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研究论文

不同诱导方式下小鼠抑郁模型的比较研究

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摘 要：本文旨在比较不同抑郁模型诱导方式的效果。将昆明小鼠随机分为慢性温和不可预知性应激(chronic unpredictable mild stress, CUMS)组、皮质酮(corticosterone, CORT)组及CUMS+CORT组(CC组)。CUMS组接受CUMS刺激4周，CORT组每天腹股沟皮下注射20 mg/kg CORT，共给药3周；CC组同时接受CUMS刺激和CORT给药。各组分别设立正常组做对照。建模结束后，用强迫游泳试验(forced swimming test, FST)、悬尾试验(tail suspension test, TST)和糖水偏好试验(sucrose preference test, SPT)检测小鼠行为学变化，用ELISA试剂盒检测小鼠血清脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)、5-羟色胺(5-hydroxytryptamine, 5-HT)和CORT水平，同时采集和分析小鼠血清衰减全反射(attenuated total refraction, ATR)谱图，最后用HE染色法检测小鼠脑组织形态变化。结果显示，CUMS及CC组小鼠的体重显著降低。三组小鼠在FST和TST中不动时间没有显著变化，而CUMS及CC组小鼠糖水偏好显著降低($P < 0.05$)。CORT及CC组小鼠血清5-HT水平显著降低，CUMS、CORT及CC组小鼠血清BDNF和CORT水平无显著变化。和各自的正常组相比，三组小鼠血清ATR一维谱图没有显著差异；谱图一阶导数的差谱分析结果显示，CORT组与自身正常组差异最大，其次是CUMS处理组。三组小鼠海马区结构均遭到了破坏。以上结果提示，CORT和CC处理均能成功构建抑郁模型，CORT模型效果优于CC模型，因此可利用CORT诱导进行昆明小鼠抑郁模型的建立。

关键词：小鼠抑郁模型；慢性温和不可预知性应激；皮质酮

Comparison of mouse models of depression induced by different modeling methods

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Abstract: The present article was aimed to compare the effectiveness of different induction methods for depression models. Kunming mice were randomly divided into chronic unpredictable mild stress (CUMS) group, corticosterone (CORT) group, and CUMS+CORT (CC) group. The CUMS group received CUMS stimulation for 4 weeks, and the CORT group received subcutaneous injection of 20 mg/kg CORT into the groin every day for 3 weeks. The CC group received both CUMS stimulation and CORT administration. Each group was assigned a control group. After modeling, forced swimming test (FST), tail suspension test (TST) and sucrose preference test (SPT) were used to detect the behavioral changes of mice, and the serum levels of brain-derived neurotrophic factor (BDNF), 5-hydroxytryptamine (5-HT) and CORT were detected with ELISA kits. Attenuated total refraction (ATR) spectra of mouse serum were collected and analyzed. HE staining was used to detect morphological changes in mouse brain tissue. The results showed that the weight of model mice from the CUMS and CC groups decreased significantly. There was no significant change in immobility time of model mice from the three groups in FST and TST, while the glucose preference of model mice from the CUMS and CC

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groups was significantly reduced ($P < 0.05$). The serum 5-HT levels of model mice from the CORT and CC groups were significantly reduced, while the serum BDNF and CORT levels of model mice from the CUMS, CORT, and CC groups showed no significant changes. Compared with their respective control groups, the three groups showed no significant difference in the one-dimensional spectrum of serum ATR. The difference spectrum analysis results of the first derivative of the spectrogram showed that the CORT group had the greatest difference from its respective control group, followed by the CUMS group. The structures of hippocampus in the model mice from the three groups were all destroyed. These results suggest that both CORT and CC treatments can successfully construct a depression model, and the CORT model is more effective than the CC model. Therefore, CORT induction can be used to establish a depression model in Kunming mice.

Key words: depression model; chronic unpredictable mild stress; corticosterone

抑郁症是一种常见的精神类疾病，主要表现为情绪低落、快感缺失、易怒、注意力不集中、食欲和睡眠异常[1]。因其治愈困难、易复发，且部分抑郁症患者常伴有自杀倾向及行为，给家庭和社会造成了严重的负担[2]。实验动物模型为抑郁症机制研究及药物研发做出了重要贡献[3]，常用抑郁模型由应激刺激和化学诱导，应激刺激模型如慢性束缚应激 (chronic restraint stress, CRS)[4, 5]、慢性社会挫败应激 (chronic social defeat stress, CSDS) 模型[1]、慢性温和不可预知性应激 (chronic unpredictable mild stress, CUMS) 模型[6, 7]、阈下社会挫败应激 (subthreshold social defeat stress, SSDS)[8]、习得性无助模型 (learned helplessness, LH)[9]，其中 CUMS 模型因其症状与人类抑郁较相似，使用较多；化学诱导常用的试剂有皮质酮 (corticosterone, CORT)[10, 11]、脂多糖 (lipopolysaccharide, LPS)[12]。也有学者将不同建模方法组合起来建模，如游泳 +CUMS[7]、CUMS+ 坐骨神经慢性压迫[13]、CUMS+ 孤养[14]、CUMS+LPS[15]。

