NEUROPROTECTIVE EFFECTS OF CHRYSIN ON ADULT MALE ALBINO RATS EXPOSED TO ACRYLAMIDE AND RADIATION

By

Laila A. Rashed*, Hanan F. Al-Saeed* and Mohammad M. El-Shawwa*

Department of Biochemistry, Faculty of Medicine, Cairo University and Department of Physiology, Faculty of Medicine for Girls, Al-Azhar University*

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ABSTRACT

Background: Acrylamide is a well-known industrial toxic substance that produces neurotoxicity, which is characterized by neuronal degeneration. In addition, radiation derived-brain injury is a prominent side effects of brain radiotherapy. On the other hand, chrysin (CN) is a natural biologically active compound with antioxidant and neuroprotective.

Objective: Determination of the neuroprotective effects of chrysin on brain tissue of adult male albino rats exposed to acrylamide toxicity and radiation.

Material and Methods: Seventy adult male albino rats of local strain weighed 140-160 g were used in this study. They were divided into six equal groups: Control group (A), acrylamide group (B), radiation group (C), acrylamide and radiation group (D), acrylamide and chrysin group (E), radiation and chrysin group (F) and acrylamide, radiation and chrysin group (G). By the end of the experimental period (4 weeks), sera were separated for measurement of tumor necrosis factor alpha (TNF-α) and brain derived neurotrophic factor (BDNF) level. Brain of each rat was dissected out carefully for measurement of gamma-aminobutyric acid (GABA), malondialdehyde (MDA) and glutathione (GSH) content.

Results: Chrysin increased GSH and decreased both MDA and TNF-α levels in ACR-treated rats. Moreover, it decreased the level of GABA, while it increased the BDNF level. On the other hand, adding radiation to ACR did not reduce the protective effects of chrysin regarding to all parameters except BDNF.

Conclusion: Chrysin reverses the oxidative stress and pro-inflammatory status in rats exposed to both acrylamide and radiation. Therefore, it might be used as a supportive treatment for persons frequently exposed to these environmental hazards.

Keywords: Acrylamide, radiation, chrysin, GSH, TNF-α, BDNF, GABA and MDA.

INTRODUCTION

Acrylamide is incorporated into grout and soil-stabilizer products that are used to plug leaks in dams, tunnels, and other structures. It is also transformed into polyacrylamides, which are used extensively in chemical industries including cosmetics, waste water management, road construction, papermaking and gel electro-

phoresis for laboratory research (**Mehri et al., 2015**).

Acrylamide can be absorbed into the body by many ways, such as the respiratory system, digestive system, skin, and muscles. Additionally, long exposure to acrylamide may lead to toxic accumulations and result in toxic symptoms (**Tian et al., 2015**). The single (monomer) form of acrylamide, is discovered to be present in food e.g. french-fries, potato chips, jarred baby foods and infant biscuits (**Mojska et al., 2010 and 2012**). Moreover, acrylamide is formed through Maillard reaction when carbohydrate-rich food is cooked in high temperature as in baking, frying, and roasting (**Krishnakumar and Visvanathan, 2014**). Thus, diet is another main source of environmental ACR exposure in human (**Mehri et al., 2015**).

Radiation therapy has been commonly used as the standard treatment for brain tumors (**Kantor et al., 2008**). Controlled high energy rays such as x-ray and γ-ray are used to either kill cancer cells directly or interfere with their ability to grow. However, the use of radiation therapy for treatment of brain tumors is limited by the risk of radiation-induced damage to the normal, healthy brain tissue that can subsequently lead to devastating functional de?cits (**Moulder and Cohen, 2007**).

Both radiations and acrylamide are present in the general environment and workplaces. Therefore, combined exposure to both agents is possible, especially at low doses (**Dobrzynska, 2007 and Rao et al., 2015**). The pro-oxidative and pro-in?ammatory environments caused by exposure to either radiations or ACR could be implicated in the pathophysiological process of brain injury, and subsequent development of various neurodegenerative diseases (**Dheen et al., 2007 and Kim et al., 2014**).

Chrysin (5,7-dihydroxyflavone) is a natural flavonoid extracted from many plants, honey and propolis (**Williams et al., 1997**). It is also present in chamomile and mushroom (**Anandhi et al., 2013**). Several studies have shown that chrysin has multiple biological activities, such as anti-inflammatory, antioxidant and vaso-relaxant (**Lapidot et al., 2002**). Some studies suggested that chrysin could be considered as a neuroprotective agent in different animal models (**Mercer et al., 2005 and He et al., 2012**).

