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浅析味精过量对男性不育的影响

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摘　要

背景：味精在食品工业及餐饮烹调中被广泛使用，一直被认为是安全的食品添加剂，2017年，欧盟食品安全局最新评估报告规定成年人每日味精摄入量不应超过1.8 g，在我国，味精的使用量一直没有明确的限制。自味精问世以来，虽然其安全性屡受质疑，但从未受到实质性挑战。近年来不孕不育率逐年上升，男性生殖系统非常容易受到许多因素的影响，饮食因素就是一个不可忽视的方面。目的：对味精的食用安全性及危害性展开讨论，并对过量味精可能导致生殖毒性的机制进行归纳总结，以期引起人们对于饮食健康因素造成疾病的重视。方法：通过检索近几年PubMed数据库、中国知网等中英文期刊全文数据库相关内容文章，并系统整理相关重要文献进行综述。结论：过量的味精摄入可导致神经毒性，并可能通过下丘脑－垂体－性腺轴来影响睾丸的质量及生精功能，以及可能通过氧化应激途径和谷氨酸受体途径导致生殖细胞的凋亡。虽然味精的使用对正常成年人群不会造成危害，但是可能会对高龄、婴幼儿以及某些致血脑屏障功能不全的疾病人群产生一定的负面影响。

关键词

味精，谷氨酸，谷氨酸受体，神经毒性，生殖毒性，内分泌紊乱

Analysis of the Possible Relationship between Excessive Monosodium Glutamate and Male Infertility

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Abstract

BACKGROUND: Monosodium glutamate (MSG) is widely used in food industry and catering cooking, and has always been regarded as a safe food additive. In 2017, the latest assessment report of the EU Food Safety Agency stipulates that adults' daily intake of MSG should not exceed 1.8 g. In China, there has been no clear limit on the use of MSG. Since the advent of monosodium glutamate, although its safety has been repeatedly questioned, it has never been substantially challenged. In recent years, the rate of infertility has increased year by year, the male reproductive system is very easy to be affected by many factors, diet is an aspect that can not be ignored. OBJECTIVE: To discuss the edible safety and harmfulness of monosodium glutamate, and summarize the mechanism of reproductive toxicity caused by excessive monosodium glutamate, in order to make people pay more attention to the diseases caused by dietary health factors. METHODS: The relevant articles in PubMed database, China knowledge Network and other Chinese and English periodical full-text databases in recent years were searched, and the relevant important literatures were systematically reviewed. CONCLUSION: Excessive intake of monosodium glutamate can lead to neurotoxicity, and may affect testicular quality and spermatogenic function through hypothalamus-pituitary-gonad axis, and may lead to germ cell apoptosis through oxidative stress pathway and glutamate receptor pathway. Although the use of monosodium glutamate will not cause harm to normal adults, it may have a negative impact on the elderly, infants and some diseases that cause blood-brain barrier dysfunction.

Keywords

Monosodium Glutamate, Glutamic Acid, Glutamate Receptor, Neurotoxicity, Reproductive Toxicity, Endocrine Disorders

1. 味精的特性及使用现状

味精作为一种风味增强剂，其主要成分是 L-谷氨酸钠盐，最早是由日本化学家池田居苗发现的[1]，因味精解离出的谷氨酸能够刺激人的味蕾产生一种“鲜”的味觉，因此在世界范围内被广泛应用于食品工业及食物烹调的过程中。先前联合国粮农组织和世卫组织的食品添加剂联合专家组认为味精没有安全方面的担心，认为至少味精在调味料的使用量上，对人体没有危害。2017 年，欧盟食品安全局最新评估报告规定成年人每日味精安全摄入量不应超过 1.8 g [2]。在我国，对于味精的使用量上一直没有明确的限制，因此，我们在 PubMed 数据库、中国知网等中英文期刊全文数据库中输入“味精，安全，谷氨酸钠，动物模型，内分泌，神经毒性”等关键词检索相关文章，并对其进行综述，就味精的安全性及可能存在的危害展开讨论。

