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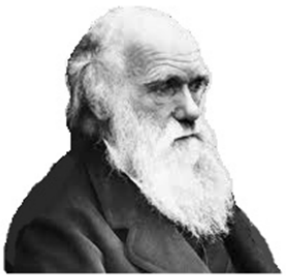

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Changes in the reproductive hormone levels of male and female rats consuming monosodium glutamate and soybean extracts

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ABSTRACT

The present study sought to analyze the possible changes that might be caused by MSG and soybean on the secretion of both the male and female reproductive hormones in wistar rats. Two hundred and ten wistar rats (105 female and 105 male rats) were used for this study. The 105 female rats were equally divided into three groups representing the various experimental durations of 2, 4, and 6 months. Each of these groups consisting of 35 rats were further divided equally into 7 subgroups each containing 5 rats. 3 out of the 7 subgroups were orally administered MSG, another 3 out of the 7 subgroups were orally administered soybean according to the established LD_{50} as follows: 1000 mg/kg b.w (low dose, LD), 2000 mg/kg b.w (medium dose, MD), 3000 mg/kg b.w (High dose, HD) daily, while the 7th group served as the control group and was given only water and normal rat chow. The 105 male rats were also grouped in same manner and orally administered the MSG and soybean. The levels of LH, FSH, progesterone (PRG), oestrogen (E_2) and testosterone were analyzed by ELISA technique. Long period administration of MSG significantly ($p<0.05$) decreased the levels of LH, PRG, E_2 and FSH in the female rats when compared with the control group. Consumption of soybean for a long period of time significantly ($p<0.05$) decreased the level of E_2 and FSH in the female rats, while short period administration significantly ($p<0.05$) increased the PRG level and long period administration significantly ($p<0.05$) decreased the PRG level in comparison with the control. Long and short period consumption of MSG as well as soybean significantly ($p<0.05$) decreased the levels of testosterone and LH in the male rats, while only long period administration of both significantly ($p<0.05$) decreased the level of FSH in the male rats when compared with the control group. The consumption of both small and large amounts of MSG and soybean elicit reproductive hormonal imbalance irrespective of the gender through the alteration of the levels of FSH, LH, E_2, testesterone and PRG.

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***Keywords*:** Monosodium glutamate, Soybean, Reproductive hormones, Luteinizing hormone

1. INTRODUCTION

Monosodium glutamate (MSG) is a subset of glutamate, an important but "non-essential amino acid", that is contained in various foods, and plays a significant role in human metabolism. MSG is formulated from glutamate, sodium and water, and it serves as a crucial food flavor enhancer that amplifies the inbuilt flavor of foods (Kayode et al., 2020; Bob-Chile Agada et al., 2021, Bob-Chile Agada et al., 2021a, Bob-Chile Agada et al., 2023).

Soybean is a product with balanced content of essential amino acids, polyunsaturated fatty acids, vitamins, mineral elements and lecithin. The health effects associated with soybean consumption has been linked to the content of isoflavones; and it is the main class of the phytooestrogens (Orgaard and Jensen, 2008).

The toxicity impact of MSG on the male and female reproductive systems has been elucidated in various studies. The hypogonadism initiated by MSG in mice was reversed through the administration of physiological concentrations of oestradiol (Elefteriou et al., 2003). Pregnant mice exposed to MSG through oral gavage were observed to have their foetal tissues affected negatively (Yu et al., 1997).

Male albino rats fed with MSG supplemented meal for 40 days suffered from shrunken nuclei in spermatogenic, Sertoli, and Leydig cells, as well as swollen mitochondria, cytoplasmic vacuolations, impairment in tubular basement membrane, destroyed seminiferous tubules and germ cells, reduction in the diameter and height of the epithelium lining, and alterations in spermatogenic cells (Sarhan, 2018). However, in female virgin rats, after administration of MSG through oral gavage for a period of 30 to 40 days, there was significant increase in the duration of the diestrus phase; diestrus index; numbers of primary and primordial follicles; while there was a reduction in the phases of the proestrus, estrus, and metestrus, furthermore, there was an increase and decrease in the sizes of the graafian follicle and corpus luteum respectively (Mondal et al., 2018).