The present study was performed to investigate the neuroprotective effects of chrysin on rats exposed to ACR and/or exposure to radiation and the possible underlying mechanisms of all these effects.

MATERIALS AND METHODS

Animals and experimental design: This study was performed on 70 adult male albino rats of local strain weighing 140–160 gm. The animals were housed in laboratory animal cages (45 x 40 x 25 per 5 rats) They were kept at room temperature in normal day/night rhythm with free access to food and water all over the period of the work (4 weeks) in the animal house of National Center for

Radiation Research and Technology, Cairo, Egypt. After seven days of acclimatization the rats were randomized into 6 equal groups as follows:

1. **Control group (A):** Each rat received 1ml normal saline (0.9%) by oral gavage for 4 weeks.

2. **Acrylamide group (B):** Each rat received 40 mg/kg/day of ACR in a volume of 1 ml normal saline day by oral gavage for 4 weeks **(Pan et al., 2015).**

3. **Radiation group (C):** Rats were given fractionated brain radiation 5 Gy/day for 5 days/week for 4 weeks **(Zhoua et al., 2011 and Martin et al., 2013).**

4. **Acrylamide and radiation group (D):** Rats were given both ACR (40 mg/kg/day) and fractionated radiation (5 Gy/day for 5 days/week) for 4 weeks.

5. **Acrylamide and chrysin group (E):** Rats were given ACR (40 mg/kg/day) and treated with chrysin (100 mg/kg/day) by oral gavage **(Wang and Morris, 2007).**

6. **Radiation and chrysin group (F):** Rats were given fractionated radiation (5 Gy/day for 5 days/week) and chrysin (100 mg/kg/day by oral gavage) for 4 weeks.

7. **Acrylamide, radiation and chrysin group (G):** Rats were exposed to ACR (40 mg/kg/day by oral gavage), radiation (5 Gy/day for 5days/week) and chrysin (100 mg/kg/day by oral gavage) for 4 weeks.

Drugs and chemicals: ACR and chrysin were purchased from Sigma chemical company (USA).

Irradiation processing: Irradiation was performed using Canadian gamma cell-40, (137Cs) at the National Center for Radiation Research and Technology, Cairo, Egypt. Animals were exposed to fractionated whole body γ-radiation delivered as 5 Gy/day for 5 days/week at a dose rate of 0.61 Gy/minute **(Zhoua et al., 2011 and Martin et al., 2013).**

Sample collection and biochemical assays: The animals were anesthetized at the end of the experiments and blood samples were obtained from the orbital sinus of overnight fasted rats. Blood was immediately centrifuged at 3000 rpm for 20 minutes. Sera were separated and stored at -80∘C for measurement of TNF-α and BDNF levels. Brain of each rat was dissected out carefully, wrapped with aluminum foil and kept frozen at -80° C for measurement of GABA, MDA and GSH contents.

● **Estimation of GABA in brain tissue:** It was measured by using ELISA kit supplied by MyBioSource, USA, according to the manufacturer`s instructions **(Cai et al., 2010).**

Estimation of MDA in brain tissue (Tüközkan et al., 2006).

Estimation of GSH in brain tissue (Khan et al., 2012).

● **Measurement TNF- α in serum:** It was measured by using ELISA kit supplied by quantikine R&D system

USA, according to the manufacturer`s instructions **(Tian et al., 2005).**

● **Measurement BDNF in serum:** It was measured by using ELISA kit supplied by MyBioSource, USA, according to the manufacturer`s instructions **(Rios et al., 2001).**

Statistical analysis: Data were expressed as means ± standard deviation (SD). Statistical comparison between different groups were done using one-way analysis of variance (ANOVA) followed by Tukey HSD multiple comparison test to judge the difference between various groups. All calculations were performed using the SPSS 16.0 software package. Significance was accepted at P< 0.05.

RESULTS

The brain tissue TNF-α level in control group (A) was significantly lower than all other groups, while in acrylamide and radiation group (D) was significantly the highest among the all groups. The TNF-α levels in acrylamide and chrysin group (E), radiation and chrysin group (F) and acrylamide, radiation and chrysin group (G) were significantly lower than acrylamide group (B), radiation group (C) and (D). There were no significant changes between (B) and (C). Also, there were no significant changes between (E), (F) and (G) regarding to brain tissue TNF-α level.

