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基于数据挖掘的功能性消化不良动物模型的评价

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【摘要】 目的 通过系统的文献检索, 收集、整理并分析现存的功能性消化不良动物模型制备方法与常用检测指标, 以完善其模型的制备与评价。**方法** 以“功能性消化不良, 动物模型”“functional dyspepsia, animal model”等为检索词, 在中国知网、万方、维普和中国生物医学、PubMed、Web of Science、Cochrane Library、Embase 数据库进行检索, 检索时间为建库至 2022 年 6 月 21 日。**结果** 共纳入 71 篇文献, 包括中文 63 篇和英文 8 篇。研究对象均为鼠类, 雌雄皆有选择, 年龄在 1 ~ 84 d。造模方式共有 32 种, 其中单因素造模 7 种, 多因素造模 25 种。造模周期从 6 ~ 98 d。检测指标涵盖一般情况, 胃肠功能和精神状态等主要方面。**结论** (1) 功能性消化不良的动物模型主要以 6 ~ 8 月龄的雄性 SD 大鼠为造模对象, 造模方式以单因素的夹尾刺激法和多因素的不规则饮食+夹尾刺激法为主, 选择最多的检测指标分别为胃排空/残留率, 实验动物一般情况和小肠推进比。(2) 成模标准尚无统一规定, 造模因素的选择仍需进一步的探究。

【关键词】 功能性消化不良; 动物模型; 评价指标; 综述

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Analysis of the application characteristics of functional dyspepsia animal models based on data mining

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【Abstract】 Objective Through a systematic literature search, we collected, organized and analyzed the existing method for preparing animal models of functional dyspepsia and commonly used assays to improve model research method. **Methods** The search terms “functional dyspepsia, animal model” and “functional dyspepsia, animal model” were search CNKI, WanFang, VIP and SinoMed, PubMed, Web of Science, Cochrane Library, and Embase databases, and the search time was from the establishment of the database to June 21, 2022. **Results** A total of 71 articles were included, including 63 articles in Chinese and 8 articles in English. The subjects of the study were all rats, with male and female selection, and the age ranged from 1 day to 84 days. There were 32 modeling method, including 7 single-factor modeling and 25 multi-factor modeling. Modeling cycles ranged from 6 to 98 days. Test indicators covered the general situation, gastrointestinal function and mental state and other major aspects. **Conclusions** (1) For animal models of functional dyspepsia, male SD rats of 6 ~ 8 months old are mainly used for modeling, and the modeling method are mainly single-factor tail-clamping stimulation and multi-factor irregular diet+tail-clamping stimulation. The most selected detection indicators are gastric emptying/residual rate, general conditions of the experimental animals and small intestinal propulsion ratio,

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respectively. (2) There is no unified regulation on modeling standard, and the selection of modeling factors needs further investigation.

【Keywords】 functional dyspepsia; animal models; evaluation indicators; review

Conflicts of Interest: The authors declare no conflict of interest.

功能性消化不良 (functional dyspepsia, FD) 是一种以胃和十二指肠功能障碍为特点的非器质性疾病, 症状表现为上腹痛综合征 (epigastric pain syndrome, EPS) 和餐后窘迫综合征 (postprandial distress syndrome, PDS) 两种类型。近年来, 新冠病毒的流行加重了公众焦虑抑郁的情绪, 导致罹患 FD 的人群增多, 原有 FD 症状加重^[1], 演变为不可忽视的公共卫生问题, 国内外学者对 FD 发病机制和治疗方法的研究也随之增加。目前, FD 的治疗方法包括幽门螺杆菌根除^[2]、质子泵抑制剂^[3]和促胃动力药^[4]等, 艾灸^[5]、针刺^[6]和心理干预^[7]等补充替代疗法也起到一定作用, 但 FD 的一线治疗方案仍以药物干预为主^[8]。作为研究 FD 的重要手段, 稳定而可靠的 FD 动物模型是开展相关研究的关键和基础, 但目前模型动物的品系和造模方式尚未有统一标准^[9]。因此, 本研究对已有的 FD 动物实验文献进行收集、整理和分析, 通过探讨动物种类、造模方式及主要检测指标的选择依据, 旨在提供科学且可重复的 FD 动物模型制备方法。