The imbalance caused by MSG in the secretion of various reproductive hormones have been extensively reported elsewhere (Giovambattista et al., 2003; Kaledin et al., 2005; Kuznetsova et al., 2005; Wilkinson et al., 2005; Franca et al., 2006; Leitner and Bartness, 2008; Bojanic et al., 2009; Fernandes et al., 2012; Iamsaard et al., 2014; Yuan et al., 2014; Zia et al., 2014; Ochiogu et al., 2015).

Exposure to phytoestrogens, especially the isoflavones, which are compounds that are abundantly present in soybean, may affect fertility by altering testicular and ovarian endocrine functions as well as other events involved in reproduction (Cederroth et al., 2011). Mitchell et al. (2001) reported that the consumption of 40 mg/day of soy-isoflavones (including genistein, glycitein, daidzein) for 2 months had no significant effect on the sexual hormones or semen quality of young males.

Some studies reported no reproductive defects in animal models administered soybean (Fielden et al., 2003; Kang et al., 2002; Nagao et al., 2001), while others reported variable persistent phenotypic and behavioral reproductive abnormalities such as reduction in the secretion of FSH (Atanassova et al., 2000) and testosterone levels (Wisniewski et al., 2003), as well as altered reproductive behavior (Wisniewski et al., 2003, 2005), reduced spermatogenesis

(Atanassova et al., 2000; West et al., 2005), reduced testicular weight or size (Atanassova et al., 2000; West et al., 2005; Wisniewski et al., 2003). Nevertheless, there is paucity of studies on the effect of soybean on the rate of secretion of reproductive hormones.

There are numerous conflicting results concerning the toxicity and safety of MSG and soybean on the reproductive system. It is therefore very necessary to carry out more studies to clarify the effects of MSG and soybean on the secretion of reproductive hormones. The present study therefore assesses the possible changes that might be caused by MSG and soybean on the secretion of both the male and female reproductive hormones in wistar rats.

2. METHODS

2. 1. Sample Procurement and Preparation

Ajinomoto, a brand of monosodium glutamate (MSG), manufactured by Ajinomoto co., inc. Tokyo, Japan was obtained from Relief Market Owerri Imo State, Nigeria. Soybean used for this study was equally obtained from Ekeonunwa Market Owerri Imo State, Nigeria. Aqueous extracts were obtained on weekly basis for the duration (181 days) of feeding adopted in this study. It was stored and kept away from direct sunlight.

2. 2. Acute Toxicity (LD_{50}) determination

Acute toxicity study of the two samples were carried out according to the method of Lorke (1983) using 39 albino mice of both sexes of average weight between 13.2g – 19.2g. They were dosed orally with different gradual does (10 – 5000 mg/kg body weight). The LD_{50} was calculated using the formular below:

$$LD_{50} = LD_{100} - \sum (a \times b)/n$$

n = total number of animals in a group. a = the difference between two successive doses of administered extract. b = the average number of dead animals in two successive doses. LD_{100} = Lethal dose causing the 100% death of all test animals.

2. 3. Animals/Experimental design

A total of two hundred and ten (210) weanly Wistar rats (105 female and 105 male wistar rats) weighing 70 – 78g were obtained from Biochemistry Department, Federal University of Technology, Owerri, Imo State. The rats were allowed to acclimatize for 14 days, maintained *ad libitum* on water and growers mash.

The 105 female rats were equally divided into three groups representing the various experimental durations of 2, 4, and 6 months. Each of these groups consisting of 35 rats were further divided equally into 7 subgroups each containing 5 rats, labelled, and orally administered MSG and soybean according to the established LD_{50} as shown in Table 1 below.

The 105 male rats were also grouped in same manner and orally administered the MSG and soybean as shown in Table 1. After completion of the feeding duration, the animals were sacrificed by cervical decapitation under mild anaesthesia of ethyl ether. Both blood (collected by cardiac puncture) and sera was prepared for analysis to be carried out.