抑郁小鼠在行为学指标、血清学指标、组织形态等方面都发生了变化。研究表明抑郁可使机体 5-羟色胺 (5-hydroxytryptamine, 5-HT)、多巴胺 (dopamine, DA)、去甲肾上腺素 (norepinephrine, NE)、脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF) 含量降低，并使肿瘤坏死因子 -α (tumor necrosis factor-α, TNF-α)、白细胞介素 -6 (interleukin-6, IL-6) 等炎症因子含量升高[16–20]；与此同时，抑郁小鼠快感缺失、求生欲降低，主要表现在强迫游泳试验 (forced swimming test, FST) 及悬尾试验 (tail suspension test, TST) 中不动时间减少，糖水偏好试验 (sucrose preference test, SPT) 中糖水偏好降低等[21, 22]；此外，抑郁小鼠海马区结构发生变化，大脑神经细胞增殖减少[23]。

本研究分别设立了物理刺激组、化学诱导组和物理 + 化学诱导组，即 CUMS 组、CORT 组、CUMS+ CORT 组 (CC 组)，通过测定血清中 BDNF、5-HT、CORT 的含量及行为学指标来比较不同抑郁模型诱导方式的效果，为昆明小鼠抑郁模型的建立提供较合适的方法。

1 材料与方法

1.1 试剂 CORT (C104537，上海阿拉丁生化科技股份有限公司)，二甲基亚砜 (dimethyl sulfoxide，DMSO，AR，麦克林生化科技有限公司)，苏木素 - 伊红染液、小鼠 5-HT ELISA (干粉法)、小鼠 CORT ELISA (干粉法)、小鼠 BDNF ELISA (干粉法) 试剂盒均购自南京建成生物工程研究所。

1.2 仪器 冷冻切片机 (LEICA CM 1860 UV)，低温冷冻高速离心机 (Centrifuge 5424 R，德国艾本德股份公司)，酶标仪 (MULTISKAN FC，赛默飞世尔科技有限公司)，荧光正置显微镜 (DS-Ri2，尼康仪器有限公司)，迷你离心机 (WTL，长沙湘仪离心机仪器有限公司)，孵育机 (HB 120-S，大龙兴创实验仪器股份公司)，傅里叶变换红外光谱仪 (Nicolette iS50，赛默飞世尔科技有限公司)。

1.3 实验动物与分组 所用实验动物为 4 周龄雄性昆明 (KM) 小鼠 (西安交通大学医学部实验动物中心，许可证号：SCXK 2018-001)，小鼠养于恒温 (25 °C) 动物房中，12 h 光照 /12 h 黑暗循环。将小鼠随机分为 CUMS 组、CORT 组及 CC 组 (每组 10 只小鼠)，各组分别设正常组 (每组 5 只小鼠) 做对照。需要进行慢性温和刺激的小鼠 1 只 / 笼，其余小鼠 5 只 / 笼。CUMS 模型建立时，小鼠在开始诱导前进行一次行为学实验，在开始刺激 2 周后再进行一次行为学实验，一周测定一次体重，共刺激 4 周，正常组小鼠不做任何处理。造模期间每天刺激方式如表 1 所示。CORT 模型建立时采用腹股沟皮下注

射的方式，正常组注射含 1% DMSO 的生理盐水，模型组按 20 mg/kg (0.1 mL) 剂量给予 CORT，于每天 9:00~16:00 间随机给药，共给药 3 周。CC 组建模结合了物理及化学诱导方式，化学给药方式同 CORT 组，物理刺激方法见表 2。本研究动物实验方案遵循中国科学院西北高原生物研究所实验动物伦理委员会的规定。