1 资料与方法

1.1 数据来源

以“功能性消化不良”和“动物模型”为主题, 在中国知网、万方、维普和中国生物医学数据库进行检索; 以“functional dyspepsia”“non-ulcer dyspepsia”“epigastric pain syndrome”“postprandial distress syndrome”“models, animal”“laboratory animal model”“animal model”“experimental animal model”为关键词, 在 PubMed、Web of Science、Cochrane Library、Embase 数据库进行检索。检索时间为建库至 2022 年 6 月 21 日, 共检索到期刊文献 311 篇。

1.2 文献筛选标准

(1) 纳入标准: 研究功能性消化不良并造模成功的动物实验文献; (2) 排除标准: 学位论文、会议和综述; 资料不全的文献。最终纳入符合标准的文献 71 篇, 文献检索流程见图 1。

1.3 统计学分析

实验动物名称、种类等均按照《实验动物和动物实验技术》进行规范, 将收集的实验动物种类、造

模方式、造模周期、检测指标等录入 Excel 2019 建立数据库, 对纳入文献的研究结果采用频数和百分比进行统计描述, 对数据进行整理、统计和分析。

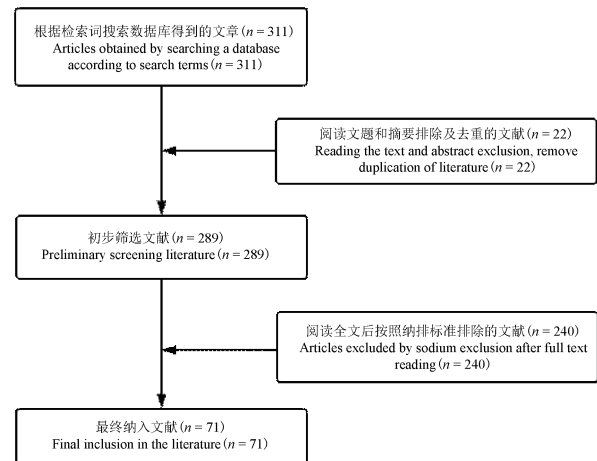


图 1 文献检索流程图

Figure 1 Document retrieval flow chart

2 结果

2.1 实验动物选择

71 篇文献涉及的造模动物种类均为鼠类, 共有 3 种品系, 包括 SD 大鼠 (40 次, 56.34%)、Wistar 大鼠 (27 次, 38.03%) 和 KM 小鼠 (4 次, 5.63%), 具体见表 1。动物性别主要选择雄性 (34 次, 47.89%), 雌雄各半 (25 次, 35.21%), 具体见表 2。动物年龄多选用 6 ~ 8 月龄 (12 次, 16.90%), 但有 33 篇文献未对实验动物年龄进行描述 (33 次, 46.48%), 具体见表 3。

表 1 FD 模型动物种类及频次

Table 1 Species and frequency of functional dyspepsia model animals

种类 Strain	频数 (次) Frequency (Times)	频数/总数 (%) Frequency/Total (%)
Sprague Dawley 大鼠 Sprague Dawley rats	40	56.34
Wistar 大鼠 Wistar rats	27	38.03
KM 小鼠 KM mice	4	5.63
合计 Total	71	100.00

表 2 FD 模型动物性别及频次

Table 2 Sex and frequency of functional dyspepsia

model animals		
性别 Sex	频数(次) Frequency (Times)	频数/总数(%) Frequency/Total (%)
雄性 Male	34	47.89
雌性 Female	3	4.23
雌雄各半 Half male and half female	25	35.21
雌雄兼用 Both male and female	4	5.63
未提及 Not mentioned	5	7.04
合计 Total	71	100.00

表 3 FD 模型动物年龄及频次

Table 3 Age and frequency of functional dyspepsia

model animals		
年龄 Age	频数(次) Frequency (Times)	频数/总数(%) Frequency/Total (%)
1 d	2	2.82
3 d	1	1.41
6 d	2	2.82
7 d	7	9.86
10 d	2	2.82
21 d	1	1.41
21 ~ 28 d	2	2.82
30 d	2	2.82
42 d	1	1.41
42 ~ 56 d	1	1.41
56 d	10	14.08
60 d	1	1.41
56 ~ 84 d	1	1.41
70 d	1	1.41
70 ~ 84 d	2	2.82
84 d	2	2.82
未提及 Not mentioned	33	46.48
合计 Total	71	100.00