2. 味精引发的思考

1968 年，Kwok 首次报道了中国餐馆综合症，因患者食用中餐后症状发作而命名，症状是麻木、虚弱、脸红、出汗、头晕和头痛[3]，被认为是与味精中的谷氨酸钠有关。此外，摄入谷氨酸钠被认为可能会引起或加重多种疾病，包括哮喘、荨麻疹、特应性皮炎、室性心律失常、神经病变和腹部不适，概括

为“谷氨酸钠症状复合体”[4]。此后，人们对于谷氨酸单钠作为主要成分的味精食用安全性展开了探索。

3. 关于味精安全性的探索

谷氨酸(Glutamic acid, Glu)是人及哺乳动物脑内含量最高的兴奋性氨基酸，具有潜在的神经毒性[5]。谷氨酸钠(monosodium glutamate, MSG)在体内吸收后在生理 pH 值下解离为谷氨酸，具有很强的极性，理论上不易透过血脑屏障(Brain-Blood Barrier, BBB) [6]。关于人体对 GLU 的摄入量，只有有限的数据可用。根据欧洲饮食、亚洲饮食的共识，人平均每天从食物中获取的天然谷氨酸约为 10 克[7]，来自食品添加剂的谷氨酸个体摄入量具有广泛的差异，欧洲的高消费者可能高达 1 克/天，在亚洲国家高消费者可能高达 4 克/天，在调味极高的餐厅用餐中，摄入量最高可能达 5 克/天[8]，各种来源的 Glu 经肠上皮细胞被吸收，根据先前的共识，最大摄入量为 16 克/千克体重被认为是安全的[9]，因此认为正常情况下味精的使用不会对人群造成危害。Stegink 等人的恒河猴实验也表明，即使静脉输注非常大的剂量的谷氨酸钠，也只有很小的程度上的 Glu 渗透到胎儿血液循环中，只有母猴在最高暴露水平的谷氨酸钠(0.40 g/kg 体重)时，其胎儿血浆 Glu 水平才升高至 440 mmol/l，认为即使口服摄入 Glu 得量很高，从母亲透过胎盘屏障向胎儿转移 glu 的可能性也很小，孕妇食用添加味精的食物不易对胎儿造成影响[10]。

然而，Jubaidi 等人根据亚洲人体平均每日味精摄入量进行人与实验动物之间的剂量换算，此剂量相当于大鼠 120 mg/kg 体重[11] [12]。并以此剂量的 MSG 连续 28 天对雄性大鼠灌胃，结果 MSG 处理组大鼠所有的器官的重量均显著降低，生殖器官重量减少显著($P < 0.05$) [13]。同位素示踪实验也表明，[^{3}H]-Glu 可以透过成年小鼠血脑屏障进入中枢神经系统[14]，只是神经系统单位组织的摄入量比外周组织低[15]。对妊娠晚期昆明种小鼠[^{3}H]-Glu 灌胃示踪实验也表明谷氨酸可透过胎盘屏障并分布在胚胎组织中[16]，小鼠胚胎中枢神经系统对谷氨酸单钠的摄入量是母鼠中枢神经系统的 2 倍[17]。此外，新生哺乳动物血脑屏障功能不完善[18]，以及某些病理情况如衰老[19]、神经系统疾病如缺血及缺氧性脑损伤、帕金森氏病、肌萎缩侧索硬化、阿耳茨海默病、癫痫等[20]、II 型糖尿病[21]和高血压[22]等也会导致 BBB 通透性增加，BBB 通透性也随着血浆渗透压的增加而增加[23]，并且在给予某些药物后 BBB 通透性的增加将允许所有分子从血浆中增加进入，包括 GLU 等分子[24]。在这些情况下，血液中的 GLU 可能会穿过屏障，甚至在生理血浆水平下也可能引起毒性效应。更有甚者，Ka He 等人对 10095 名中国健康成年人的大型开放性队列研究中，得出味精摄入量与基础体重指数(Basic body mass index, BMI)和超重发生率呈正相关，与基线 BMI、体力活动、总能量摄入和其他潜在混杂因素无关的结论，并认为可能的解释是长期摄入味精可能会引起了弓状核神经元的病理变化，扰乱下丘脑瘦素作用的信号级联反应，导致与超重和肥胖相关的瘦素抵抗的结果[25]。由此看来，如此“安全”的食品添加剂并不安全。

