注射和多通道温度信号监测技术研究MnPO微量注射PGE_2对雌性小鼠体核温度的影响,并探讨其受体和温控效应器机制。

1 材料与方法

1.1 材料

1.1.1 *实验动物* 实验用SPF级8周龄成年雌性C57BL/6小鼠27只,体质量22~25 g,均自由饮食和进水,饲养温度(25±1)℃,明暗时间各12 h。实验动物购自成都达硕实验动物有限公司,生产许可证号:SCXK(川)2020-030。动物实验所需程序经过了成都医学院实验动物伦理委员会的批准,动物伦理审查批号:2017-58。

1.1.2 *实验试剂和仪器* 异氟烷(货号:R510)购自深圳瑞沃德生命科技有限公司;PGE_2、EP3受体拮抗剂(antagonist, ant)L-798106、EP4 ant L-161982、EP1 ant SC-51322(货号:P5640、L4545、SML0690、PZ0132)购自美国Sigma公司;微量注射套管购自深圳瑞沃德生命科技有限公司。小动物麻醉机(型号:R500)、颅钻(型号:78001)和脑立体定位仪(型号:F68018)购自深圳瑞沃德生命科技有限公司;微量注射泵(型号:LEGATO 130)购自美国kd Scientific公司;多通道温度信号测量系统(型号:JK808)购自常州金艾联电子科技有限公司;红外线加热器(型号:CQ-61P)购自重庆航天火箭电子技术有限公司;冷光源(型号:QAXK-TY)购自南京千奥星科生物科技有限公司。

1.2 方法

1.2.1 *实验动物分组和处理* 为观察MnPO注射PGE_2的体温调节作用,将12只小鼠随机分为生理盐水对照组(n=6)和PGE_2组(n=6),分别往MnPO注射0.1 μL生理盐水和0.1 μL PGE_2(2.8 mmol/L)。为了确定EP1、EP3或EP4受体是否介导PGE_2的体温调节作用,将15只小鼠均分为3组,每组5只。往各组小鼠的MnPO分别先注射0.1 μL PGE_2(2.8 mmol/L),待体温回复至基线水平后,再注射EP1、EP3或EP4拮抗剂(ant)(20 mmol/L) + PGE_2(2.8 mmol/L)混合液,观察各受体拮抗剂是否起到抑制PGE_2的作用。

1.2.2 *脑立体定位及微量注射套管植入* 2%异氟烷麻醉小鼠。剃除颅顶鼠毛后,将小鼠固定于脑立体定位仪上,在其眼部涂红霉素软膏,并用碘伏对颅顶皮肤进行消毒。此后沿颅骨中线切开小鼠颅顶皮肤,充分暴露颅骨表面并将其调平,参照Paxinos-Watson图谱定位MnPO。利用颅钻钻孔后将注射套管植入至MnPO(植入坐标为:前囟后0 mm,旁开0.8 mm,深4.35 mm)。此后在注射套管周围埋置螺丝钉,依次使用454胶水、502胶水和牙科水泥将注射套管和螺丝钉固定。待牙科水泥凝固后,将套管帽插入注射套管,并将小鼠移至铺有宠物加热垫的笼中复苏。术后连续3天肌肉注射0.1 mL头孢曲松钠(0.2 g/mL),至少恢复1周后开展后续实验。

1.2.3 *小鼠直肠和BAT温度检测* 2%异氟烷麻醉小鼠。室温设置为25 ℃,利用恒温加热板和红外加热灯将小鼠体核温度维持在37 ℃左右。此后,剔除小鼠背部肩胛间区鼠毛,75%乙醇消毒后沿肩胛间区正中线切开皮肤,暴露BAT,将多通道温度信号采集系统的温度探头插入右侧BAT内,采用缝合线将温度探头固定于背部肌肉上。另一温度探头直接插入直肠中,以同步测量BAT和直肠温度,测量的直肠温度可代表体核温度。温度信号采集通过JK80X软件进行。计算给药前30 s的温度平均值作为基础值;计算给药后持续30 s的最高(或最低)温度平均值作为给药后的响应值。给药后直肠和BAT温度的变化幅度值(△T)=给药后持续30 s的最高或最低温度平均值–给药前30 s的温度平均值。