The brain tissue MDA level in (A) was significantly lower than all other groups and in (E) and (F) was significantly lower than (B), (C) and (D). There were no significant changes between (B), (C) and (D). Also, there were no significant changes between (E), (F) and (G) regarding brain tissue MDA level.

The brain tissue GSH level in (A) was significantly higher than all other groups, while in groups (E) and (F) were significantly higher than (B), (C) and (D). There were no significant changes between (B), (C) and (D). Also, there were no significant changes between (E), (F) and (G) regarding brain tissue GSH level.

The brain tissue BDNF level in (A) was significantly higher than in all other groups, and in (E) and (F) was significantly higher than (B), (C) and (D). BDNF level was significantly lower in (D) compared to (B) and (C), while no significant difference was observed between (B) and (C). Also, they decreased significantly in (G) compared to (E) and (F) .

The brain tissue GABA level in (A) was significantly lower than in other groups, and in (E) and (F) was significantly lower than (B), (C) and (D). GABA level was significantly higher in (D) compared to (B) and (C), while no significant difference was observed between (B) and (C). Also, there were no significant changes between (E), (F) and (G) regarding brain tissue GABA level **(Table 1)**.

Table (1): Serum levels of TNF-α and BDNF as well as brain contents of GABA, MDA and GPx in various groups at the end of the treatment period (Mean ± SD).

Parameters	Control group (A)	Acrylamide group (B)	Radiation group (C)	Acrylamide and radiation group (D)	Acrylamide and chrysin group (E)	Radiation and chrysin group (F)	Acrylamide radiation, and chrysin group (G)
TNF-α (ng\ml)	40.26±3.39	105.70±9.11[adefg]	107.20±11.30[adefg]	133.13±9.61[abcefg]	77.23±3.53[abcd]	76.53±11.19[abcd]	78.53±11.19[abcd]
MDA (µmol)	106.17±6.41	288.43±22.32[aefg]	271.70±19.93[aefg]	298.80±11.94[aefg]	138.50±20.98[abcd]	139.83±21.80[abcd]	144.83±21.80[abcd]
GSH (units)	81.70±7.66	38.30±9.39[aefg]	38.73±14.22[aefg]	25.80±5.24[abefg]	51.76±6.56[abcd]	52.20±3.18[abcd]	49.20±3.18[abcd]
BDNF (µg/ml)	160.20±37.30	52.90±8.10[adef]	70.33±9.58[aef]	48.50±13.33[abef]	103.10±9.05[abcdg]	99.96±7.74[abcdg]	93.96±7.74[abcdef]
GABA? (units)	43.66±3.65	54.80±15.02[adefg]	55.33±3.77[aefg]	59.43±3.84[aefg]	48.13±3.17[abcd]	47.10±8.87[abcd]	49.10±8.87[abcd]

(a) Significant values versus control group.
(b) Significant values versus acrylamide group.
(c) Significant values versus radiation group.
(d) Significant values versus acrylamide and radiation group.
(e) Significant values versus acrylamide and chrysin group.
(f) Significant values versus radiation, and chrysin group.
(g) Significant values versus acrylamide, radiation and chrysin group.

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DISCUSSION

In this study, the brain tissue TNF-α level increased after exposure to either ACR or irradiation compared to control group with no significant difference between either ACR or irradiation groups. TNF-α level in rats co-exposed to ACR and irradiation was significantly the highest among the all groups. Many intracellular pathways are set in motion by the binding of TNF to its cell surface receptors. Major steps in the TNF-mediated cytotoxicity cascade include G protein-coupled activation of phospholipases, generation of free radicals, and damage to nuclear DNA by endonucleases. Eventually the cells undergo apoptosis and die **(Wang et al 2015).**

The result of this work is compatible with the study of **Xue et al., (2014).**

In this study, rats exposed to ACR and/or irradiation showed significant increase in brain content of MDA. On the other hand, the brain content of GSH decreased significantly in the same groups. There were no significant changes between these groups regarding to both parameters. These results indicated that ACR induces oxidative stress leading to protein and lipid peroxidation **(Venkataswamy et al., 2013).**

ACR is metabolized by 2 main pathways-conjugation with glutathione and excretion as mercapturic acids and by oxidation to glycidamide, a reactive epoxide. Glycidamide undergoes further metabolism by conjugation with glutathione, to form several mercapturic acids, and by hydrolysis **(Fennell et al., 2015).** This conjugation leads to depletion of GSH compounds that have a role in neutralization of free radicals that is produced by ACR and its metabolite glutathione **(Swaran and Flora, 2009).**

Increased MDA is associated with increased oxidative stress, declined antioxidant capacity in nervous tissue and sciatic nerve and induced apoptosis in cerebral cortex of rats **(Lakshmi et al., 2012 and Nixon et al., 2012). Matveychuk et al. (2011)** reported that lipid and protein peroxidation play a significant role in neurodegenerative disorders including Alzheimer's disease.