1.4 行为学测试

1.4.1 FST 实验前将小鼠放于待测试房间适应 30 min。将小鼠置于直径 18 cm 的圆形容器中，水温 25 °C，使其自由游泳 6 min，记录后 4 min 小鼠不动时间。

1.4.2 TST 实验前将小鼠放于待测试房间适应 30 min。用医用胶带黏住距小鼠尾尖约 2 cm 处的尾部皮肤，使之处于悬挂状态，试验进行 6 min，记录后 4 min 小鼠不动时间。

1.4.3 SPT 对小鼠进行糖水适应性训练 48 h，同时给小鼠水和 1% 糖水，每 12 h 将水、糖水的位置互换，糖水适应性训练结束后禁食、禁水 22 h，然后检测各小鼠 2 h 内的水、糖水消耗量，计算糖水

表1. CUMS模型的刺激方式

Table 1. The stimulation during CUMS modeling

Day	Stimulation mode	Day	Stimulation mode
1	Odour stimulation	15	Daylight protection for 12 h
2	Odour stimulation + Water deprivation for 24 h	16	Overnight illumination for 12 h
3	Restraint stress for 5 h	17	Warm water swim (38 °C, for 30 min)
4	Soiled cage + cage tilting (45°, for 24 h)	18	Food deprivation for 24 h
5	Soiled cage + cage tilting (45°, for 24 h)+food deprivation for 24 h	19	Water deprivation for 24 h + empty bottle stimulation
6	Food deprivation for 24 h + cold water swim (8 °C, for 5 min)	20	Water deprivation for 24 h + empty bottle stimulation + cold water swim (8 °C, for 5 min)
7	Day and night reversed	21	Restraint stress for 5 h
8	Tail pinch restraint for 1 min + no packing	22	Cage tilting (45°, for 24 h)
9	Restraint stress for 5 h + noise stimulation	23	Warm water swim (38 °C, for 30 min)
10	Warm water swim (38 °C, for 30 min)	24	Tail pinch restraint for 1 min + day and night reversed
11	Water deprivation for 24 h + empty bottle stimulation	25	Odour stimulation
12	Soiled cage	26	Odour stimulation + soiled cage
13	Cage tilting (45°, for 24 h)	27	Water deprivation for 24 h + empty bottle stimulation
14	Restraint stress for 5 h + tail pinch restraint for 2 min	28	Restraint stress for 5 h

表 2. CC组小鼠每天刺激方式

Table 2. The stimulation during CC modeling

Day	Stimulation mode	Day	Stimulation mode
1	Food deprivation for 24 h	12	Food deprivation for 24 h
2	Water deprivation for 24 h + empty bottle stimulation	13	Restraint stress for 5 h
3	Water deprivation for 24 h + empty bottle stimulation + cold water swim (8 °C, for 5 min)	14	Cage tilting (45°, for 24 h) + overnight illumination for 12 h
4	Restraint stress for 5 h	15	Soiled cage
5	Cage tilting (45°, for 24 h)	16	Soiled cage + odour stimulation
6	Warm water swim (38 °C, for 30 min)	17	No packing + overnight illumination for 12 h
7	Tail pinch restraint for 1 min + day and night reversed	18	Daylight protection for 12 h
8	Odour stimulation	19	Warm water swim (38 °C, for 30 min)
9	Odour stimulation + soiled cage	20	Water deprivation for 24 h + empty bottle stimulation
10	Food and water deprivation for 24 h	21	Restraint stress for 5 h
11	Food and water deprivation for 24 h		

偏好度。糖水偏好 (%) = 糖水消耗 / (水消耗 + 糖水消耗) × 100%。

1.5 血清分析 采用眼球取血法进行采血，采血完毕室温放置 2 h，然后于 4 °C 下，3 500 r/min 离心 15 min，取上部血清，血清于 −80 °C 下保存。用 ELISA 试剂盒对 BDNF、CORT、5-HT 水平进行测定，读取 OD_{450} 后通过标准曲线计算各指标含量。各组小鼠血清采集衰减全反射 (attenuated total refraction, ATR) 谱图采集条件为采集次数 32 次，分辨率 4 cm^{-1} (n = 3)。计算各组中正常组和模型组的均谱，以各自正常组为标准，计算一维谱图与一阶导谱图条件下模型组的相似系数。

1.6 HE 染色 小鼠眼球取血后，立刻取大脑进行冰冻切片，切片厚度为 8 μm，切片保存于 −20 °C 备用。进行 HE 染色时将切片从 −20 °C 拿到室温回温；然后水中浸泡 40 s 进行水合；苏木精染色 5 min 后水洗 5 s；利用 0.5% 盐酸乙醇分化 5 s，水洗 5 s；伊红染色 1 min 后水洗 2 s；切片依次于 80%、95%、100% 乙醇中脱水 1~2 s；二甲苯透明 2 次，5 s/ 次；自然晾干后用中性树胶封存。

1.7 数据分析 数据用 mean ± SD 表示，用 Graphpad Prism 7 进行血清因子含量、行为学指标等的方差分析 (两两比较用 LSD 法) 及作图，$P < 0.05$ 时认为差异具有显著性。ELISA 试剂和标准曲线由 ELISA 软件进行拟合，小鼠大脑切片全貌由 Nicolet 软件合成，利用 OMNIC 软件进行血清的红外光谱分析。