4. 味精与男性不育的关系

近年来不孕率逐年上升，不孕人群呈现年轻化趋势，据最新统计，除亚洲地区外，全球约有 15%的夫妇受不孕症影响，总数达 4850 万对[26]，目前中国不孕不育患者已超过 4000 万人口，不孕率高达 18% [27]，男性生殖系统非常容易受到许多因素的影响，包括化学物质、环境和工业污染物以及饮食[13] [28]。导致不孕不育的影响因素众多，随着外卖行业的兴起，味精滥用引发的食品安全问题愈发不可忽视。

5. 味精可能通过下丘脑－垂体－性腺轴引起生殖毒性

在神经系统，Glu 受体主要有离子型和代谢型两种类型，两种受体均与 Glu 结合引起突触后膜的去极化[29]，过量 Glu 的神经毒性作用主要损毁神经细胞体，对神经纤维没有显著影响[30]。Glu 导致神经毒性的主要机制有：① Glu 作用于细胞膜上的 α-氨基-3-羟基-5-甲基-4-异唑－丙酸盐(α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate, AMDA)、KA (kainic acid)受体，使 Na^+通透性增加；Na^+大量内流，使膜

电位发生变化，Cl^-顺电位差大量内流，水大量内流引起神经元急性肿胀；② Glu 可作用于细胞膜上 N-甲基-D-天冬氨酸(N-methyl-D-aspartate, NMDA)受体，使 Ca^{2+}通透性增加；Ca^{2+}大量内流，并通过亲代谢受体导致细胞内三磷酸肌醇生成量增多，后者刺激内质网 Ca^{2+}释放，激活磷酸酶及蛋白酶，使细胞受损害，引起一系列生化反应，最终导致迟发性神经元坏死[31] [32] [33]。过量的 Glu 对大多数脑区有广泛的损伤作用，并不特异性地损伤脑内某一核团[34]。可导致下丘脑 ARC-ME 多巴胺能和胆碱能结节漏斗系统的破坏，导致“内分泌缺陷综合征”的出现，并可通过干扰瘦素介导的下丘脑信号级联，导致能量平衡被破坏，使个体发育迟缓、肥胖、脂肪组织生理紊乱、甲状腺功能减退、性腺机能减退和垂体萎缩的现象[18] [35] [36] [37]。

幼年动物实验表明 MSG 的损毁作用主要局限于视网膜和下丘脑的弓状核，而促性腺激素释放激素(GnRH)神经元又主要分布在下丘脑正中隆起和视前区的内侧[38] [39] [40]，促性腺激素释放激素(GnRH)的释放对哺乳动物生殖系统的发育至关重要，谷氨酸钠的生殖毒性可能是由于导致了下丘脑－垂体－性腺轴以及随后的卵泡刺激素(FSH)、黄体生成素(LH)和睾酮(T)的水平变化，进而导致了性腺发育障碍和生精功能发生变化[41] [42] [43] [44]。在雄性大鼠服用 MSG 后，已有不育、睾丸出血、形态变化和精子产生障碍的报道[45]，Gong 和 Nemeroff 等人的动物实验结果证实了谷氨酸的生殖毒性，过量的谷氨酸钠可导致严重的少精子症，通过精子数量和形态的退化和改变与男性不育有关。Ochiogu 等人的实验结果表明，服用了 MSG 的雄性大鼠睾丸质量、血清 GnRH、LH、睾酮、和附睾尾部精子储备均显著降低[46]，睾丸重量取决于分化的生精细胞的质量，睾丸重量的减少可能是由于生殖细胞和成熟精子细胞密度的降低，精子产生的减少也会导致附睾尾部精子储备减少[47] [48]，这一结果支持了 Glu 通过下丘脑－垂体－性腺轴引起生殖毒性的猜想。

