Sys Rev Pharm 2020; 11(4): 491 – 497
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Oral Glycine and L-Arginine Administration Attenuates Monosodium Glutamate Complications on Pancreas Structure in Albino Rats

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Article History: *Submitted: 15.01.2020* *Revised: 12.03.2020* *Accepted: 19.04.2020*

ABSTRACT
The current work endeavored to elucidate any histological alterations in pancreas islets tissue of rats meanwhile treated with the usually used food additive, Monosodium glutamate (MSG) were accurately studied. The rats (n=70), average weightiness of (240 ± 20) gm were randomly assigned into seven groups (n=10): control groups, others rats in the practice groups received 10 mg/200ml distilled water (DW) for each group of (glycine, l-arginine (ARG), MSG, glycine + MSG, ARG + MSG and the last group were combinations groups (glycine + ARG + MSG) for forty-five days. The rats were sacrificed after the latest date of treatments. A piece of pancreatic tissue was dissected out and fixed in 10% buffered neutral formal saline and prepared for usual stained with hematoxylin and eosin (H&E). The histological findings after H&E methods for pancreas sections from various treatment groups showed varying degree of necrosis, apoptosis, hyperplasia, swallowing and hypertrophic in nucleus in the pancreatic islet cells as well as, irregularity in shape and hypertrophic in islet with hyperplasia in connective tissues, we can assume that MSG indication pancreas toxicity and tissue alteration in return to combination group which showed slightly normal architecture, in the shape and size of pancreatic islet and acini to control group. These conclusions confirmed that glycine and ARG may act as an antioxidant to prevent distortion affected by MSG consumption and may have some deleterious effects on the pancreas of adult Wistar rats which is reversible and does not lead to permanent infarctions, but the normal structure of the pancreas would need a long time to be regained. It is recommended that further investigations aimed at authenticating these findings be carried out.

Key words: Monosodium glutamate (MSG), Glycine, L-arginine, Rats Pancreas , histological changes

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DOI: 10.31838/srp.2020.4.74

INTRODUCTION

Glycine is a non-essential amino acid (Fig.1)which is used in the creation of muscle tissue and the conversion of glucose into energy(Lynch,2004, Razak *et al.*,2017).(Zafra and Gime, 2008) documented that glycine has many different functions in living organisms although its composition is very simple, apart from its role in protein synthesis and metabolism. (Weaver *et al.*, 1998) Discovered that the function of glycine in the endocrine pancreas is scarce well understood and its negotiated receptor rejoinders (strychnine sensitive) is being on a cell line descended from pancreatic B cells (GK-P3 cells). The cellular and subcellular plenty of glycine in islet tissue is yet unexplored. While (Gammelsaeter *et al* .,2004) identified that both A- and B-cells possess the molecular method for the provoked deliverance of glycine from synaptic-like macrovesicles' implies that both of the key inhibitory antennae in the brain participate in paracrine signaling in the pancreas. Recent studies have shown that glycine, with the help of antioxidants and protect the body from cancer.

Figure 1: The structure of glycine (Lynch, 2004).

On the other hand L-arginine (ARG) is a major metabolite and an amino acid (fig.6) necessary for protein synthesis, these effect related to NO synthesis, which is plays an important role in the host defense mechanisms (Appleton,2002, Egbuonu *et al* .,2010) . It is a basic amino acid present in only nuts and naturally found in foods such as red meat, poultry, fish and dairy products, also commonly used in supplements (Furst and Stehle, 2004, Bruno, 2012) also reported that is implicated ARG for increasing system blood pressure in rats and other pathological conditions via excessive production of nitric oxide (NO) (Lokhande *et al.*, 2010).

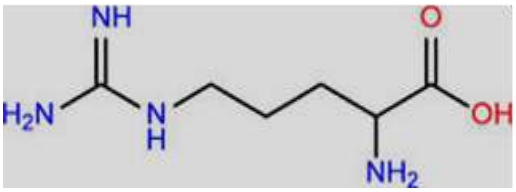

Figure 2: The structure of L –arginine (Appleton, 2002).