1.2.4 *MnPO核团微量注射* 实验当天上午9时开始用2%异氟烷诱导小鼠进入麻醉状态,此后用1%异氟烷维持其麻醉状态。连续记录直肠和BAT温度1 h后,利用微量注射泵经套管向MnPO注射不同试剂。为观察PGE_2的体温调节作用,实验当天上

午10时，往生理盐水组和PGE_2组小鼠MnPO分别注射0.1 μL生理盐水或0.1 μL PGE_2（2.8 mmol/L），此后持续记录直肠和BAT温度直至其恢复基线水平。为明确介导PGE_2体温调节作用的受体机制，实验当天上午10时，往需注射EP1 ant、EP2 ant或EP3 ant的各组小鼠MnPO微量注射0.1 μL PGE_2（2.8 mmol/L）。待直肠和BAT温度恢复至基础水平后，再往小鼠MnPO微量注射0.1 μL EP1 ant（20 mmol/L）+ PGE_2（2.8 mmol/L）、0.1 μL EP3 ant（20 mmol/L）+ PGE_2（2.8 mmol/L）或0.1 μL EP4 ant（20 mmol/L）+ PGE_2（2.8 mmol/L），此后持续记录直肠和BAT温度直至其恢复基线水平。MnPO核团微量注射后，异氟烷麻醉小鼠，制作小鼠脑组织冠状切片，在显微镜下检测导管定位。

1.2.5 统计学处理 采用Graphpad prism 9软件对数据进行统计分析和作图，各组小鼠直肠温度和BAT温度以均数 ± 标准误表示。PGE_2组和生理盐水组样本均数比较采用独立样本t检验进行分析。小鼠MnPO注射PGE_2和各EP ant + PGE_2混合液后的样本均数比较采用配对t检验进行分析，$P<0.05$为差异有统计学意义。

2 结果

2.1 微量注射套管定位图 为观察微量注射导管是否位于MnPO，在显微镜下检测了导管在小鼠脑组织冠状切片上的定位。如图1所示：小鼠脑片上的MnPO两侧可见解剖标志前联合（anterior commissure，AC），套管植入位置位于MnPO上方左侧，表明套管定位准确。

2.2 MnPO注射PGE_2对雌性小鼠直肠和BAT温度的影响 与基础水平比较，MnPO注射生理盐水后，小鼠的直肠温度[(37.0 ± 0.1)℃ *vs* (37.1 ± 0.1) ℃，t=0.50，P>0.05]和BAT温度[(34.4 ± 0.2)℃ *vs* (34.3 ± 0.3)℃，t=0.65，P>0.05]均无明显改变。与基础水平比较，MnPO注射PGE_2后，小鼠的直肠温度[(37.5 ± 0.4)℃ *vs* (38.8 ± 0.4)℃，t=5.68，$P<0.01$]和BAT温度[(33.8 ± 0.5)℃ *vs* (36.3 ± 0.6)℃，t=7.39，$P<0.001$]均显著升高。PGE_2组小鼠直肠温度的上升幅度[(1.3± 0.2)℃ *vs* (0.1 ± 0.1)℃，t=5.33，$P<0.001$]和BAT温度[(2.6 ± 0.3)℃ *vs* (−0.1 ± 0.1)℃，t=7.36，$P<0.000\ 1$]明显大于生理盐水组。往MnPO注射PGE_2后，小鼠BAT温度的上升幅度明显大于直肠温度的上升幅度[(2.6 ± 0.3)℃ *vs* (1.3 ± 0.2)℃，t=7.78，$P<0.001$]。此外，如图2A所示，与直肠温度的变化比较，BAT温度开始上升的时间更早，上升的速率更快，到达峰值的时间也更早。这些结果表明雌性小鼠MnPO注射PGE_2可引起体核温度和BAT温度明显升高。见图2。

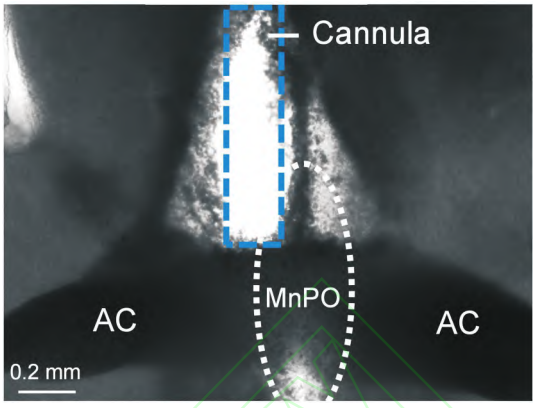

图1 雌性小鼠冠状脑片上MnPO的微量注射套管定位图

Fig. 1 Localization of microinjection cannula in the MnPO of coronal brain sections of female mice

MnPO: median preoptic nucleus; AC: anterior commissure; Cannula: a microinjection tube that enables precise reagent infusion into the MnPO.