6. 味精可能通过氧化应激途径和谷氨酸受体途径引起细胞凋亡导致生殖毒性

Rahimi 等人的研究中，MSG 组的上皮生发高度也降低了，认为生精小管及其生发上皮的变性可能是由于 MSG 引起的细胞凋亡[49] [50] [51]。Glu 导致细胞凋亡的机制有：过量 Glu 可以通过产生氧自由基和过氧化氢诱导氧化应激，导致 DNA 氧化损伤和细胞膜过氧化，导致细胞死亡[49] [52]。此外，许多研究表明在不同的组织中存在谷氨酸系统，包括代谢性(MGlu)和离子性谷氨酸受体和转运蛋白。Storto 及其同事发现 mGlu5 和 mGlu1 受体在大鼠和人类睾丸或人类精子中表达[53] [54]，摄入过量谷氨酸的存在会导致谷氨酸受体的严重激活。mGlu5 受体的激活有可能在细胞中产生细胞内的 Ca^{2+}波，从而激活许多在持久性、分化和细胞生长中起基础作用的反应[55]。另一方面，当细胞中的 Ca^{2+}增加或大量钙进入细胞器如内质网、细胞核和线粒体时，钙依赖的酶，如蛋白酶和内切酶(Caspases)变得活跃，为凋亡提供初步条件，并最终导致细胞凋亡的发生[56]。这可能是 MSG 导致睾丸组织病理变化的另一种机制。

7. 结论

关于味精的危害性探究，主要是在啮齿动物、非人类灵长动物身上，对于人群的食用安全性，尚需要进一步的研究，以制定合适的管理政策、明确的剂量使用规范。在我们的综述中，过量的味精摄入可导致神经毒性，并可能通过下丘脑－垂体－性腺轴来影响睾丸的质量及生精功能，以及可能通过氧化应激途径和谷氨酸受体途径导致生殖细胞的凋亡。味精的使用虽然能对食品工业带来巨大的好处，但这种食品添加剂的普遍使用可能会对高龄、婴幼儿以及某些疾病如神经系统疾病、II 型糖尿病和高血压等致血脑屏障功能不全的人群产生一定的负面影响。如果能够提供味精对这类人群危害的实质性证据，那么将对我国制定的合理的味精使用剂量、合适的味精管理政策具有重大的意义。

参考文献

[1] Vorhees, C.V. (2018) A Test of Dietary Monosodium Glutamate Developmental Neurotoxicity in Rats: A Reappraisal. *Annals of Nutrition and Metabolism*, **73**, 36-42. https://doi.org/10.1159/000494781

[2] Samuels, A. (1999) The Toxicity/Safety of Processed Free Glutamic Acid (MSG): A Study in Suppression of Information. *Accounting Research Journal*, **6**, 259-310. https://doi.org/10.1080/08989629908573933

[3] Kwok, R.H. (1968) Chinese-Restaurant Syndrome. *New England Journal of Medicine*, **278**, 796. https://doi.org/10.1056/NEJM196804042781419

[4] Williams, A.N. and Woessner, K.M. (2009) Monosodium Glutamate "Allergy": Menace or Myth. *Clinical & Experimental Allergy*, **39**, 640-646. https://doi.org/10.1111/j.1365-2222.2009.03221.x

[5] Bojanic, V., Bojanic, Z., Najman, S., *et al*. (2009) Diltiazem Prevention of Toxic Effects of Monosodium Glutamate on Ovaries in Rats. *General Physiology and Biophysics*, **28**, 149-154.