2 结果

2.1 体重

不同抑郁模型诱导方式下，小鼠体重变化如图 1 所示。结果显示，与正常组比较，模型组小鼠体重增长缓慢，CUMS 及 CC 组小鼠在处理过程中体重降低显著，CUMS 组小鼠体重在造模第 1、2 和 4 周显著低于正常组，CC 组小鼠体重在每周都显著低于正常组 (均 $P < 0.01$)，而 CORT 组小鼠体重没有显著变化。

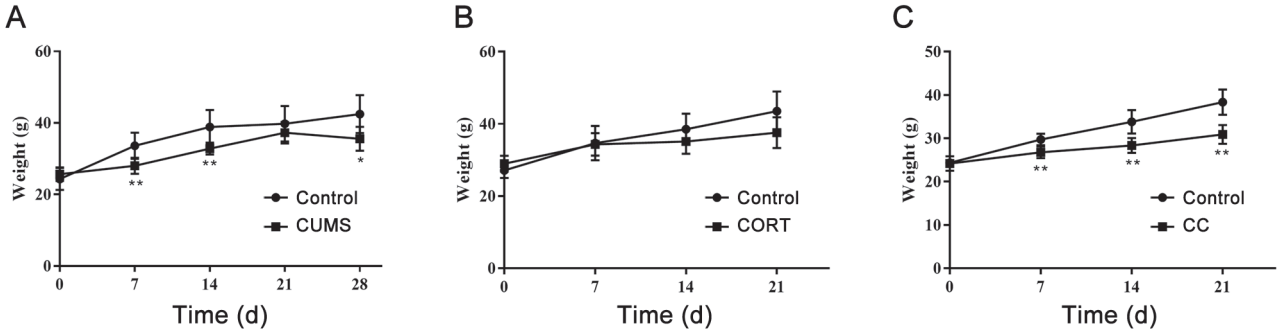

图 1. 不同处理组体重变化

Fig. 1. The body weight changes of different groups. *A*: Chronic unpredictable mild stress (CUMS) group; *B*: Corticosterone (CORT) group; *C*: CUMS+CORT (CC) group. Mean ± SD, n = 5 (control groups) or 10 (model groups). $^{*}P < 0.05$, $^{**}P < 0.01$ *vs* control group.

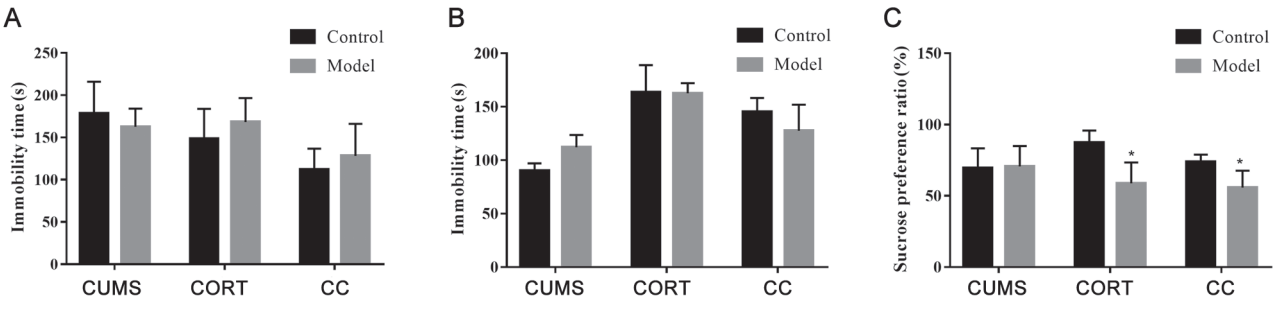

图 2. 不同处理条件下各组小鼠行为学变化

Fig. 2. The changes of behavioral tests during different groups. *A*, *B*: The immobile time in forced swimming test (FST, *A*) and tail suspension test (TST, *B*); *C*: The sucrose preference in sucrose preference test (SPT). Mean ± SD, n = 5 (control groups) or 10 (model groups). $^{*}P < 0.05$ *vs* control group.