Table 1. Dosing schedule of rats with MSG and soybeans

Groups	Administration
Female rats	
1	Female rats administered daily 1000 mg/kg b.w (low dose, LD) MSG
2	Female rats administered daily 2000 mg/kg b.w (medium dose, MD) MSG
3	Female rats administered daily with 3000 mg/kg b.w (high dose, HD) MSG
4	Female rats administered daily 1000 mg/kg b.w (low dose, LD) soybean
5	Female rats administered daily 2000 mg/kg b.w (medium dose, MD) soybean
6	Female rats administered daily with 3000 mg/kg b.w (high dose, HD) soybean
7	Female rats fed normal rat chow and water (control, C)
Male rats	
1	Male rats administered daily 1000 mg/kg b.w (low dose, LD) MSG
2	Male rats administered daily 2000 mg/kg b.w (medium dose, MD) MSG
3	Male rats administered daily with 3000 mg/kg b.w (high dose, HD) MSG
4	Male rats administered daily 1000 mg/kg b.w (low dose, LD) soybean
5	Male rats administered daily 2000 mg/kg b.w (medium dose, MD) soybean
6	Male rats administered daily with 3000 mg/kg b.w (high dose, HD) soybean
7	Male rats fed normal rat chow and water (control, C)

2. 4. Analysis of hormone levels

The levels of luteinizing hormone (LH), folliclestimulating hormone (FSH), progesterone (PRG), Oestrogen (estradiol) and testosterone were analyzed by the enzyme-linked immunosorbent assay (ELISA). Analytical procedures were performed according to the manufacturer's instructions.

3. RESULT

3. 1. Female reproductive hormone levels

The results for the female reproductive hormones of rats administered MSG and soybeans for 2, 4, and 6 months are shown in Table 2. No significant changes were observed in the luteinizing hormone (LH) levels of rats administered MSG for 2 and 4 months when compared

to the control levels while only the MD and HD administration for 6 months significantly ($p<0.05$) decreased the LH levels. Administration of soybeans produced no significant ($p>0.05$) effect on the LH levels for the 2, 4, and 6 months feeding period. The result for the progesterone (PRG) levels of the rats showed that the MSG and soybean doses administered for 2 and 6 months respectively caused no significant ($p>0.05$) changes. The 4 months administration of the MD and HD of both MSG and soybean significantly ($p<0.05$) decreased the progesterone (PRG) levels when compared to the control level. The results for the 6 months administration of MSG showed significant ($p<0.05$) decrease in the PRG levels when compared to the control level, however, there was a significant ($p<0.05$) increase in the PRG level for LD, MD and HD of soybean after 2 months administration. No significant change was observed in the oestrogen levels after the 2 months administration of LD, MD, and HD MSG while the HD soybean significantly ($p<0.05$) decreased the oestrogen levels when compared to the control level. The administration of the extracts respectively for 4 and 6 months significantly ($p<0.05$) decreased the oestrogen levels when compared to the control. The result for the follicle stimulating hormone (FSH) levels showed that the administration of all the doses of MSG and soybean for 2 and 4 months produced no significant ($p>0.05$) effect. The LD, MD, and HD administration of MSG for 6 months significantly ($p<0.05$) decreased the FSH levels relative to the control level while only the 6 months HD soybean administration significantly ($p<0.05$) decreased the FSH levels relative to the control.

Table 2. Female reproductive hormones of rats administered monosodium glutamate and soybean

DURATION	GROUPS	LH (mIU/ml)	LH (mIU/ml)	PRG (ng/ml)	PRG (ng/ml)	E2 (pg/ml)	E2 (pg/ml)	FSH (mIU/ml)	FSH (mIU/ml)
		MSG	SOY	MSG	SOY	MSG	SOY	MSG	SOY
2 MONTHS	C	0.54±0.12a	0.54±0.12a	11.80±1.16a	11.80±1.16a	62.65±3.19a	62.65±3.19a	0.25±0.04a	0.25±0.04a
	LD	0.57±0.01a	0.57±0.31a	10.10±2.54a	12.60±2.40b	69.50±1.60a	68.50±6.36b	0.23±0.05a	0.22±0.01a