2.2 造模方式

71 篇文献共有 32 种造模方式,其中单因素造模方式 7 种,使用最多的为夹尾刺激法(19 次,26.76%);多因素造模方式 25 种,使用最多的为不规则饮食+夹尾刺激法(11 次,15.49%)(见表 4)。

2.3 造模周期

71 篇文献共存在 17 种造模时间,其中以 7 d 为周期进行造模最多(18 次,25.35%),其次为 14 d(15 次,21.13%)和 21 d(8 次,11.27%)(见表 5)。

2.4 检测指标

71 篇文献共涉及 102 种检测指标,累计频数 346 次,其中胃排空/残留率检测最多(41 次,11.56%),其次为一般情况(40 次,11.56%),排名第三为小肠推进比(28 次,8.09%),具体见表 6。

3 讨论

目前 FD 的发病机制尚未明确,越来越多的研究表明,FD 可能是多种致病因素共同作用而产生,包括心理疾病^[10]、幽门螺旋杆菌感染^[2]、十二指肠嗜酸性粒细胞增多^[11]、不良饮食习惯^[12]和肠-脑相互作用障碍(disorders of gut-brain interaction, DGBI)^[13]等,因此,在造模方式的选择中应当有针对性的选择干预因素和造模周期,并根据造模方式的特点选择合适的动物品系、性别和生长阶段,检测指标应根据 FD 的症状表现和具体研究目的进行选择。

3.1 造模动物属性

3.1.1 动物种类

文献挖掘结果表明,目前 FD 造模选取的动物品种以大鼠为主,其中 SD 大鼠和 Wistar 大鼠为主要选择品系,也有 4 篇文献^[14-17]选取 KM 小鼠进行造模。选择鼠类的原因在于其饲养成本低,易于繁殖且生长速度快。与 SD 大鼠相比,Wistar 大鼠更易受应激因素影响^[18],干预效果更明显。但 SD 大鼠生长发育较 Wistar 更快,且对性激素敏感程度高。

3.1.2 动物年龄

71 篇文献共包含 16 种不同的年龄阶段,从出生后 1 d 的新生大鼠到 12 周的成年大鼠均有。其中,选择出生后 7 d 的幼鼠及 6 ~ 8 周的成年大鼠进行研究最为频繁。研究发现,早期生活事件会导致大鼠成年后产生抑郁行为^[19],而选择幼鼠进行早期母婴分离也会导致成年后抑郁状态。同时,不同年龄阶段的动物胃肠敏感性不同,在大鼠幼年时期进行干预更易导致成年后的 FD 症状。而选择成年大鼠则更贴近 FD 患者的真实胃肠状态。

3.1.3 动物性别

造模动物多选择雄性为主,也有部分文献选择雌雄各半或雌性兼用。研究表明,在人类群体中相比于男性,女性更易产生 FD 症状^[20],而动物实验发现雌性动物更易受精神因素的影响^[21-22],这可能是由于焦虑、抑郁情绪通过影响下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis, HPA)中激素