2.2 行为学测试

小鼠 3 种行为学实验结果如图 2 所示。在 FST 中，和各自的正常组相比，CUMS 组小鼠不动时间减少，CORT 及 CC 组小鼠不动时间增加，但是这些差异没有显著性 ($P > 0.05$)(图 2*A*)。在 TST 中，和各自的正常组相比，CUMS 小鼠不动时间增长，CC 小鼠不动时间减少，但是这些差异也不显著 ($P > 0.05$)，CORT 小鼠不动时间与正常组相当 (图 2*B*)，上述结果提示，3 种模型诱导方式不能诱发小鼠在 FST 和 TST 中的绝望行为。在 SPT 中，与各自正常组相比，CUMS 组小鼠糖水偏好没有显著变化，而 CORT 和 CC 组小鼠的糖水偏好显著降低 ($P < 0.05$)。

2.3 血清分析

2.3.1 生化指标

和各自的正常组相比，模型组小鼠血清 5-HT 水平均呈降低趋势，其中 CORT 及 CC 组小鼠血清 5-HT 水平显著降低 ($P < 0.01$)。和各自的正常组相比，CUMS、CORT 和 CC 组小鼠血清 BDNF 含量无显著变化 ($P > 0.05$)(图 3*B*)。和各自的正常组相比，CUMS、CORT 和 CC 组小鼠血清 CORT 水平无显著变化 ($P > 0.05$)(图 3*C*)。

2.3.2 血清红外光谱分析

采集各小鼠血清 ATR 谱图，所得谱图如图 4*A* 所示。各小鼠血清 ATR 谱图有差异，但不能区分不同处理之间的区别，也不能区分模型组与正常组间的区别。小鼠血清 ATR 吸收有 5 个峰，分别在 3281、2116、1636、1555 和 514 cm^{-1} 处。

不同处理方法正常组和模型组一维谱图、一阶导数谱图分别如图 4*B*、*C* 所示，各组 ATR 谱图相差不大，但是各组相关系数有差距，CC 组相似性最小，CORT 组相似性最大 (表 3)。为了进一步找到不同组的差异，利用差谱进行分析 (以正常组为标准谱图，模型组为样品谱图)。差谱结果显示，各组主要差异在 480 cm^{-1}，但是 < 500 cm^{-1} 吸收峰杂质较多，此处波段不作分析。对 4 000~500 cm^{-1} 波段吸收分析结果显示，CORT 组差异最大，其次是 CUMS 处理组；CORT 组差异集中在 3 700~2 900 cm^{-1}、1 750~1 500 cm^{-1}、1 050 cm^{-1} 3 个波段，CUMS 组差异主要在 1 700~1 500 cm^{-1} 波段，而 CC 组在 1 700~1 500 cm^{-1} 波段有微弱差异 (图 4*D*~*F*)。

2.4 HE染色

小鼠大脑全切片 HE 染色结果显示，正常组小鼠大脑呈显著的蝴蝶状，齿状回、锥体层结构正常，而各模型组小鼠大脑蝴蝶状均不明显，海马区齿状回、锥体层结构发生变化甚至消失 (图 5*E*)。进一步的小鼠海马区 HE 染色结果显示，正常组小鼠海马区结构完整，表现为齿状回、胼胝体、锥体层结构完整，胼胝体细胞结构排列紧密；而各模型组小鼠大脑均变化显著，小鼠海马边界不清楚，细胞空泡化严重，且细胞质不均匀；齿状回消失；胼胝体结构松散，细胞凋亡 (图 5*A*~*E*)。

3 讨论

好的动物抑郁模型是相关研究成功的基础。不同动物模型其发病机制不尽相同，即使是使用应激刺激进行建模，也会因应激源的不同造成抑郁发病机制不同。对不同应激方式诱导的大鼠模型进行行

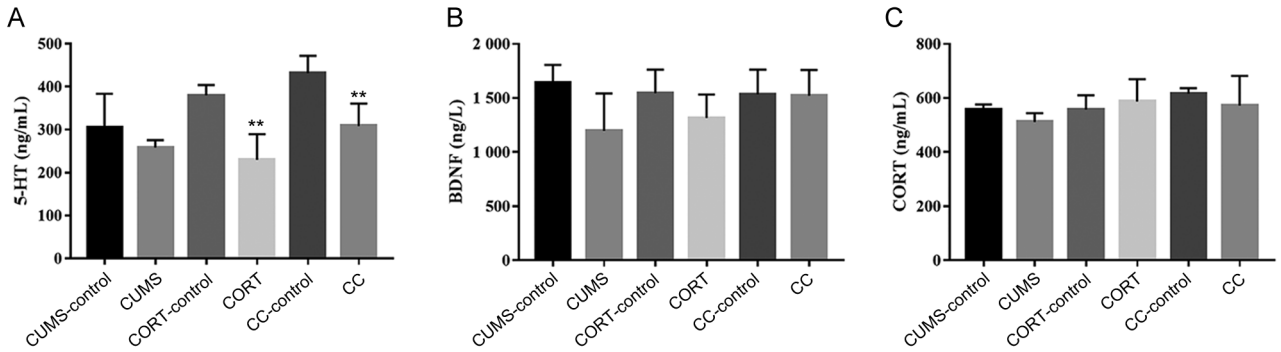

图 3. 各组小鼠血清因子含量

Fig. 3. The levels of serum factors of different groups detected by ELISA kit. *A*: 5-hydroxytryptamine (5-HT); *B*: Brain-derived neurotrophic factor (BDNF); *C*: Corticosterone (CORT). Mean ± SD, $n = 5$ (control groups) or 10 (model groups). $^{*}P < 0.05$, $^{**}P < 0.01$ *vs* control group.