2.3 EP3 ant对MnPO注射PGE_2引起的小鼠直肠和BAT温度改变的影响 与基础水平比较，MnPO注射PGE_2后，小鼠的直肠温度[(37.1 ± 0.2)℃ *vs* (38.3 ± 0.2)℃，t=11.43，$P<0.001$]和BAT温度[(34.4 ± 0.1)℃ *vs* (37.3 ± 0.4)℃，t=7.72，$P<0.01$]均明显上升。与基础水平比较，MnPO注射EP3 ant + PGE_2后，小鼠的直肠温度[(37.4 ± 0.2)℃ *vs* (37.8 ± 0.1)℃，t=3.38，$P<0.05$]和BAT温度[(34.9 ± 0.3)℃ *vs* (36.0 ± 0.2)℃，t=2.89，$P<0.05$]仍有小幅度的上升。EP3 ant + PGE_2组小鼠直肠温度的上升幅度[(0.4 ± 0.1)℃ *vs* (1.2 ± 0.1)℃，t=8.94，$P<0.001$]和BAT温度的上升幅度[(1.0 ± 0.4)℃ *vs* (2.8 ± 0.4)℃，t=12.14，$P<0.001$]均明显小于PGE_2组。此外，PGE_2组小鼠BAT温度的上升幅度明显大于直肠温度的上升幅度[(2.8 ± 0.4)℃ *vs* (1.2 ± 0.1)℃，t=5.77，$P<0.01$]。EP3 ant + PGE_2组小鼠BAT温度的上升幅度虽略大于直肠温度的上升幅度，但差异无统计学意义[(1.0 ± 0.4)℃ *vs* (0.4 ± 0.1)℃，t=2.51，P>0.05]。这些结果表明，MnPO注射EP3 ant可以抑制相同位点注射PGE_2引起的体核温度和BAT温度升高。见图3。