表 4 FD 动物模型造模因素及方式

Table 4 Model factors and method of functional dyspepsia animal model

造模因素 Modeling factors	造模方式 Modeling method	频数(次) Frequency (Times)	频数/总数(%) Frequency/ Total(%)
单因素 Single factor	夹尾刺激 Tail clamping stimulus	19	26.76
	碘乙酰胺蔗糖混合液 Iodoacetamide sucrose mixture	3	4.23
	物理因素刺激 Physical stimulation		
	番泻叶灌胃 Folium sennae intragastrically	1	1.41
	利血平腹腔注射 Intraperitoneal injection of reserpine	1	1.41
	食醋 Table vinegar	1	1.41
	化学因素刺激 Chemical stimulation		
	稀盐酸 Dilute hydrochloric acid	1	1.41
	早期生活事件 Early life events		
	母婴分离 Separation of mother and child	1	1.41
	慢性不可预见性刺激 Chronic unpredictable stimulation		
	不规则饮食+冰水游泳+热环境+水平震荡+夹尾刺激+明暗颠倒 Irregular diet+iced water swimming+hot environment+horizontal oscillation+tail-clamping stimulation+light and dark reversed	1	1.41
	不规则饮食+过度疲劳+束缚+倒悬摇晃+夹尾刺激 Irregular diet+excessive fatigue+restraint+upside down shaking+tail stimulation	1	1.41
	不规则饮食+夹尾刺激 Irregular diet+tail stimulation	11	15.49
	不规则饮食+夹尾刺激+冰水饮用 Irregular diet+tail stimulation+iced water to drink	1	1.41
	不规则饮食+夹尾刺激+跑步 Irregular diet+tail stimulation+running	1	1.41
	不规则饮食+夹尾刺激+束缚+游泳 Irregular diet+tail stimulation+restraint+swimming	1	1.41
	物理因素刺激 Physical stimulation		
	不规则饮食+夹尾刺激+游泳 Irregular diet+tail stimulation+swimming	1	1.41
多因素 Multiple factors	不规则饮食+束缚+游泳 Irregular diet+restraint+swimming	1	1.41
	不规则饮食+噪音刺激 Irregular diet+noise stimulation	1	1.41
	夹尾刺激+跑步 Tail clamping stimulation+running	1	1.41
	不规则饮食+稀盐酸 Irregular diet+dilute hydrochloric acid	5	7.04
	不规则饮食+左旋精氨酸 Irregular diet+L-arginine	1	1.41
	不规则饮食+夹尾刺激+碘乙酰胺蔗糖混合液 Irregular diet+tail clamping stimulation+iodoacetamide sucrose mixture	1	1.41
	不规则饮食+夹尾刺激+番泻叶 Irregular diet+tail irritation+folium sennae	1	1.41
	不规则饮食+夹尾刺激+稀盐酸 Irregular diet+tail stimulation+dilute hydrochloric acid	2	2.82
	不规则饮食+碘乙酰胺蔗糖混合液+小平台站立 Irregular diet+iodoacetamide sucrose mixture+standing on a small platform	1	1.41
	不规则饮食+碘乙酰胺蔗糖混合液+游泳+左旋精氨酸 Irregular diet+iodoacetamide sucrose mixture+swimming+L-arginine	1	1.41
	物理因素刺激+化学因素刺激 Physical stimulation+chemical stimulation		
	碘乙酰胺+夹尾刺激 Iodoacetamide+tail-clamping stimulation	2	2.82

续表 4

造模因素 Modeling factors	造模方式 Modeling method	频数(次) Frequency (Times)	频数/总数(%) Frequency/ Total(%)
多因素 Multiple factors	碘乙酰胺蔗糖混合液+夹尾刺激 Iodine acetamide sucrose mixture+tail stimulation	2	2.82
	碘乙酰胺蔗糖混合液+小平台站立 Iodoacetamide sucrose mixture+standing on a small platform	3	4.23
	番泻叶+高脂饮食+束缚+游泳 Senna+high-fat diet+restraint+swimming	1	1.41
	高脂+大黄煎剂+束缚+游泳 High fat+rhubarb decoction+bound+swimming	1	1.41
	物理因素刺激+早期生活事件 Physical stimulation+early life events	1	1.41
	母婴分离+束缚 Separation of mother and child+restraint	1	1.41
	母婴分离+碘乙酰胺+小平台站立 Separation of mother and child+iodoacetamide+standing on a small platform	1	1.41
	物理因素刺激+化学因素刺激+早期生活事件 Physical stimulation+chemical stimulation+early life events	1	1.41
合计 Total		71	100.00

表 5 造模时间、方式及频次
Table 5 Modeling time, method and frequency

造模时间 Modeling time	频数(次) Frequency (Times)	频数/总数(%) Frequency/ Total(%)	造模方式 Modeling method	频数(次) Frequency (Times)
6 d	2	2.82	碘乙酰胺蔗糖混合液 Iodoacetamide sucrose mixture	2
7 d	18	25.35	夹尾刺激 Tail clamping stimulus	17
			不规则饮食+夹尾刺激 Irregular diet+tail stimulation	1
8 d	1	1.41	不规则饮食+碘乙酰胺蔗糖混合液+游泳+左旋精氨酸 Irregular diet+iodoacetamide sucrose mixture+swimming+L-arginine	1
			不规则饮食+稀盐酸 Irregular diet+dilute hydrochloric acid	1
			番泻叶+高脂饮食+束缚+游泳 Senna+high-fat diet+restraint+swimming	1
10 d	5	7.04	食醋 Table vinegar	1
			不规则饮食+夹尾刺激+跑步 Irregular diet+tail stimulation+running	1
			夹尾刺激+跑步 Pinch tail stimulation+running	1
			不规则饮食+左旋精氨酸 Irregular diet+L-arginine	1
12 d	2	2.82	利血平腹腔注射 Intraperitoneal injection of reserpine	1
			碘乙酰胺蔗糖混合液+夹尾刺激 Iodine acetamide sucrose mixture+tail stimulation	1
13 d	1	1.41	不规则饮食+夹尾刺激 Irregular diet+tail stimulation	6
			不规则饮食+夹尾刺激+稀盐酸 Irregular diet+tail stimulation+dilute hydrochloric acid	2
			不规则饮食+稀盐酸 Irregular diet+dilute hydrochloric acid	2
			不规则饮食+噪音刺激 Irregular diet+noise stimulation	1