L-arginine(ARG) is included in various fields of human biochemistry, including collagen organization, attenuation of the anxiety response, hormone flow, ammonia detoxification, immune modulation and wound healing (Egbuonu *et al.*, 2010, El-Sheikh and Khalil, 2011 ,Bruno ,2012,). L-arginine and nitric oxide affect the cardiovascular system as endogenous anti-athermogenic molecules (Milovanovic *et al.*, 2015).Nevertheless, exposure to ARG plus MSG may significantly develop fodder efficiency, lipid metabolism and antioxidant capability in the male rats (Anthony,2012).

Although Monosodium glutamate (MSG) is the sodium salt of the glutamic acid (Fig. 2), it is a food additive applied to shield flavour and improve the taste (Dief *et al* .,2014, Rosa ,2015,Airaodion *et al* .,2019). Glutamate is non-essential

amino acid introduced in various proteins and most tissues (Mahieu *et al.,* 2016). Glutamate is an example of the abundant amino acids in nature and is the chief ingredient of various proteins and peptides of greatest tissues. Glutamate is additionally offered in the body and performs a vital purpose in human metabolism. When being in its "free" form, not "bound" collectively with distinct amino acids in a protein (Eweka, and OmIniabohs, 2007). Glutamate receptors have been expressed in the central nervous system, liver, kidney, spleen, lung, pancreas and testicle (Mahieu *et al.,*2016). Where this salt utilized in substantial amounts may have impressions on cell maturity, chromosomes and may lead to cancer (Kumer, and Panneer, 2007). Moreover, plentiful- course intake of this salt denoted to induce physiological alterations such as liver, renal abnormalities, sex hormones, thyroid tissue function, impair function in pancreas, ovary and testis lesions, endocrine disturbance, immune toxic effects, inflammation in articular cartilages, degradation of the cartilage matrix as a result of the oxidative stress of MSG (Khalaf and Arafat ,2015, Ateya *et al.,* 2016,Ibegbulem *et al.,*2016, Mosaad, and Sabry,2017), hepatic cellular toxicity (Waer And Edress,2006) behavioral dysfunctions, oxidative stress with neuronal damage in brain tissue and Alzheimer disease with memory deficits (Rosa,2015) , Parkinson disease, Amyotrophic lateral sclerosis and Huntingtons disease (Platt,2007), hyperphgia, obesity, asthma (Pavlovic and Sarac,2010), immunosuppressive agent on chicks (Bruno,2012). ARG is often deliberately added to foods and either as the purified MSG salt or hydrolyzed protein. Monosodium glutamate contains 78% glutamic acid, 22% sodium and water (Kumar *et al.,* 2015).

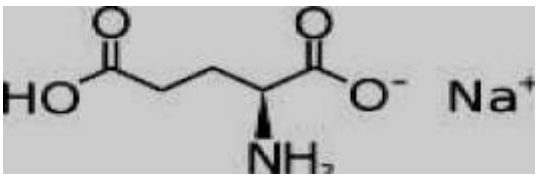

Figure 3: The structure of Monosodium glutamate (MSG) (Airaodionet al ., 2019).

The bases ARG and MSG may be existing in human nutrition and medications, however data on the influence coincident ingestion of ARG and MSG in animal, the experience are no critical thus, there are amazing reports of the toxic effect of MSG on the pancreas (Kumar *et al.,* 2015).

The plan of the existing investigation is to explore glycine protection, independently, in combinations facing MSG - induced variations in the pancreas of male albino rats by histopathological differences study.

DETAILS EXPERIMENTAL

2.1. Materials and Procedures

2.2. Animals and housing.

The male albino rats (Rattus norvegicus), (n=70), designates the weight of (240 ± 20) gm, (12-14) weeks old did work. Animals were settled in plastic gathers bedded with wooden chips. The experiment was carried within November 2018 – December 2018 in the animal house at Biology department / Education College / Salahaddin University -Erbil. They remained under official laboratory requirements, about 12:12 light/dark photoperiod (LD) at 22 ± 4 ºC (Krinke, 2000). Orderly 12-hours diurnal cycles were managed using an automated light-switching device. The animals were supplied conventional rats pellets and tap water ad libitum. The official pellet contains wheat 66.6%, soya 25.6%, sunflower oil 4.4%, limestone 1.5%, salt 0.63%, methionine 0.158%, choline chloride 0.062%, lysine 25% and trace elements 0.05% (Laird *et al* .,1996).