6 MONTHS		4 MONTHS							
C	LD	HD	MD	LD	C	HD	MD		
0.78±0.06c	0.83±0.11c	0.65±0.03b	0.65±0.05b	0.67±0.06b	0.65±0.03b	0.51±0.15ba	0.49±0.17a		
0.78±0.06a	0.77±0.02a	0.80±0.02a	0.71±0.01a	0.67±0.04a	0.65±0.03a	0.63±0.38a	0.51±0.16a		
15.15±0.49b	12.35±0.77c	10.80±1.41a	11.30±1.41a	14.40±1.13b	15.05±0.21b	11.60±2.12a	13.05±0.91a		
15.15±0.49c	14.55±0.70bc	14.10±0.70b	13.55±2.05b	15.85±0.77c	15.05±0.21c	15.15±6.57bc	14.85±3.74b		
87.50±3.53b	75.50±4.94c	63.00±4.24a	65.50±3.53a	78.00±1.41c	86.00±2.82b	66.50±9.19a	70.00±1.14a		
87.50±3.53d	79.50±0.70c	73.5±3.53ac	70.5±2.12ab	75.00±7.07ac	86.00±2.82e	56.50±6.36d	76.00±2.82c		
0.53±0.02c	0.48±0.04d	0.32±0.06b	0.31±0.02b	0.35±0.06b	0.38±0.04b	0.21±0.06a	0.20±0.03a		
0.53±0.02c	0.51±0.02c	0.36±0.03b	0.34±0.05b	0.39±0.05b	0.38±0.0b	0.21±0.05a	0.25±0.04a		

	MD	0.60±0.12b	0.79±0.01a	9.45±0.63d	15.35±0.77c	76.00±2.82c	74.00±4.24ac	0.43±0.06e	0.48±0.03c
	HD	0.51±0.11ba	0.82±0.02a	9.55±1.20d	15.75±0.49c	56.00±5.65d	66.50±3.53b	0.35±0.02b	0.40±0.04d

Values are means ± standard deviations n=5. Values with different superscript letter (s) (a-f) ($p < 0.05$) down the column for each parameter are significantly different. MSG – Monosodium glutamate, SOY – Soybean, LH – Luteinizing hormone, PRG – Progesterone, E_2 – Oestrogen (estradiol), FSH – Follicle stimulating hormone

3. 2. Male reproductive hormone levels

Table 3. Male reproductive hormones of rats administered monosodium glutamate and soybean

DURATION	GROUPS	Ttos (ng/ml)	Ttos (ng/ml)	LH (mIU/ml)	LH (mIU/ml)	FSH (mIU/ml)	FSH (mIU/ml)
		MSG	SOY	MSG	SOY	MSG	SOY
2 MONTHS	C	4.48±0.00^{a}	4.48±0.00^{a}	0.82±0.04^{a}	0.82±0.04^{a}	0.32±0.05^{a}	0.32±0.05^{a}
	LD	4.25±0.19^{a}	4.86±0.09^{a}	0.56±0.09^{b}	0.73±0.23^{b}	0.28±0.05^{a}	0.30±0.04^{a}
	MD	2.59±0.15^{b}	3.61±0.26^{b}	0.45±0.05^{c}	0.71±0.11^{b}	0.30±0.03^{a}	0.31±0.01^{a}
	HD	0.92±0.09^{c}	3.25±0.19^{b}	0.42±0.06^{c}	0.70±0.07^{b}	0.33±0.04^{a}	0.29±0.03^{a}
4 MONTHS	C	4.40±0.36^{a}	4.40±0.36^{a}	0.74±0.05^{d}	0.80±0.05^{a}	0.45±0.02^{b}	0.45±0.02^{be}
	LD	4.20±0.26^{a}	4.66±0.11^{a}	0.71±0.04^{d}	0.82±0.02^{a}	0.40±0.04^{b}	0.40±0.04^{bc}
	MD	3.12±0.08^{d}	3.61±0.28^{b}	0.71±0.02^{d}	0.85±0.04^{a}	0.36±0.03^{a}	0.42±0.02^{b}
	HD	3.14±0.14^{d}	3.30±0.28^{b}	0.70±0.01^{d}	0.82±0.01^{a}	0.31±0.05^{a}	0.38±0.03^{b}
6 MONTHS	C	6.78±0.35^{e}	6.78±0.35^{c}	0.82±0.02^{a}	0.82±0.02^{a}	0.69±0.04^{c}	0.69±0.04^{d}
	LD	6.50±0.27^{e}	6.82±0.12^{c}	0.73±0.03^{d}	0.80±0.02^{a}	0.62±0.06^{c}	0.64±0.02^{d}
	MD	5.72±0.28^{f}	5.68±0.37^{d}	0.54±0.04^{b}	0.70±0.02^{b}	0.53±0.05^{d}	0.67±0.03^{d}
	HD	4.41±0.12^{a}	5.12±0.17^{d}	0.52±0.03^{b}	0.60±0.02^{c}	0.44±0.06^{b}	0.50±0.06^{e}