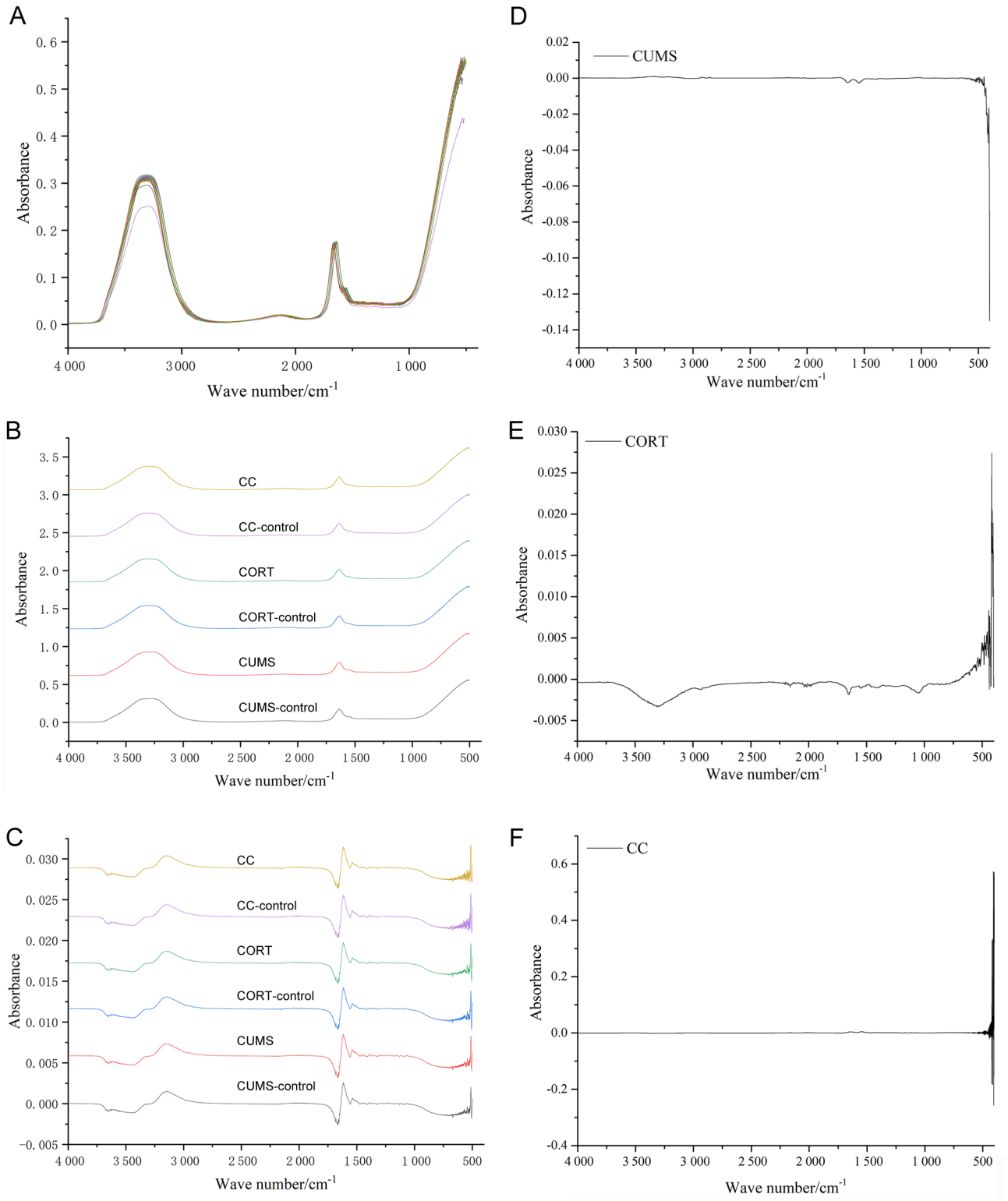

图　4. 小鼠血清衰减全反射(ATR)谱图分析

Fig. 4. The attenuated total refraction (ATR) spectra analysis of mouse serum. *A*: The serum ATR spectra (resolution ratio: 4 cm^{-1}, scan time: 32 times) of all mice. Different colors represent different mice. *B*, *C*: The mean spectra of different groups (*B*) and the corresponding D1 spectra (*C*). *D*–*F*: The differential spectra between model groups and their respective control groups.