2.3 Experimental Design: the trial rats were distributed randomly to seven groups (each of ten animals. This research was conducted out for 45 days as illustrated following:

Group 1: Control rats: Rats were supplied with organized chow +tap water ad libitum.

Group 2: Glycine employed rats: rats were supplied with organized chow + Glycine (10mg/200 ml drinking water ad libitum).

Group 3: L-arginine employed rats: rats were supplied with organized chow + L-Arginine (10mg/200ml drinking water ad libitum).

Group 4: Mono Sodium Glutamate employed rats: rats were supplied with organized chow + MSG (10mg/200ml drinking water ad libitum).

Group 5: Glycine employed rats + MSG: rats were supplied with organized chow + Glycine (10mg/200ml drinking water ad libitum) + MSG (10mg/200ml drinking water ad libitum).

Group 6: L-arginine employed rats plus MSG: rats were supplied with organized chow + L-Arginine (10mg/200ml drinking water *ad libitum*) + MSG (10mg/200ml drinking water *ad libitum*).

Group 7: Glycine plus L-arginine plus MSG employed rats: rats were supplied with organized chow + Glycine (10mg/200 mL drinking water *ad libitum*) + L-Arginine (10mg/200mL drinking water *ad libitum*) + MSG (10mg/200ml drinking water *ad libitum*).

2.4 Anesthesia, Dissection and Removal of Pancreas: All animals were anaesthetized with ketamine (35mg/kg B.W.) and xylazine (5mg/kg B.W.), (Laird *et al.,* 1996). A piece of pancreatic tissue was amputated out and fixed in 10% buffered neutral formalin (Saleh *et al*., 2015). After fixation tissues were cut at 5 µm and dyed with hematoxylin and eosin. The sections were checked under an optical microscope (Olympus microscope, Letiz Wetzler, Germany) and photomicrographs were taken by a digital camera (Sony DSC-W30, Korea). The entire magnification of is measured of the magnifying skill of the objective multiplied by the

magnification of the eyepiece and, where applicable, multiplied by original magnifications.

RESULTS

In the end of experiment appear effect of MSG, glycine and ARG on rats' panaceas. Fig. (4) showed normal pancreas structure for the control groups of animals while Fig. (5) were treated with the glycine at dose level 10mg/200 ml DW showed normal architecture with respects to (a) acini but in the (b)pancreatic islet cells there were hyperplasia especially in periphery of it. The effect of ARG at dose level 10mg/200 ml DW treated rats in Fig.(6) showed normal architecture, regular in shape and size with moderate (a) hyperplasia in the pancreatic islet cells as well as (b) dilation in the blood capillary. Fig. (7) of MSG at dose level 10mg/200 ml DW treated rats showed (a) irregular in shape of islet with hypertrophic in size as well as (b)vaculation ,(c)hyperplasia and (d) necrosis in the pancreatic islet cells also, on the other hand, Fig.(8) showed normal in shape of (a)islet with (b) bleeding as well as (c) necrosis ,(d) apoptosis and (e)swallowing in the pancreatic islet cells with (f) hypertrophic in nucleus.

Fig. (9) for glycine plus MSG treated rats showed normal architecture, in size of (a) islet with (b) strong hyperplasia in the pancreatic islet cells as well as (c) necrosis in acini and (d) hyperplasia in connective tissues. In addition, Fig. (10) from ARG plus MSG treated rats at dose level 10mg/200 ml DW showed (a) irregularity in shape and hypertrophic in islet as well as (b) hyperplasia with (c) necrosis in the pancreatic islet cells and acini Fig. (11 and 12) Photomicrograph from Glycine plus ARG plus MSG treated rats showed normal architecture, in (a) shape and size of pancreatic islet and (b) acini.