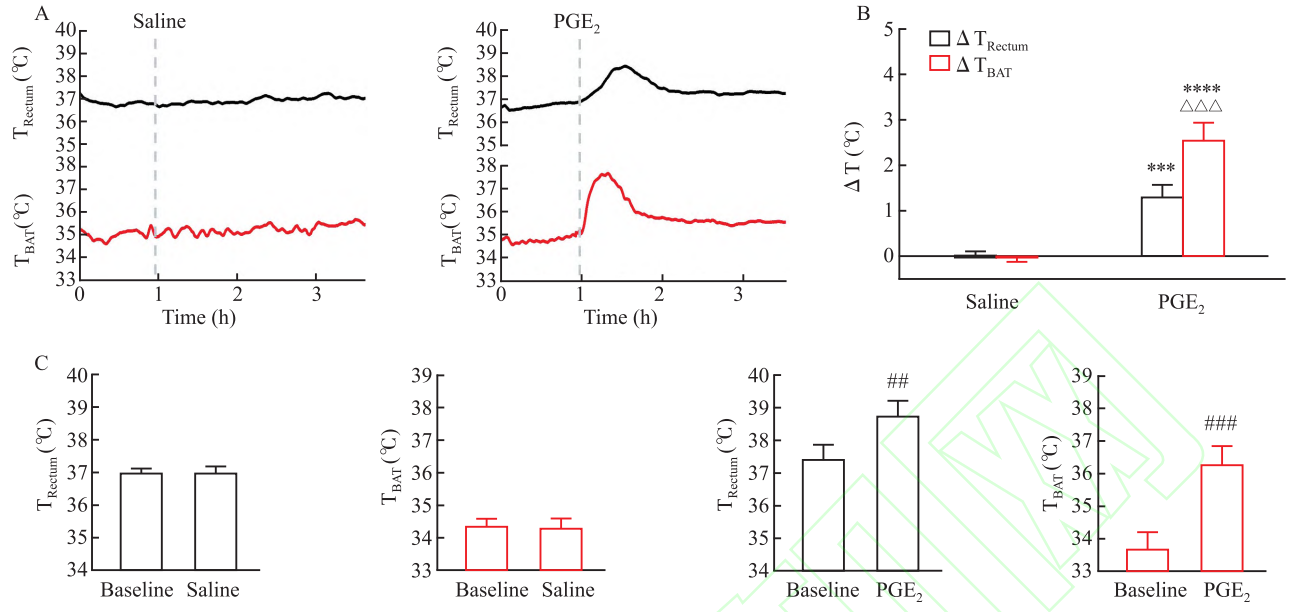

图2 MnPO微量注射PGE_2引起BAT温度和直肠温度上升

Fig. 2 Intra-MnPO injection of PGE_2 induced increases in both BAT temperature and rectal temperature

A: Representative BAT and rectal temperature curves in different groups; B: Quantified changes in BAT and rectal temperatures across experimental groups; C: Group-wise comparison of BAT and rectal temperature; ***P<0.001, ****P<0.000 1 *vs* Saline group; $^{\triangle\triangle\triangle}P$<0.001 *vs* $\triangle T_{Rectum}$ group; $^{\#\#}P$<0.01, $^{\#\#\#}P$<0.001 *vs* Baseline group; △T: Change in temperature; T_{Rectum}: Rectal temperature; T_{BAT}: BAT temperature.

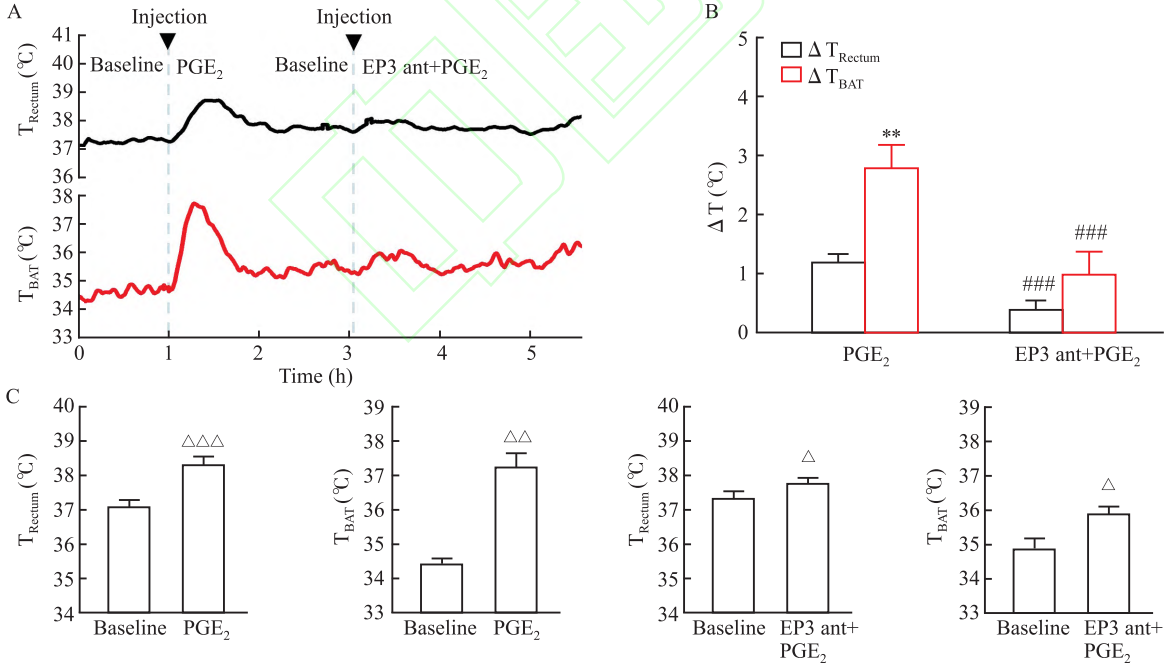

图3 EP3 ant可抑制MnPO注射PGE_2引起的BAT温度和直肠温度上升

Fig. 3 EP3 ant could inhibit the increases in BAT temperature and rectal temperature induced by PGE_2 injection into the MnPO

A: Representative BAT and rectal temperature curves after microinjection of different agents; B: Quantified changes in BAT and rectal temperatures across experimental groups; C: Group-wise comparison of BAT and rectal temperature; **P<0.01, ***P<0.01 *vs* $\triangle T_{Rectum}$ group; $^{\#\#\#}P$<0.001*vs* PGE_2 group; $^{\triangle}P$<0.05, $^{\triangle\triangle}P$<0.01, $^{\triangle\triangle\triangle}P$<0.001 *vs* Baseline group; △T: Change in temperature; T_{Rectum}: rectal temperature; T_{BAT}: BAT temperature.