为学观察发现，CUMS、LH、CRS、SSDS 模型诱导大鼠糖水偏好降低、FST 中不动时间增加，表现出抑郁样行为，而只有 CUMS 模型大鼠在旷场试验和高架十字迷宫试验中表现出焦虑样行为；代谢

表 3. 不同模型组谱图与各自正常组的相关性

Table 3. Correlation between spectrograms of different model groups and their respective control groups

Modeling method	Group	Correlation coefficient of ATR	Correlation coefficient of D1
CORT	Control	1.0000	1.0000
	Model	0.9933	0.9535
CUMS	Control	1.0000	1.0000
	Model	0.9695	0.6997
CC	Control	1.0000	1.0000
	Model	0.4016	0.2997

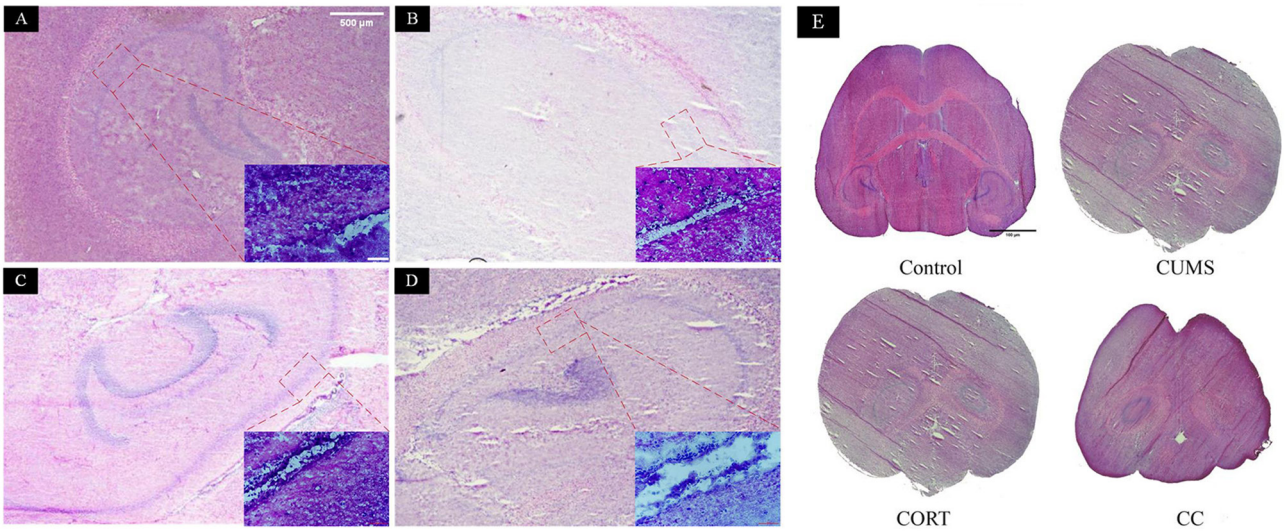

图 5. 各组小鼠脑部HE染色结果

Fig. 5. HE staining results of brain in mice from the different groups. *A–D*: The slices (Scale bar, 500 μm) and partial magnified images (Scale bar, 50 μm) of hippocampi in control (*A*), CUMS (*B*), CORT (*C*), and CC (*D*) groups. *E*: The structures of cerebra of different groups. Scale bar, 100 μm.

组学分析结果显示，躯体应急模型 (CUMS、LH) 与心理应激模型 (CRS、SD) 差异代谢物涉及的信号通路差距较大 [24]。因此，应根据不同的研究目的选择合适的动物模型。

慢性压力诱发抑郁症是公认的健康问题，慢性压力模型是经典的抑郁模型，其中，CUMS 模型较为常用，由 Willner 等于 1987 年建立 [25]，而 CORT 是造成抑郁样行为的重要因子，慢性高 CORT 处理可建立可靠的抑郁动物模型 [26]。抑郁小鼠体重呈降低趋势 [27, 28]，本研究结果显示，CORT 诱导模型小鼠体重没有明显变化，而 CUMS 及 CC 诱导的模型小鼠体重较正常组小鼠变化差异显著，这可能与 CUMS 及 CC 模型小鼠在建模过程中所受禁食、禁水、束缚等刺激有关，这些刺激延长了小鼠的禁食时间、增加了小鼠的禁食时常。行为学实验广泛应用于神经精神类动物模型的评价，可评估动物的绝望、焦虑等行为，常用的 SPT 反映了动物的快感缺失状况，FST 及 TST 是基于绝望行为的检测方法 [29]。抑郁动物模型常表现出快感缺失、行为绝望等现象，具体表现在糖水偏好降低，FST 及 TST 中求生欲降低、不动时间增加 [22, 30, 31]。本研究结果显示，和正常组小鼠相比，3 种方法诱导的抑郁模型小鼠在 FST 及 TST 中不动时间变化不显著，表明小鼠并未产生显著的绝望行为，但是 CORT 及 CC 组小鼠糖水偏好显著降低，表明抑郁组小鼠快感缺失，而研究人员通常在建模结束后选择糖水偏好降低的小鼠为建模成功小鼠，以进行后续实验 [32, 33]。