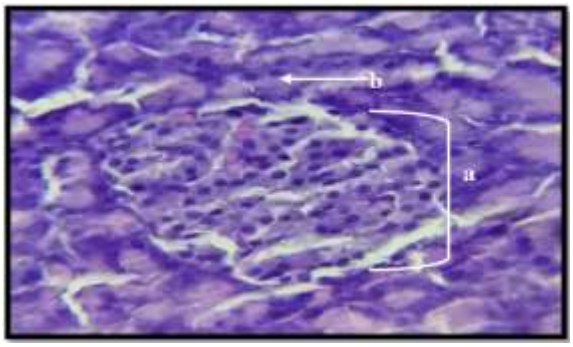

Figure 4: Photomicrograph from negative control rat showed normal architecture, regular in shape and size of (a) pancreatic islet cells and (b) acini (H&E 400X).

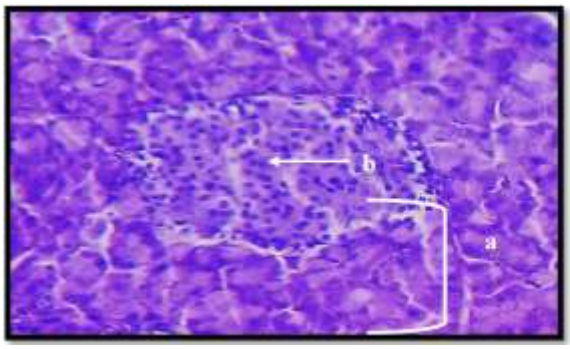

Figure 5: Photomicrograph from glycine treated rat showed normal architecture with respects to (a) acini but in the (b) pancreatic islet cells there were hyperplasia especially in periphery (H&E 400X).

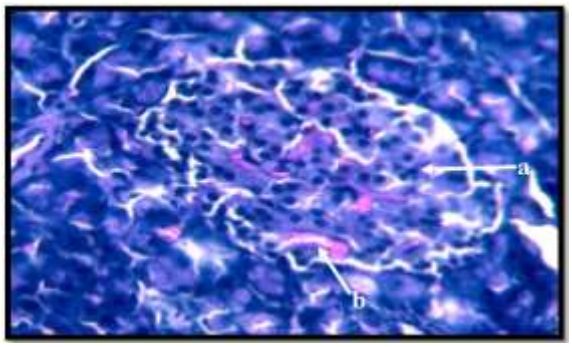

Figure 6: Photomicrograph from l-arginine treated rats showed normal architecture, regular in shape and size with moderate (a) hyperplasia in the pancreatic islet cells as well as (b) dilation in the blood capillary (H&E 400X).

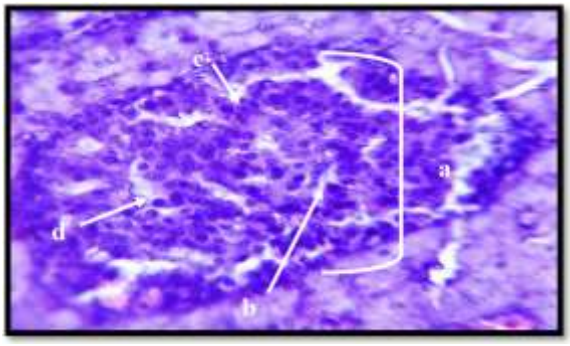

Figure 7: A- Photomicrograph from MSG treated rats showed: (a) irregular in shape of islet with hypertrophic in size as well as (b) vacuolation, (c) hyperplasia and (d) necrosis in the pancreatic islet cells (H&E 400X).

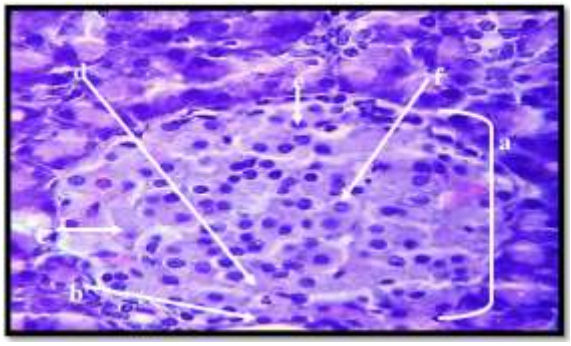

Figure 8: B- Photomicrograph from MSG treated rats showed normal in shape of (a) islet with (b) bleeding as well as (c) necrosis, (d) apoptosis and (e) swallowing in the

pancreatic islet cells with (f) hypertrophic in nucleus (H&E 400X).