Values are means ± standard deviations n=5. Values with different superscript letter(s) (a-f) down the column for each parameter are significantly different ($p < 0.05$). MSG - Monosodium glutamate., SOY – Soybean, Ttos – Testosterone, LH – Luteinizing hormone, FSH – Follicle stimulating hormones

A meticulous look at Table 3 showed that 2, 4, and 6 months administration of LD MSG and soybean produced no significant ($p>0.05$) effect on the testosterone levels while the MD and HD MSG and soybean significantly ($p<0.05$) decreased the testosterone levels of the rats. The LD, MD and HD MSG and soybean significantly ($p<0.05$) decreased the luteinizing hormone of the male rats when administered for 2 months while no significant ($p>0.05$) effect was observed with 4 months administration. For the 6 months administration, the MSG doses significantly ($p<0.05$) decreased the luteinizing hormone levels of the male rats relative to the control level while only the MD and HD soybean significantly ($p<0.05$) decreased the luteinizing hormone level. The result for the FSH level showed no significant ($p>0.05$) change observed for 2 months administration of LD, MD, and HD MSG and soybean. At 4 and 6 months, only the administration of MD and HD MSG significantly ($p<0.05$) decreased the FSH level while only the HD soybean significantly ($p<0.05$) decreased the FSH level after 6 months administration.

4. DISCUSSION

Consumption of large amounts of MSG is accompanied by reproductive hormonal imbalance including the FSH, LH, estradiol, testesterone and progesterone as well as leading to sexual dysfunction and eventually sterility (Mondal et al., 2018; Haddad et al., 2021). Soy and soy products remain the major source of isoflavones, a particular class of phytoestrogen that interacts with endogenous estrogen signaling pathways and interfere with the synthesis, secretion, transport, metabolism, binding action or elimination of natural hormones in the body which are responsible for reproduction as well as other important processes. Thus, exposure to large amounts of these compounds may negatively affect fertility by altering the various events associated with reproduction (Cederroth et al., 2012).

Among the female hormones, only LH was not affected by both soybean intake. Soybean consumption even at minimal doses for short periods distorted progesterone and oestrogen levels, whereas a prolonged and excessive intake of soybean disrupted FSH levels. These observations agrees with the study of Kurzer (2002). The effects of soybean on both estrogen and progesterone were mainly due to the presence of therapeutic doses of oestrogen-like compounds in soybeans. A cross-sectional study of 50 premenopausal Japanese women carried out by Nagata et al. (1997) reported an inverse association between soy intake and blood estradiol concentrations.

The MSG when administered for short periods produced no effect on the female reproductive hormones, however, short term administration of soybean altered the PRG and estradiol levels. Mondal *et al*., (2018) posited that MSG impairs the functions of the ovary probably by augmenting the release of FSH, LH and estradiol; promoting the follicular maturation and improving the biochemical mechanism for antioxidant defense. This however, contradicted the findings of this study. Both medium and high dose MSG produced similar reduction effects on the PRG levels after 4 and 6 months administration. These findings were similar to the findings of Zia *et al*, (2014) who initially reported decreased levels of

progesterone in the plasma and interstitial tissue in MSG treated animals, which were significantly lower than those found in control animals.