2.4 EP1 ant对MnPO注射PGE_2引起的小鼠直肠和BAT温度改变的影响 与基础水平比较，MnPO注射PGE_2后，小鼠的直肠温度[(37.0 ± 0.1)℃ *vs* (38.1 ± 0.2)℃，t=7.48，P<0.01]和BAT温度

[(34.1 ± 0.2)℃ *vs* (37.3 ± 0.2)℃, *t*=23.12, *P*<0.001]均明显上升。与基础水平比较,MnPO注射EP1 ant + PGE_2后,小鼠的直肠温度[(37.2 ± 0.2)℃ *vs*(38.4 ± 0.2)℃,*t*=8.14,*P*<0.01]和BAT温度[(34.5 ± 0.3)℃ *vs*(37.6 ± 0.2)℃,*t*=23.17,*P*<0.001]同样明显上升。与PGE_2组比较,EP1 ant + PGE_2组小鼠直肠温度的上升幅度[(1.1 ± 0.1)℃ *vs* (1.1 ± 0.2)℃,*t*=0.25,*P*>0.05]和BAT温度的上升幅度[(3.2 ± 0.1)℃ *vs*(3.2 ± 0.1)℃,*t*=0.44,*P*>0.05]差异均无统计学意义。此外,PGE_2组和EP1 ant + PGE_2组小鼠BAT温度的上升幅度均大于直肠温度的上升幅度[(3.2 ± 0.1)℃ *vs*(1.1 ± 0.1)℃,*t*=9.70,*P*<0.001];[(3.1 ± 0.1)℃ *vs*(1.1 ± 0.2)℃,*t*=8.65,*P*<0.001]。这些结果表明,MnPO注射EP1 ant无法抑制相同位点注射PGE_2引起的体核和BAT温度上升。见图4。

2.5 EP4 ant对MnPO注射PGE_2引起的小鼠直肠和BAT温度改变的影响 与基础水平比较,MnPO注射PGE_2后,小鼠的直肠温度[(37.2 ± 0.2)℃ *vs* (38.3 ± 0.2)℃, *t*=5.64, *P*<0.01]和BAT温度[(34.3 ± 0.4)℃ *vs*(37.4 ± 0.5)℃,*t*=5.65,*P*<0.01]均上升。与基础水平比较,MnPO注射EP4 ant + PGE_2后,小鼠的直肠温度[(37.2 ± 0.2)℃ *vs*(38.3 ± 0.4)℃, *t*=3.47, *P*<0.05]和BAT温度[(34.8 ± 0.4)℃ *vs* (37.8 ± 0.7)℃, *t*=5.73, *P*<0.01]同样明显上升。与PGE_2组比较,EP4 ant + PGE_2组小鼠直肠温度的上升幅度[(1.1 ± 0.2)℃ *vs*(1.1 ± 0.3)℃, *t*=0.32, *P*>0.05]和BAT温度的上升幅度[(3.0 ± 0.5)℃ *vs*(3.0 ± 0.5)℃, *t*=0.00, *P*>0.05]均差异无统计学意义。此外,PGE_2组和EP4 ant + PGE_2组小鼠BAT温度的上升幅度均大于直肠温度的上升幅度[(3.0℃ ± 0.5) ℃ *vs*(1.1 ± 0.2)℃, *t*=5.02, *P*<0.01];[(3.0 ± 0.5)℃ *vs*(1.1 ± 0.3)℃, *t*=5.67, *P*<0.01]。这些结果表明,MnPO注射EP4 ant无法抑制相同位点注射PGE_2引起的体核和BAT温度上升。见图5。

3 讨论

雄性和雌性哺乳动物的发热反应具有明显差异,其发生机制也不尽相同[10]。目前雄性哺乳动物发热的神经机制已经得到了广泛的研究,但是雌性发热的神经机制仍待阐明[5,11]。既往研究[12]显示,MnPO是介导雄性哺乳动物发热反应形成的关键核团。因为靶向损毁小鼠MnPO神经元可以抑制致热源诱导的发热反应。此外,往雄性大鼠包含MnPO在内的环终板血管器区域注射PGE_2可引起大于