续表 5

造模时间 Modeling time	频数(次) Frequency (Times)	频数/总数(%) Frequency/ Total(%)	造模方式 Modeling method	频数(次) Frequency (Times)
14 d	15	21.13	不规则饮食+束缚+游泳 Irregular diet+restraint+swimming	1
			不规则饮食+夹尾刺激+番泻叶 Irregular diet+tail irritation+folium sennae	1
			不规则饮食+夹尾刺激+游泳 Irregular diet+tail stimulation+swimming	1
			稀盐酸 Dilute hydrochloric acid	1
			番泻叶 Folium sennae	1
15 d	1	1.41	夹尾刺激 Tail clamping stimulus	2
			不规则饮食+冰水游泳+热环境+水平震荡+夹尾刺激+明暗颠倒 Irregular diet+iced water swimming+hot environment+horizontal oscillation+tail-clamping stimulation+light and dark reversed	1
			不规则饮食+夹尾刺激+束缚+游泳 Irregular diet+tail stimulation+restraint+swimming	1
			不规则饮食+夹尾刺激+冰水饮用 Irregular diet+tail stimulation+iced water to drink	1
			不规则饮食+过度疲劳+束缚+倒悬摇晃+夹尾刺激 Irregular diet+excessive fatigue+restraint+upside down shaking+tail stimulation	1
21 d	8	11.27	高脂+大黄煎剂+束缚+游泳 High fat+rhubarb decoction+bound+swimming	1
			不规则饮食+夹尾刺激 Irregular diet+tail stimulation	1
			不规则饮食+夹尾刺激 Irregular diet+tail stimulation	3
			不规则饮食+稀盐酸 Irregular diet+dilute hydrochloric acid	2
			不规则饮食+夹尾刺激+碘乙酰胺蔗糖混合液 Irregular diet+tail clamping stimulation+iodoacetamide sucrose mixture	1
28 d	5	7.04	碘乙酰胺蔗糖混合液 Iodoacetamide sucrose mixture	1
			母婴分离+碘乙酰胺蔗糖混合液+游泳 Maternal and infant separation+iodoacetamide sucrose mixture+swimming	1
			碘乙酰胺蔗糖混合液+夹尾刺激 Iodine acetamide sucrose mixture+tail stimulation	1
			碘乙酰胺+夹尾刺激 Iodoacetamide+tail-clamping stimulation	1
			碘乙酰胺蔗糖混合液+小平台站立 Iodoacetamide sucrose mixture+standing on a small platform	1
42 d	2	2.82	碘乙酰胺蔗糖混合液+小平台站立 Iodoacetamide sucrose mixture+standing on a small platform	1
			碘乙酰胺蔗糖混合液+小平台站立 Iodoacetamide sucrose mixture+standing on a small platform	1
			碘乙酰胺蔗糖混合液+小平台站立 Iodoacetamide sucrose mixture+standing on a small platform	1
			碘乙酰胺+夹尾刺激 Iodoacetamide+tail-clamping stimulation	1
			母婴分离+碘乙酰胺+小平台站立 Mother-infant separation+iodoacetamide+small platform standing	1
46 d	4	5.63	母婴分离 Mother-infant separation	1
			不规则饮食+碘乙酰胺蔗糖混合液+小平台站立 Irregular diet+iodoacetamide sucrose mixture+standing on a small platform	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离 Mother-infant separation	1
			母婴分离 Mother-infant separation	1
47 d	1	1.41	不规则饮食+碘乙酰胺蔗糖混合液+小平台站立 Irregular diet+iodoacetamide sucrose mixture+standing on a small platform	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
49 d	2	2.82	母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
56 d	2	2.82	母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
60 d	1	1.41	母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
98 d	1	1.41	母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
			母婴分离+束缚 Separation of mother and child+restraint	1
合计 Total	71	100.00		71