The reason for decrease in PRG and estradiol levels was possibly due to decreased levels of LH as a result of MSG treatment. LH is known to induce the release of egg from the ovary and encourages the formation of corpus luteum, a structure that secretes progesterone and estradiol (Dozortsev and Diamond, 2020), thus a reduction in the level of LH will eventually lead to a decrease in PRG and estradiol levels. PRG is an endogenous steroid and progestogen sex hormone involved in the menstrual cycle, pregnancy, and embryogenesis of humans and other species (King and Brucker, 2010).

Similarly, the estrogen (estradiol) levels were unaffected by low dose of MSG whereas medium and high doses of MSG suppressed the synthesis of estrogen. Estrogen, or oestrogen, is the primary female sex hormone that is responsible for the development and regulation of the female reproductive system and secondary sex characteristics (Hamilton et al., 2014). The decrease in the estrogen levels found in this study from MSG and soybean treatments, and as well by Soltysik and Czekaj (2013), was probably because MSG and soybean cause inactivation of the enzyme aromatase which catalyzes the conversion of testosterone to estradiol, therefore resulting in decreased estradiol synthesis (Ishikawa et al., 2006). For the male reproductive hormones, low doses of both MSG and soybean were not toxic to testosterone activities. However, medium and high doses suppressed testosterone production. The lowering of testosterone concentrations suggests marked tubular degeneration, meiotic interruption, depletion of sperm concentration and degradation of germinative epithelium (Richburg and Boekelheide, 1996). This suggested the development of male infertility. Subcutaneous administration of MSG in experimental animals reduced the concentration of testosterone (Sun et al., 1991; Ochiogu et al., 2015). Administration of high doses of MSG significantly reduced plasma testosterone levels in male rats, leading to partial infertility in other studies (Franca et al., 2006; Iamsaard et al., 2014). Feminization was induced in male mice through reduction in testosterone and increase in corticosterone using MSG in the study by Kuznetsova et al. (2005). The mechanism of the negative effect of MSG and soybean on the testosterone levels of the male rats might be through the indirect suppression of hepatic enzymes which play central role in the production of testosterone and other sex steroids such as cytochrome P450 2A2 (CYP2A2) and cytochrome P450 3A2 (CYP3A2) (Waxman et al., 1995).

The LH was extensively suppressed by both soybean and MSG. The intake of excessive amounts of soybeans was toxic to the testes. However, the results showed no effect on the FSH levels up to 4 months administration of any of the low, medium or high dose of soybean. The MSG decreased FSH levels only after prolonged intake of either medium or high dose MSG. In this study, the reproductive toxicities of the soybean were evident at prolonged and excessive administration. FSH and LH play a vital role in the maturation of reproductive organs as well as the production of the gametes, however, the detrimental effect of MSG on the production and secretion of these hormones have been reported (Franca et al., 2006; Haddad et al., 2021; Fernandes et al., 2012). The studies by Franca et al. (2006) and Fernandes et al. (2012) have shown that there was reduction in the level of FSH/LH hormones in experimental animals after oral gavage with MSG. The negative effects of long time exposure of soy and phytoestrogens on the male fertility in rodents have been reported in other studies (Atanassova et al., 1999; Nagao et al., 2001; Tan et al., 2006). Cederroth et al. (2010) reported that gestational, post-natal, and adult chronic exposure to soy or isoflavone altered the level of testosterone, LH and FSH in male experimental animals.

5. CONCLUSION

The consumption of both small and large amounts of MSG and soybean elicit reproductive hormonal imbalance irrespective of the gender through the alteration of the levels of FSH, LH, E_2, testesterone and PRG. Thus, the intake of MSG and soybean requires serious caution over the impending reproductive toxicities caused. Further research is needed to develop appropriate management policies and the exact maximum dosage of MSG and soybean to be consumed by people.

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