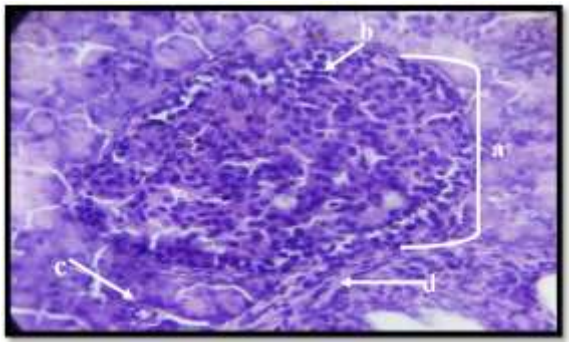

Figure 9: Photomicrograph from glycine plus MSG treated rats showed normal architecture, in size of (a) islet with (b) strong hyperplasia in the pancreatic islet cells as well as (c) necrosis in acini and (d) hyperplasia in connective tissues (H&E 400X).

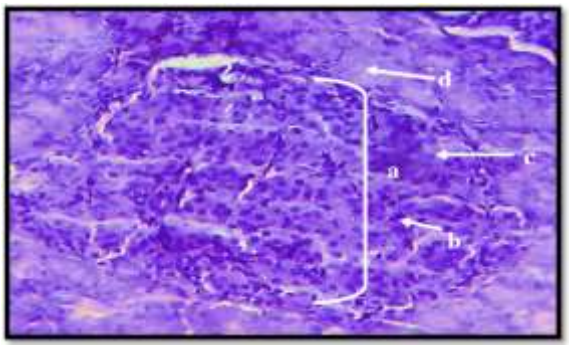

Figure 10: Photomicrograph from l-arginine plus MS treated rats showed (a) irregularity in shape and hypertrophic in islet as well as (b) hyperplasia with (c) necrosis in the pancreatic islet cells and (d) acini (H&E 400X).

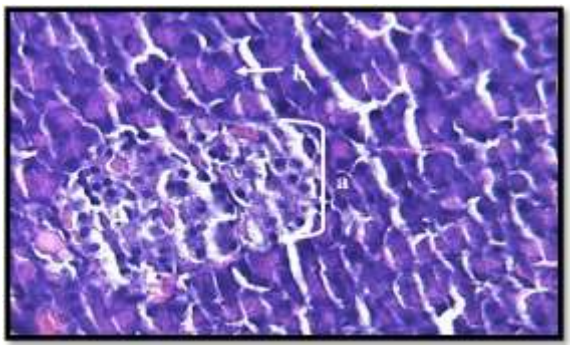

Figure 11: Photomicrograph from glycine plus l-arginine plus MSG treated rats showed normal architecture, in (a) shape and size of pancreatic islet and (b) acini, (H&E 400X).

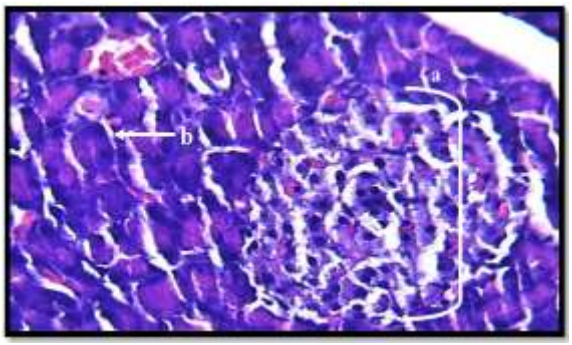

Figure 12: Photomicrograph from glycine plus l-arginine plus MSG treated rats showed normal architecture, in (a) shape and size of pancreatic islet and (b) acini, (H&E 400X).

DISCUSSION

Although the monosodium glutamate is frequently used in modern nutrition worldwide as a food additive (Hassan et al .,2014) has shown that continuous administration or excessive use of MSG leads to serious adverse effects on the general health and caused many infarctions to the organs(Kumar ,2015,Kumar *et al* .,2015). Also recorded that showed that sodium selenite and vitamin C enhancing testicular injuring effect of MSG through modulation of oxidative stress and apoptotic modifications in rats (Sarhan,2018, Rahimi *et al.*,2019). Thus, alteration of pancreas tissue in response to MSG consumption could exhibit MSG urged cytotoxicity and the possibility of glycine and arginine in reducing of these harmful changes.