表 6 检测指标分类及频次
Table 6 Classification and frequency of test indexes

检测指标 Detection Indicator	具体指标 Specific indicators	频数(次) Frequency(Times)	占比(%) Frequency/Total(%)
整体情况 Overall situation	一般情况 General run of things	40	11.56
	进食量 Food-intake	14	4.05
	进食饮水量 Food and water	18	5.20
	糖水消耗实验 Sugar water consumption experiment	6	1.73
	旷场实验 Open field experiment	5	1.45
	3 h 摄食量 3 h food consumption	2	0.58
	抓力时间 Grabbing time	2	0.58
	强迫游泳时间 Forced swimming time	1	0.29
	血常规 Routine blood test	1	0.29
	肝肾功 Liver and kidney function	1	0.29
胃肠功能 Gastrointestinal function	胃排空率/残留率 Gastric emptying rate/residual rate	41	11.85
	小肠推进比 Small intestine propulsion ratio	28	8.09
	胃肠平滑肌收缩频率 Gastrointestinal smooth muscle contraction frequency	3	0.87
	胃肌电图 Gastric electromyography	3	0.87
	胃离体肌条张力 Gastric isolated muscle strip tension	2	0.58
	胃十二指肠电活动 Gastroduodenal electrical activity	1	0.29
	胃敏感性 Gastric sensitivity	4	1.16
	胃顺应性 Gastric compliance	1	0.29
	胃液游离酸度及总酸度 Free acidity and total acidity of gastric juice	1	0.29
	胃蛋白酶活性 Pepsin activity	1	0.29
形态学检查 Morphological examination	胃组织病理学形态 Pathological morphology of gastric tissue	11	3.18
	胃肠组织病理学形态 Pathological morphology of gastrointestinal tissue	7	2.02
	十二指肠组织病理学形态 Histopathological morphology of duodenum	1	0.29
	下丘脑组织病理学形态 Histopathological morphology of duodenum	1	0.29
细胞学检查 Cytologic examination	ICCs	4	1.16
	嗜酸性粒细胞 Eosinophilic granulocyte	2	0.58
	Cx43	2	0.58
	CD3 ⁺	1	0.29
	肥大细胞 Mast cell	1	0.29
	杯状细胞 Goblet cell	1	0.29
	MTL	13	3.76
	GAS	13	3.76
血清生化指标 Serum biochemical indexes	CCK	5	1.45
	VIP	4	1.16
	D-木糖排泄率 D-xylose excretion rate	3	0.87
	SP	2	0.58
	LA	2	0.58
	IL-2	2	0.58
	IL-6	2	0.58
	NO	2	0.58
	SS	1	0.29
	AMS	1	0.29
	PGE2	1	0.29
	IL-α	1	0.29
	IL-4	1	0.29
	IL-1β	1	0.29
	LEP	1	0.29
	NT	1	0.29
	LDH	1	0.29
	CNP	1	0.29
	Ghrelin	1	0.29
	消化酶 Digestive enzyme	1	0.29

续表 6

检测指标 Detection Indicator	具体指标 Specific indicators	频数(次) Frequency (Times)	占比(%) Frequency/Total(%)
血浆生化指标 Plasma biochemical indexes	MTL	8	2.31
	SP	2	0.58
	CCK	1	0.29
	MOT	1	0.29
	SST	1	0.29
	Ghrelin	1	0.29
	5-HT	1	0.29
	CRF	1	0.29
	COR	1	0.29
相关蛋白表达 Expression of related proteins	NO	3	0.87
	mTOR	3	0.87
	Ghrelin	2	0.58
	CRF	2	0.58
	LEP	2	0.58
	CRF	2	0.58
	IREI	1	0.29
	TRAF2	1	0.29
	AMPK α	1	0.29
	MOT	1	0.29
	SST	1	0.29
	iNOS	1	0.29
	NPR- β	1	0.29
	cAMP	1	0.29
	cGMP	1	0.29
	MTL	1	0.29
	CCK	1	0.29
	MTL	1	0.29
	CCK	1	0.29
	MUC2	1	0.29
	CRF	1	0.29
	PGE2	1	0.29
	p-P38MAPK	1	0.29
	NF- κ B65	1	0.29
相关 mRNA 表达 Related mRNA expression	TRH	1	0.29
	VIP	7	2.02
	CCK	5	1.45
	SP	2	0.58
	NF- κ B	2	0.58
	MTL	2	0.58
	GAS	2	0.58
	IREI	1	0.29
	TRAF2	1	0.29
	AMPK α	1	0.29
	mTOR	1	0.29
	p-P38MAPK	1	0.29
	MUC2	1	0.29
	MLCK	1	0.29
	EP1	1	0.29
	EP4	1	0.29
	TLR9	1	0.29
		71	100.00
合计 Total		71	100.00