5-HT、CORT、BDNF 在抑郁发生过程中发挥重要作用，5-HT 是脑内重要的抑制性神经递质，通过与不同的受体结合达到介导神经递质释放、调节细胞信号通路、使神经元去极化等功能；BDNF 是神经营养因子，可增加神经发育及突触可塑性；

而 CORT 是导致动物抑郁的重要因子，因此抑郁模型小鼠 5-HT 及 BDNF 含量会降低，CORT 含量升高 [20, 34]。本研究结果显示，CORT 和 CC 组小鼠血清 5-HT 水平相较正常组显著下降，各模型组小鼠血清 BDNF 及 CORT 水平相较各自正常组无显著差异。

血清中包含蛋白质、脂类、糖类、水、无机盐等，这些成分均可通过光谱表现出来，已有研究表明正常人体血清及癌症患者血清中红外谱图信息具有差异，这些差异反映了血清中糖原及蛋白质结构的变化 [35, 36]。抑郁模型小鼠血清多种生化指标发生变化，为了简单快速地分析不同处理下模型组小鼠血清的变化，本研究采用红外光谱技术对各组小鼠血清 ATR 谱图进行分析，结果显示，ATR 一维谱图并不能明确表征不同处理下正常组与模型组间的差异，为了找到不同处理下模型组与正常组的差异，本研究进一步利用差谱对小鼠血清进行分析，结果显示，CORT 组小鼠血清与正常组差异最大，其次是 CUMS 组，而 CC 小鼠仅在 1 700~1 500 cm^{-1} 波段与正常组有微弱差异。

本研究脑部 HE 染色结果显示，抑郁模型组小鼠脑部结构被破坏，海马区齿状回、锥体层结构发生变化甚至消失，细胞空泡化严重，且细胞质不均匀。海马区是抑郁发生的关键脑区，抑郁症常伴随海马区结构异常，神经元细胞遭到破坏会严重影响大脑对信息的处理能力 [37, 38]。

有研究表明，CORT 与 CUMS 诱导建模条件下小鼠均能产生抑郁样行为，小鼠下丘脑 - 垂体 - 肾上腺轴紊乱，且两种模型在小鼠海马结构改变及大脑 BDNF-pCREB 和 ERK 信号通路激活等方面无显著差异 [39]；也有研究显示，CORT 诱导 C57BL/6J 小鼠抑郁样行为更明显，造模效果优于 CUMS 模型 [40]，这与本研究结果一致。CUMS 及 CC 模型效果不好的原因可能与 CUMS 模型及 CC 模型中出现的运动刺激有关，有研究显示，运动可改善动物模型的抑郁样行为 [31–43]。Luo 等 [28] 利用慢性浸水束缚刺激诱导大鼠抑郁模型，并观察自主跑轮运动对抑郁行为的影响，结果显示，自主跑轮运动可显著改善小鼠的抑郁样行为，并显著降低抑郁大鼠血清中炎症因子白介素 1β (interleukin-1β, IL-1β) 和 IL-6 的水平，提高 IL-4 和 IL-10 的水平，而 LPS 可逆转自主跑轮运动的抗抑郁作用，其机制是自主跑轮运动可通过 STAT3 信号通路调控小胶质细胞的分化类型，介导中枢神经系统免疫反应和神经炎症功能。也有研究显示，高强度间歇训练可通过上调糖皮质激素受体及下调肿瘤坏死因子 α 的蛋白表达对 CUMS 小鼠起到抗抑郁作用 [31]。同时，CUMS 模型及 CC 模型中的禁食处理同样对雌性小鼠的抑郁样行为具有改善作用 [44]。

综上所述，本研究结果表明，在不同的诱导方式下，昆明小鼠抑郁模型在行为学、生化指标及血清红外谱图方面具有差异。在不同模型诱导方式下，小鼠海马区结构均遭到了破坏，抑郁诱导没有使小鼠产生绝望行为，但 CORT 及 CC 诱导的抑郁模型小鼠快感缺失，同时这两种抑郁模型小鼠血清 5-HT 含量显著降低，血清红外谱图分析表明 CORT 组与正常组差异最大，表明 CORT 和 CC 处理均能成功构建抑郁模型，CORT 模型效果优于 CC 模型，因此可利用 CORT 诱导进行昆明小鼠抑郁模型的建立。

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