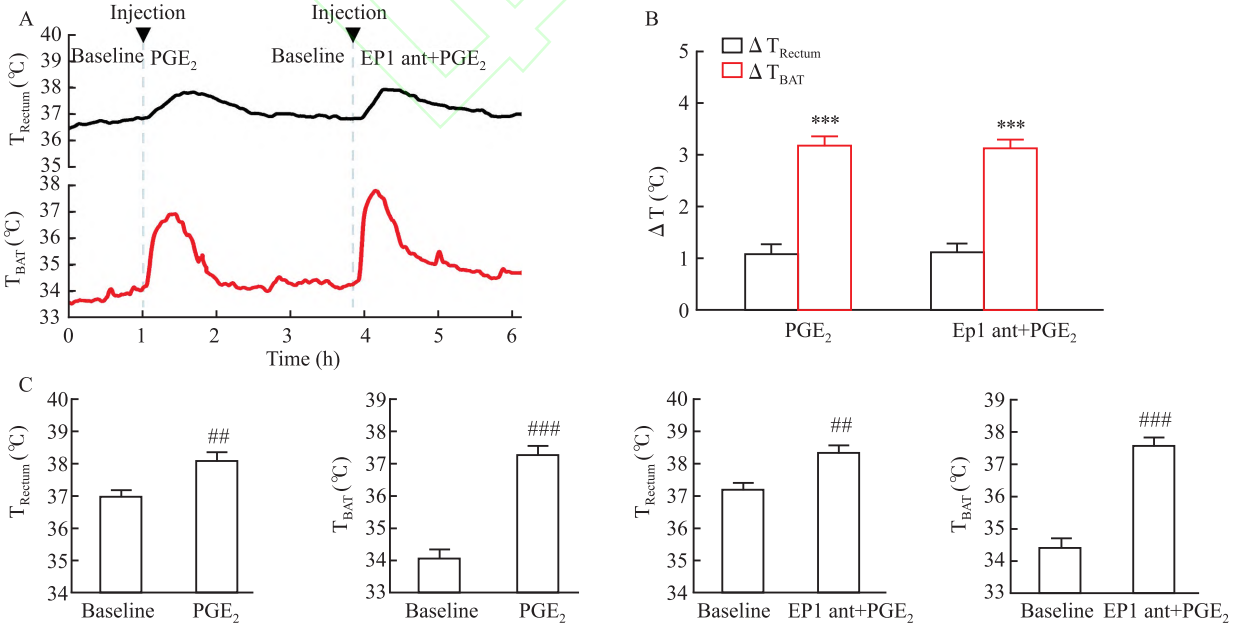

图4 EP1 ant对PGE_2引起的小鼠直肠和BAT温度改变的影响

Fig. 4 The effects of the EP1 ant on PGE_2-induced temperature changes in mouse rectum and BAT

A: Representative BAT and rectal temperature curves after microinjection of different agents; B: Quantified changes in BAT and rectal temperatures across experimental groups; C: Group-wise comparison of BAT and rectal temperature; ***P<0.001 *vs* ΔT_{Rectum} group; ##P<0.01, ###P<0.001 *vs* Baseline group; ΔT: change in temperature; T_{Rectum}: rectal temperature; T_{BAT}: BAT temperature.