[6] Fernstrom, J.D. (2018) Monosodium Glutamate in the Diet Does Not Raise Brain Glutamate Concentrations or Disrupt Brain Functions. *Annals of Nutrition and Metabolism*, **73**, 43-52. https://doi.org/10.1159/000494782

[7] Yang, W.H., Drouin, M.A., Herbert, M., Mao, Y. and Karsh, J. (1997) The Monosodium Glutamate Symptom Complex: Assessment in a Double-Blind, Placebo-Controlled, Randomized Study. *The Journal of Allergy and Clinical Immunology*, **99**, 757-762. https://doi.org/10.1016/S0091-6749(97)80008-5

[8] Brosnan, J.T., Drewnowski, A. and Friedman, M.I. (2014) Is There a Relationship between Dietary MSG and [Corrected] Obesity in Animals or Humans. *Amino Acids*, **46**, 2075-2087. https://doi.org/10.1007/s00726-014-1771-6

[9] Beyreuther, K., Biesalski, H.K., Fernstrom, J.D., *et al*. (2007) Consensus Meeting: Monosodium Glutamate: An Update. *European Journal of Clinical Nutrition*, **61**, 304-313. https://doi.org/10.1038/sj.ejcn.1602526

[10] Stegink, L.D., Pitkin, R.M., Reynolds, W.A., Filer, L.J., Boaz, D.P. and Brummel, M.C. (1975) Placental Transfer of Glutamate and Its Metabolites in the Primate. *American Journal of Obstetrics and Gynecology*, **122**, 70-78. https://doi.org/10.1016/0002-9378(75)90616-X

[11] Nair, A.B. and Jacob, S. (2016) A Simple Practice Guide for Dose Conversion between Animals and Human. *Journal of Basic and Clinical Pharmacy*, **7**, 27-31. https://doi.org/10.4103/0976-0105.177703

[12] Nair, A., Morsy, M.A. and Jacob, S. (2018) Dose Translation between Laboratory Animals and Human in Preclinical and Clinical Phases of Drug Development. *Drug Development Research*, **79**, 373-382. https://doi.org/10.1002/ddr.21461

[13] Jubaidi, F.F., Mathialagan, R.D., Noor, M.M., Taib, I.S. and Budin, S.B. (2019) Monosodium Glutamate Daily Oral Supplementation: Study of Its Effects on Male Reproductive System on Rat Model. *Systems Biology in Reproductive Medicine*, **65**, 194-204. https://doi.org/10.1080/19396368.2019.1573274

[14] 高静, 吴娟, 林凌, 柳祎, 赵晓宁, 张祖暄. 谷氨酸单钠对成年小鼠的神经毒性作用[J]. 中国药理学与毒理学杂志, 1994(4): 276-280.

[15] 白文忠, 张金平, 金凤霞, 史玉兰, 高志国, 张雪琳. 谷氨酸对大鼠不同脑区神经毒性的比较研究[J]. 解剖学杂志, 2000, 23(6): 529-532.

[16] McDonald, J.W. and Johnston, M.V. (1990) Physiological and Pathophysiological Roles of Excitatory Amino Acids during Central Nervous System Development. *Brain Research Reviews*, **15**, 41-70. https://doi.org/10.1016/0165-0173(90)90011-C

[17] Yu, T., Zhao, Y., Shi, W., Ma, R. and Yu, L. (1997) Effects of Maternal Oral Administration of Monosodium Glutamate at a Late Stage of Pregnancy on Developing Mouse Fetal Brain. *Brain Research*, **747**, 195-206. https://doi.org/10.1016/S0006-8993(96)01181-X

[18] Gilbert, A., Vidal, X.E., Estevez, R., Cohen-Salmon, M. and Boulay, A.C. (2019) Postnatal Development of the Astrocyte Perivascular MLC1/GlialCAM Complex Defines a Temporal Window for the Gliovascular Unit Maturation. *Brain Structure and Function*, **224**, 1267-1278. https://doi.org/10.1007/s00429-019-01832-w

[19] Erdo, F. and Krajcsi, P. (2019) Age-Related Functional and Expressional Changes in Efflux Pathways at the Blood-Brain Barrier. *Frontiers in Aging Neuroscience*, **11**, 196. https://doi.org/10.3389/fnagi.2019.00196