和脑肠肽的正常水平,从而导致胃肠功能障碍。因此,选择雌性动物进行造模更可能产生阳性结果。

3.2 造模方式及周期

对全部文献中 32 种造模方式进行整理后分析,可分为单因素刺激和多因素刺激两类造模方式:单因素刺激包括物理因素刺激、化学因素刺激、慢性不可预知性刺激和早期生活事件共 4 种,多因素刺激则为以上 4 种因素中选取 2 种或 3 种联用。其中,共有 27 篇文献选择单因素造模法,44 篇文献采用多因素复合造模法。通过不同指标检测均判定为造模成功。

单因素造模方式中夹尾刺激^[23-40]选择最多,主要通过夹尾后产生的应激反应,导致 HPA 兴奋增高,并出现焦虑抑郁情况。目前,研究者多复制郭海军等^[41]的夹尾刺激法进行造模,即用海绵钳夹住大鼠尾巴远端 1/3 处,每次 30 min,每日 4 次,持续 1 周。但也有学者发现,短期高频率的应激刺激会导致大鼠胃黏膜发生器质性改变,可以减少每日刺激频率,延长造模周期来进行模型改良^[42]。碘乙酰胺(iodoacetamide, IA)蔗糖混合液灌胃^[43-45]也是常用的单因素造模方式,选取幼年大鼠进行灌胃,利用 IA 将胃肠组织蛋白烷基化的特性^[46],使胃肠内壁受刺激产生炎症反应导致内脏高敏感,影响其正常发育,成年后大鼠均发生不同程度的胃肠功能障碍。但碘乙酰胺作为烷基化试剂,会对动物的胃肠黏膜造成损伤,并导致内壁产生不同程度水肿,易造成实验动物死亡,实验中需要对造模参数进行精确把控,现多采用 0.1% 的 IA 与 2.0% 的蔗糖混合后进行灌胃^[47],结果表明实验组大鼠胃敏感度增高,顺应性降低,成年后胃肠功能多有不同程度障碍。需要注意的是,采用单因素刺激造模持续时间短,往往不能代表 FD 患者的真实情况;此外,选用单一造模因素可能会导致实验动物耐受度增强,不利于进行长期实验,影响模型的成功制备。

多因素造模方式中,不规则饮食+夹尾刺激^[48-58],不规则饮食+稀盐酸^[15,59-62]和碘乙酰胺蔗糖混合液+小平台站立^[63-65]选择较多。不规则饮食通过模拟饮食失调,使大鼠处于饥饱失常状态,与夹尾刺激联用更符合 FD 的病理机制,成模效果优于单纯夹尾刺激。稀盐酸可抑制胃肠蠕动,延缓胃排空水平^[66]。与碘乙酰胺类似,采用稀盐酸造模易对大鼠造成器质性损害,现多在水中加入 10 mol/L 稀盐酸 10 mL^[59,67]稀释后供大鼠自由饮用,通过破

坏大鼠胃肠的酸碱平衡,产生内脏高敏感状态,与不规则饮食联用从饮食失调和内脏高敏感模拟 FD 患者的日常情况。小平台站立同样会使大鼠产生应激反应,同时为了防止从小平台跌落入水,大鼠需始终保持清醒状态,在应激的基础上造成过度疲劳,产生焦虑抑郁情绪。也有学者采用慢性不可预见性刺激进行造模^[68-69],需要注意的是干预因素增多并不会增加造模成功的概率。相反,采取的刺激方式越多,造模难度越大,造模过程中需要控制的变量越多。对于模型成功的评价,是某单一因素产生作用还是多种联合产生作用难以做出明确的推断。