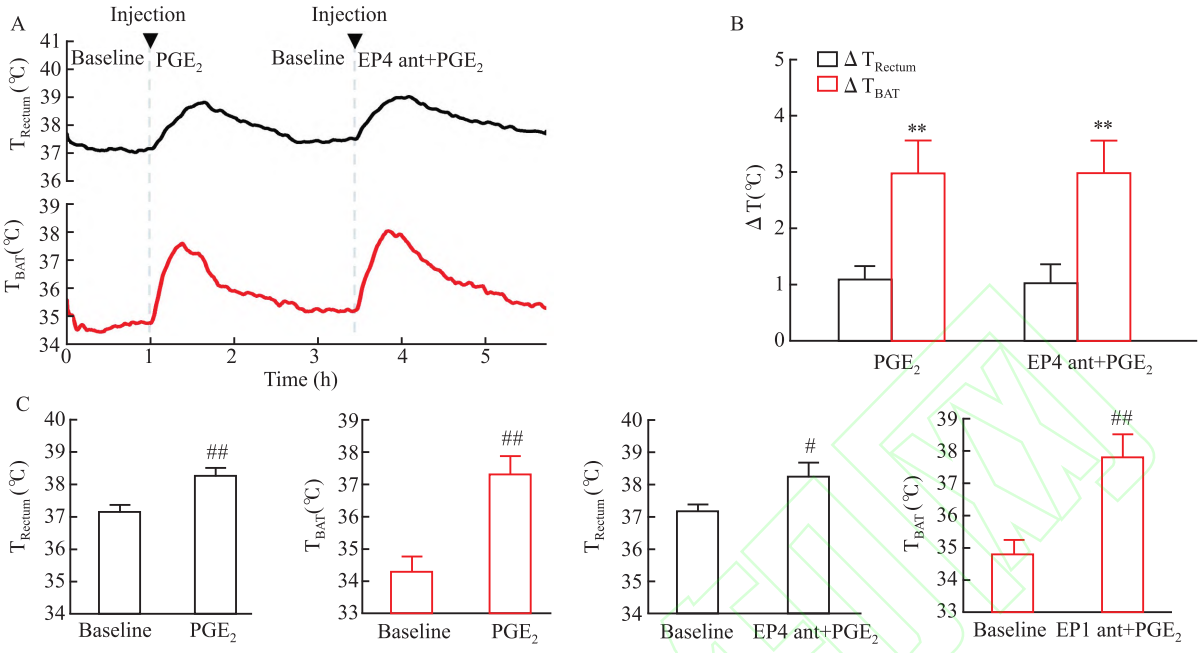

图5 EP4 ant对PGE_2引起的小鼠直肠和BAT温度改变的影响

Fig. 5 The effects of the EP4 ant on PGE_2-induced temperature changes in mouse rectum and BAT

A: Representative BAT and rectal temperature curves after microinjection of different agents; B: Quantified changes in BAT and rectal temperatures across experimental groups; C: Group-wise comparison of BAT and rectal temperature; $^{**}P<0.01$ *vs* ΔT_{Rectum} group; $^{\#}P<0.05$, $^{\#\#}P<0.01$ *vs* Baseline group; ΔT: Change in temperature; T_{Rectum}: rectal temperature; T_{BAT}: BAT temperature.

1 ℃的体温升高;但是在视前区其他亚核注射PGE_2只能引起小于0.5 ℃的小幅度体温升高[13]。与此相似,本研究结果显示往雌性小鼠MnPO注射PGE_2平均可以升高体核温度约1.3℃,表明往雌性哺乳动物的MnPO注射PGE_2同样可以引起发热反应。这些结果提示,MnPO也是PGE_2介导雌性小鼠发热反应形成的重要核团。

本研究结果显示,往雌性小鼠MnPO注射EP3 ant可以抑制相同位点注射PGE_2引起的升温作用。与此相似,国外学者发现往雄性大鼠包含MnPO在内的视前区吻部注射EP3 ant也可以抑制相同位点注射PGE_2引起的升温作用[14]。这提示,不论是雄性还是雌性哺乳动物,其EP3受体均介导了释放到MnPO的PGE_2引起的致热效应。本研究结果还显示,往雌性小鼠MnPO注射EP1和EP4 ant无法抑制相同位点注射PGE_2引起的升温作用,提示这两种受体未介导释放到MnPO的PGE_2对雌性小鼠体温的调节作用。与此相似,国外学者[14]发现往雄性大鼠视前区吻部注射EP1 ant同样无法抑制相同位点注射PGE_2引起的升温作用,提示雌性和雄性哺乳动物的EP1受体均未能介导释放到MnPO的PGE_2引起的升温作用;但与本研究结果不同的是,他们发现往雄性大鼠视前区吻部注射EP4 ant可以抑制相同位点注射PGE_2引起的升温作用,提示EP4受体介导了释放到MnPO的PGE_2对雄性大鼠体温的调节作用。这可能与该研究的注射位点与本研究不同有关:视前区吻部包含了MnPO以外的腹内侧视前区和血管终板器等区域。得到不同结果的原因还可能与PGE_2受体在视前区的分布具有性别二态性有关。比如既往研究利用原位杂交技术发现雄性大鼠MnPO神经元上分布有EP1、EP3和EP4受体[8]。但是另有研究[9]利用原位杂交和RNA酶保护实验发现,雌性小鼠视前区神经元上分布有EP1和EP3受体,却并不存在EP4受体。