[20] Ujiie, M., Dickstein, D.L., Carlow, D.A. and Jefferies, W.A. (2003) Blood-Brain Barrier Permeability Precedes Senile Plaque Formation in an Alzheimer Disease Model. *Microcirculation*, **10**, 463-470. https://doi.org/10.1080/mic.10.6.463.470

[21] Starr, J.M., Wardlaw, J., Ferguson, K., MacLullich, A., Deary, I.J. and Marshall, I. (2003) Increased Blood-Brain Barrier Permeability in Type II Diabetes Demonstrated by Gadolinium Magnetic Resonance Imaging. *Journal of Neurology, Neurosurgery, and Psychiatry*, **74**, 70-76. https://doi.org/10.1136/jnnp.74.1.70

[22] Tamaki, K., Sadoshima, S. and Heistad, D.D. (1984) Increased Susceptibility to Osmotic Disruption of the

Blood-Brain Barrier in Chronic Hypertension. *Hypertension*, **6**, 633-638. https://doi.org/10.1161/01.HYP.6.5.633

[23] Kozler, P., Sobek, O. and Pokorny, J. (2016) Biochemical Manifestations of the Nervous Tissue Degradation after the Blood-Brain Barrier Opening or Water Intoxication in Rats. *Neuroendocrinology Letters*, **37**, 114-120.

[24] Zhou, Y., Peng, Z., Seven, E.S. and Leblanc, R.M. (2018) Crossing the Blood-Brain Barrier with Nanoparticles. *Journal of Controlled Release*, **270**, 290-303. https://doi.org/10.1016/j.jconrel.2017.12.015

[25] He, K., Du, S., Xun, P., *et al*. (2011) Consumption of Monosodium Glutamate in Relation to Incidence of Overweight in Chinese Adults: China Health and Nutrition Survey (CHNS). *The American Journal of Clinical Nutrition*, **93**, 1328-1336. https://doi.org/10.3945/ajcn.110.008870

[26] Agarwal, A., Mulgund, A., Hamada, A. and Chyatte, M.R. (2015) A Unique View on Male Infertility around the Globe. *Reproductive Biology and Endocrinology*, **13**, 37. https://doi.org/10.1186/s12958-015-0032-1

[27] 刘伟信, 曾琴, 何丽冰. 建国 70 年人类辅助生殖技术快速发展及展望[J]. 中国计划生育和妇产科, 2019, 11(7): 3-5.

[28] Nordkap, L., Joensen, U.N., Blomberg Jensen, M. and Jørgensen, N. (2012) Regional Differences and Temporal Trends in Male Reproductive Health Disorders: Semen Quality May Be a Sensitive Marker of Environmental Exposures. *Molecular and Cellular Endocrinology*, **355**, 221-230. https://doi.org/10.1016/j.mce.2011.05.048

[29] Garattini, S. (2000) Glutamic Acid, Twenty Years Later. *Journal of Nutrition*, **130**, 901S-909S. https://doi.org/10.1093/jn/130.4.901S

[30] Perello, M., Moreno, G., Camihort, G., *et al*. (2004) Nature of Changes in Adrenocortical Function in Chronic Hyperleptinemic Female Rats. *Endocrine*, **24**, 167-175. https://doi.org/10.1385/ENDO:24:2:167

[31] 曹晓建, 罗永湘. 大鼠脊髓损伤后谷氨酸和天冬氨酸含量的变化及其意义[J]. 南京医科大学学报, 1998(5): 3-5.

[32] Sheldon, A.L. and Robinson, M.B. (2007) The Role of Glutamate Transporters in Neurodegenerative Diseases and Potential Opportunities for Intervention. *Neurochemistry International*, **51**, 333-355. https://doi.org/10.1016/j.neuint.2007.03.012

[33] Greene, J.G. and Greenamyre, J.T. (1996) Bioenergetics and Glutamate Excitotoxicity. *Progress in Neurobiology*, **48**, 613-634. https://doi.org/10.1016/0301-0082(96)00006-8

[34] 张金平, 白文忠, 史玉兰, 金凤霞. 学习训练对谷氨酸单钠所致大鼠海马损伤的神经保护作用[J]. 中国应用生理学杂志, 2006(1): 36-39.