综上所述,单因素造模法简单易行、成模较快,但维持时间短、动物易产生耐受性,且只能从单方面模拟 FD 患者的发病机制,而多因素复合造模更贴近 FD 患者发病的真实情况。干预因素的选择尚无统一标准,具体选择何种刺激因素联合使用仍需更多的实验予以证明。

3.3 检测指标

文献挖掘的结果表明,大鼠的一般情况如毛发光泽、活动度、大便性状、体重等为检测最多的外在指标,可通过肉眼观测直接获得。造模成功的大鼠多表现为毛色枯黄不顺、活动度降低、大便稀溏秽臭、体重减轻。但此类指标尚无统一的衡量标准,主要依据研究者的个人经验予以判断。不可否认的是,大鼠的一般情况仍是最直接且便于获取的观测指标,研究者可基于此对实验动物的成模情况进行初步评价。

胃排空^[17]、残留率^[70]和小肠推进比为检测最多的胃肠道指标,将胃肠运动功能进行量化后观测,判断成模的效果。具体的操作方式是将自制的营养性半固体糊中加入少量碳末混合后进行灌胃,然后取胃肠进行检测。造模成功的大鼠表现为胃排空延缓、小肠推进比降低。也有学者认为,灌胃产生的刺激会对大鼠精神状态产生不同程度的影响,改变胃排空状态^[71],而计算 3 h 自由摄食量^[72]可以更好地模拟日常饮食状态,并且减少灌胃不当造成的意外死亡。另外,由于 FD 无器质性病变的病理特点,取胃肠组织进行形态学检查,观察有无溃疡炎症等病理学改变,从病理机制上证明造模是否成功。

由于 FD 症状的特殊性,患者负性的情绪变化常与胃肠道症状伴随出现^[73],因此对实验动物心理

状况的检测也同样重要。目前,糖水消耗实验^[58]和旷场实验^[74]常用于检测大鼠焦虑抑郁情况,造模成功的大鼠糖水消耗量减少,水平活动范围缩小,垂直站立次数减少。另外,进食饮水量的减少同样可以表明大鼠情绪状况的改变。但是,单纯出现焦虑抑郁的情况并不能表明造模成功,应结合胃肠道功能检测进行判断。

胃排空延迟、胃顺应性降低和内脏高敏感是 FD 的主要病理机制^[75],实验动物的一般情况和情绪负性变化也是不可忽视的症状表现。另外根据不同研究的目的,采用透射电镜观测胃肠 Cajal 细胞^[69]和 Cx43 间质细胞^[28]结构变化的细胞学检查,采用 ELISA 试剂盒检测血液中 MTL^[51]、GAS^[76]和 CCK^[77]等胃肠激素含量的血清学检查,采用 Western Blot 检测胃肠组织中相关蛋白表达^[29,49-50]的分子生物学检查,以及采用 RT-PCR 检测相关 mRNA 表达^[51,78]的基因学检查也有所选择。由于 FD 发病机制的复杂性,症状涵盖消化、神经等多个系统的多维性,单一指标的检测结果并不能作为造模成功的标准。因此,应选择对应的指标进行检测,胃肠功能、精神心理状态和病理形态是选择检测指标的 3 个主要范围。

3.4 FD 动物模型的发展与展望

依据发表时间对纳入文献进行整理后发现,早期的研究者多倾向于单因素造模方式,如夹尾刺激;随着 FD 可能的发病机制和肠脑轴概念的提出,FD 模型的制备方式也随之改变,由单因素造模法逐步转变为多因素复合造模法,由单纯的物理刺激转变为多系统与多维度的复合刺激来模拟 FD 的产生。随着时间的推移,检测指标的选择也愈发广泛。研究者的目光不再局限于实验动物的外在表现和胃肠动力学指标,血清学检查、细胞学检查和分子生物学检查逐渐增多,蛋白组学、细胞组学和基因组学的研究方法也被更多学者采用,这表明对 FD 的研究方向正从器官水平向细胞和分子水平不断深入,造模成功的评判标准也更具有可信度。综上所述,对 FD 动物模型的研究仍处于不断更新与完善的过程中,但仍存在以下问题:①缺少统一且量化的造模因素与相应的造模周期;②检测指标多依据研究者的经验和研究目的进行选择,缺少统一的模型评判标准;③应结合西医病情与中医症状的特点,制作“病症结合”的动物模型,完善模型的完整度。

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