本研究显示,往雌性小鼠MnPO注射PGE_2可引起BAT温度和体核温度明显升高。此外,与体核温度的变化比较,小鼠BAT温度上升的时间更早,上升的速率更快,到达峰值的时间更早,上升的幅度也更大。与此一致,国外学者[15]发现往雌性大鼠脑室内注射PGE_2可引起相似的BAT温度和体核温度变化,且脑室内注射PGE_2可以引起支配BAT的交感神经放电活动明显增加。这就提示释放到雌性小鼠MnPO的PGE_2可能经交感神经促进BAT产热,从而升高体温。本研究还发现EP3受体介导了PGE_2的促BAT产热作用。与此一致,国外学者[16]发现,MnPO支配BAT的神经元可同时表达EP3受体。此

外，既往研究[17]显示，采用化学遗传学方法抑制雄性大鼠视前区表达EP3受体的神经元可经交感神经促进BAT产热。这些发现提示，释放到雌性小鼠MnPO的PGE_2可能通过EP3受体抑制该核团神经元，然后经交感神经促进BAT产热，从而升高体核温度。但这还有待进一步的研究验证。

综上所述，本研究结果表明：MnPO注射PGE_2可经EP3受体明显升高雌性小鼠的BAT温度和体核温度。这些发现更新了对雌性哺乳动物发热反应的神经机制的认识，可为妊娠期发热症状的治疗及药物研发提供新思路。

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Effects of prostaglandin E_2 injection into the median preoptic nucleus on body temperature in female mice and its mechanisms

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Abstract ***Objective*** To investigate the effects of prostaglandin E_2 (PGE_2) microinjection into the median preoptic nucleus (MnPO) on core body temperature in female mice, and to clarify its underlying mechanism. ***Methods*** Microinjection cannula were implanted into the MnPO of female mice using stereotaxic surgery. Subsequently, a multi-channel temperature acquisition system was used to simultaneously monitor rectal and brown adipose tissue (BAT) temperatures before and after intra-MnPO injections of different reagents. To investigate the thermoregulatory effects of the microinjection of PGE_2 into the MnPO, 12 female C57BL/6 mice were randomly divided into a saline group (n=6) and a PGE_2 group (n=6), which were injected with 0.1 μL saline and PGE_2 (2.8 mmol/L), respectively. To determine whether E-series prostaglandin receptor (EP)1, EP3, and EP4 receptors mediate the thermoregulatory effects of PGE_2, 15 female C57BL/6 mice were randomly divided into 3 groups (n=5 per group). Mice in each group first received an injection of 0.1 μL PGE2 (2.8 mmol/L) into the MnPO. After their body temperature returned to baseline levels, they were subsequently injected with a mixture of either EP1, EP3 or EP4 antagonist (ant) (20 mmol/L) + PGE2 (2.8 mmol/L). ***Results*** Compared with baseline level, the rectal temperature (P<0.01) and BAT temperature (P<0.001) of female mice both increased significantly after microinjection of PGE_2 into the MnPO. Compared with the saline group, the increases in rectal temperature (P<0.001) and BAT temperature (P<0.000 1) were significantly greater in the PGE_2 group of mice. Furthermore, following the injection of PGE_2 into MnPO, the increase in BAT temperature was found to be significantly greater than that in rectal temperature in mice (P<0.001). Compared to the administration of PGE_2 alone, co-injection of an EP3 ant + PGE_2 into the MnPO of mice resulted in a significantly smaller increase in both rectal temperature (P<0.001) and BAT temperature (P<0.001). In contrast, the increases in rectal and BAT temperatures following MnPO injection of either EP1 ant + PGE_2 or EP4 ant + PGE_2 were not statistically significant (P>0.05). ***Conclusion*** Injection of PGE_2 into the MnPO elevates BAT and core body temperature in female mice *via* the EP3 receptor.

Key words female mice; fever; brown adipose tissue; prostaglandin E2; median preoptic nucleus; EP3 receptor

Fund programs National Natural Science Foundation of China (No. 32100926); Open Project of Sichuan Clinical Medical Research Center for Geriatrics (No. 24LHLNYX1-25); Youth Innovation Research Project of Sichuan Province (No. Q22010)

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