[35] Onaolapo, A.Y., Odetunde, I., Akintola, A.S., *et al*. (2019) Dietary Composition Modulates Impact of Food-Added Monosodium Glutamate on Behaviour, Metabolic Status and Cerebral Cortical Morphology in Mice. *Biomedicine & Pharmacotherapy*, **109**, 417-428. https://doi.org/10.1016/j.biopha.2018.10.172

[36] Marshall, T.M., Dardia, G.P., Colvin, K.L., Nevin, R. and Macrellis, J. (2019) Neurotoxicity Associated with Traumatic Brain Injury, Blast, Chemical, Heavy Metal and Quinoline Drug Exposure. *Alternative Therapies in Health and Medicine*, **25**, 28-34.

[37] Araujo, T.R., Freitas, I.N., Vettorazzi, J.F., *et al*. (2017) Benefits of L-alanine or L-arginine Supplementation against Adiposity and Glucose Intolerance in Monosodium Glutamate-Induced Obesity. *European Journal of Nutrition*, **56**, 2069-2080. https://doi.org/10.1007/s00394-016-1245-6

[38] Saadi, H., Shan, Y., Marazziti, D. and Wray, S. (2019) GPR37 Signaling Modulates Migration of Olfactory Ensheathing Cells and Gonadotropin Releasing Hormone Cells in Mice. *Frontiers in Cellular Neuroscience*, **13**, 200. https://doi.org/10.3389/fncel.2019.00200

[39] Han, S.Y., Kane, G., Cheong, I. and Herbison, A.E. (2019) Characterization of GnRH Pulse Generator Activity in Male Mice Using GCaMP Fiber Photometry. *Endocrinology*, **160**, 557-567. https://doi.org/10.1210/en.2018-01047

[40] Li, Q.C., Li, Q.F., Wang, Y.L., Sun, H.L. and Jiang, Z.Y. (2018) Arcuate Nucleus Neurons Are Not Essential for the Preprandial Peak in Plasma Ghrelin after Neonatal Monosodium Glutamate Treatment. *International Journal of Molecular Medicine*, **41**, 1635-1642. https://doi.org/10.3892/ijmm.2018.3365

[41] Littlejohn, B.P., Roberts, M.C., Bedenbaugh, M.N., *et al*. (2017) Evaluation of the Influence of Prenatal Transportation Stress on GnRH-Stimulated Luteinizing Hormone and Testosterone Secretion in Sexually Mature Brahman Bulls. *Journal of Animal Science*, **95**, 129-138. https://doi.org/10.2527/jas2016.0445

[42] Iamsaard, S., Sukhorum, W., Samrid, R., *et al*. (2014) The Sensitivity of Male Rat Reproductive Organs to Monosodium Glutamate. *Acta Medica Academica*, **43**, 3-9. https://doi.org/10.5644/ama2006-124.94

[43] Gong, S.L., Xia, F.Q., Wei, J., *et al*. (1995) Harmful Effects of MSG on Function of Hypothalamus-Pituitary-Target Gland System. *Biomedical and Environmental Sciences*, **8**, 310-317.

[44] Nemeroff, C.B., Konkol, R.J., Bissette, G., *et al*. (1977) Analysis of the Disruption in Hypothalamic-Pituitary Regulation in Rats Treated Neonatally with Monosodium L-Glutamate (MSG): Evidence for the Involvement of Tuberoin-

fundibular Cholinergic and Dopaminergic Systems in Neuroendocrine Regulation. *Endocrinology*, **101**, 613-622. https://doi.org/10.1210/endo-101-2-613

[45] Eweka, A.O., Eweka, A. and Om'iniabohs, F.A. (2010) Histological Studies of the Effects of Monosodium Glutamate of the Fallopian Tubes of Adult Female Wistar Rats. *North American Journal of Medicine & Science*, **2**, 146-149.