The current study showed that MSG administration causes many histological changes in the pancreas tissue [fig7,8] such as bleeding, necrosis, apoptosis and swallowing in the islet cells with hypertrophic in nucleus. The presence of necrosis and apoptosis may be associated with depletion of ATP, which definitely prompting cellular destruction and perhaps diminish extraordinary cellular roles in the pancreas. These findings support that of a previous study (Leshchenko *et al.,* 1994, Ajibade *et al.*,2015) are found that administration of MSG induced edema, disorders in the vacuolated cytoplasm, necrosis and degeneration of pancreas tissue and degrease in cell mass. Other researchers reporting that hyperplasia, decline in acinar cells,&-cells and somatostatin cells and pancreatic islets hypertrophy (Nakayama et al .,2003, Nagata *et al*., 2006, Sasaki et at .,2009).While (Di-Cairano *et al* .,2011) demonstrated that B cells cytotoxicity associated with high oxidative stress due to excess intake glutamate causing to apoptosis and autophagy in human islets.As well as (Ivan *et al.,* 2013) recorded that the development of pancreatitis in rats with MSG induced leads to an increase in synthetic and functional agents of the pancreas cells causing obesity. While (Boonnate *et al.,* 2015) exposed that regular MSG intakes develop pancreatic B cells lack, without affect glucose sensitivity in normal adult rats.

In the contemporary study, administration of glycine Plus MSG to rats revealed their normal architecture in size of islet with strong hyperplasia and necrosis in acini as well as hyperplasia in connective tissues compared with the control [fig 4,5].These findings support those of aprevious work that glycine may prevent insuline resistance and associated with

inflammatory proccesses by inhibiting the production of cytokines (pro-inflammatory proteins) which are secreted to negotiate the immune rejoinder to infectious causes and provoke inflammation, these factors can happen as well as pointing to chronic inflammation (Kanterman *et al.,*2012).Glycine is important for detoxification of certain intermediaries accumulated in excess which is associated with metabolic disorders and obesity(Alves *et al.,* 2019).

The study here also showed that rats were given ARG plus MSG induced some histological alterations in the pancreas including irregularity in shape, hypertrophic in islet cells and acini examined with the control group. ARG and glycine alone with MSG diminished the toxic effects but did not exclude them, this may be due to the intensity of a specific dose or the period of time used is insufficient to eliminate these effects.(Lawrence *et al.,* 2011) revealed that ARG decreased the vascular superoxide anion production as a result reducing oxidative stress and enhances endothelial function in hypercholesterolemia matters as well as ARG may also improve recovery of the endocrine pancreatic function by flowed plenty of polyamines product in the pancreas of diabetic rats. Also it is found that administered of MSG with a combination of l-alanine and l-arginine enhanced fed state glycaemia in mice (Araujo *et al* .,2017).

The present study indicated that the administration of glycine and ARG plus MSG to rats exhibited sanitary architecture in the shape and size of pancreatic islet and acini [fig 11, 12] compared with the control group. It may occur as a physiological healing matters in response to the injury of the pancreatic tissue which induced by MSG.(Kondoh *etal.,*2000)revealed reduction in some toxic physiological effects of MSG with presence of both proline, alanine, glycine and glucose it is important to determine whether exposure to combinations could adversely impact on the functional capacity of the prostate , testis and pancreas structure in rats (Coskun, 2004, Ivan *et al*., 2013). The researchers revealed that intake of antioxidants with food decreased the adverse effects of MSG in human (Airaodion *et al .,* 2019).

CONCLUSIONS

The existing investigation explicated that MSG has harsh toxic performances on the pancreas tissue and the simultaneous administration of both glycine and ARG attenuate such effects through their antioxidant, anti-inflammatory and anti-atherogenic. Therefore, individuals showed be to limit dietary intake of MSG in their foods.

ACKNOWLEDGEMENTS

We would wish to appreciate all cooperators for their participation in this production particularly animal house technicians.

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