[46] Ochiog, I.S., Ogwu, D., Uchendu, C.N., Okoye, C.N., Ihedioha, J.I. and Mbegbu, E.C. (2015) Effects of Monosodium-L-Glutamate Administration on Serum Levels of Reproductive Hormones and Cholesterol, Epididymal Sperm Reserves and Testicular Histomorphology of Male Albino Rats. *Acta Veterinaria Hungarica*, **63**, 125-139. https://doi.org/10.1556/avet.2015.011

[47] Mulligan, K., Zackin, R., Clark, R.A., *et al*. (2005) Effect of Nandrolone Decanoate Therapy on Weight and Lean Body Mass in HIV-Infected Women with Weight Loss: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. *Archives of Internal Medicine*, **165**, 578-585. https://doi.org/10.1001/archinte.165.5.578

[48] Michael, B., Yano, B., Sellers, R.S., *et al*. (2007) Evaluation of Organ Weights for Rodent and Non-Rodent Toxicity Studies: A Review of Regulatory Guidelines and a Survey of Current Practices. *Toxicologic Pathology*, **35**, 742-750. https://doi.org/10.1080/01926230701595292

[49] Rahimi Anbarkeh, F., Baradaran, R., Ghandy, N., Jalali, M., Reza Nikravesh, M. and Soukhtanloo, M. (2019) Effects of Monosodium Glutamate on Apoptosis of Germ Cells in Testicular Tissue of Adult Rat: An Experimental Study. *International Journal of Reproductive BioMedicine*, **17**, 261-270. https://doi.org/10.18502/ijrm.v17i4.4551

[50] Sadeghzadeh, F., Mehranjani, M.S. and Mahmoodi, M. (2019) Vitamin C Ameliorates the Adverse Effects of Dexamethasone on Sperm Motility, Testosterone Level, and Spermatogenesis Indexes in Mice. *Human & Experimental Toxicology*, **38**, 409-418. https://doi.org/10.1177/0960327118816137

[51] Li, H.M., Gao, X., Yang, M.L., Mei, J.J., Zhang, L.T. and Qiu, X.F. (2004) Effects of Zuogui Wan on Neurocyte Apoptosis and Down-Regulation of TGF-beta1 Expression in Nuclei of Arcuate Hypothalamus of Monosodium Glutamate-Liver Regeneration Rats. *World Journal of Gastroenterology*, **10**, 2823-2826. https://doi.org/10.3748/wjg.v10.i19.2823

[52] Ahluwalia, P., Tewari, K. and Choudhary, P. (1996) Studies on the Effects of Monosodium Glutamate (MSG) on Oxidative Stress in Erythrocytes of Adult Male Mice. *Toxicology Letters*, **84**, 161-165. https://doi.org/10.1016/0378-4274(95)03612-1

[53] Storto, M., Sallese, M., Salvatore, L., *et al*. (2001) Expression of Metabotropic Glutamate Receptors in the Rat and Human Testis. *Journal of Endocrinology*, **170**, 71-78. https://doi.org/10.1677/joe.0.1700071

[54] Pavlovic, V., Cekic, S., Kocic, G., Sokolovic, D. and Zivkovic, V. (2007) Effect of Monosodium Glutamate on Apoptosis and Bcl-2/Bax Protein Level in Rat Thymocyte Culture. *Physiological Research*, **56**, 619-626.

[55] Miglio, G., Varsaldi, F., Dianzani, C., Fantozzi, R. and Lombardi, G. (2005) Stimulation of Group I Metabotropic Glutamate Receptors Evokes Calcium Signals and c-jun and c-fos Gene Expression in Human T Cells. *Biochemical Pharmacology*, **70**, 189-199. https://doi.org/10.1016/j.bcp.2005.04.038

[56] Rajaei, F., Karja, N.W., Agung, B., *et al*. (2005) Analysis of DNA Fragmentation of Porcine Embryos Exposed to Cryoprotectants. *Reproduction in Domestic Animals*, **40**, 429-432. https://doi.org/10.1111/j.1439-0531.2005.00585.x