The result of this work was compatible with the study of **Guney et al. (2005).** They reported that the decline of GSH level in the brain after irradiation might be due to its consumption during the oxidative stress induced by irradiation. Moreover, **Listy (2014)** reported that oxidative stress caused by radiation elevates MDA level in brains of rats due to increase lipid peroxidation. Irradiation caused the oxidative stress as an outcome of a disturbance between production of ROS and antioxidant defense mechanisms. Irradiation activates microglia and causes infiltration of the brain. Upon activation, these cells produce ROS and activate more microglia and immune cells that can increase the level of oxidative stress **(Balentova and Adamkov, 2015).**

Accordingly, several studies reported that oxidative stress and in?ammation in brain are the key mechanisms in ACR and irradiation induced cell injuries. (**Prasad and Muralidhara, 2014; Balentova & Adamkov, 2015 and Santhanasabapathy et al., 2015**). Interestingly, the results of this work may support this interpretation.

In the present work, the level of BDNF in rats exposed to both ACR and radiation decreased significantly compared to those exposed to only ACR or radiation suggesting additive effects of both hazards, which provide some insights to the toxicological mechanism of them. **Woehrling et al., (2013)** reported that BDNF release is decreased due to ACR toxicity in some neuronal cell culture models. It has been reported that radiation-induced brain injury can damage neuronal, glial and vascular compartments of the brain. Interference with the cell cycle regulatory proteins and consequent apoptosis are the primary mechanisms responsible for cell death that occurs within several hours after irradiation **(Balentova and Adamkov, 2015)**.

Gamma-aminobutyric acid is one of the most important inhibitory neuro-transmitters in the CNS. It plays the principal role in reducing neuronal excitability throughout the nervous system **(Watanabe et al., 2002)**. Either low GABA level or decreased GABA function in the brain is associated with several psychiatric and neurological disorders, including anxiety, depression, insomnia, and epilepsy **(Kendell et al., 2005)**. High level of GABA may cause synaptic depression and be involved in slow, long-term neuronal damage **(Tian et al., 2015)**.

In this study, the brain tissue GABA level increased after exposure to either ACR or irradiation compared to control group with no significant difference between either ACR or irradiation groups. GABA level in rats co-exposed to ACR and irradiation were significantly the highest among the all groups.

The results of this work regarding GABA level in brain is compatible with work of **Tian et al., (2015).** They found that brain content of GABA increased in rats after induction of ACR neurotoxicity, which provides an experimental evidence of the mechanism of neurotoxicity induced by ACR. Others noticed that the toxic effects of ACR on the cerebellum of rats is associated with the increased expression of GABA **(Shi et al., 2016).**

Regarding to radiation-induced changes in GABA function, **Vlkolinsk? et al. (2008)** reported that fractionated irradia-tion produces changes in expression of GABA receptors in brain of mice. Others noticed that radiation increases the surface expression of inhibitory gamma-aminobutyric acid receptors **(Wu et al., 2012).** On the other hand,

The present study demonstrated the neuroprotective effects of chrysin which led to reverse of oxidative stress and pro-inflammatory status in rats exposed to either acrylamide or radiation or both through increasing GSH and decreasing both MDA and TNF-α levels. Moreover, it decrease the level of the inhibitory neurotransmitter GABA, while it increase the BDNF level returning all parameters towards normal levels. On the other hand, adding radiation to ACR and chrysin did not reduce the protective effects of chrysin regarding to all parameters except BDNF.

Studies suggested that chrysin could be as a neuroprotective agent in different models. **Mehri et al., (2014)** reported that chrysin was able to prevent cell death and the gait abnormalities induced by ACR.

In this study, treatment of acrylamide group with chrysin led to lowering of

TNF-α which is compatible with the study of **Gresa-Arribas et al., (2010).**

The result of this work was also compatible with **Souza et al., (2015)** who reported that chrysin prevents age-related cognitive decline via attenuation of oxidative stress and modulation of BDNF level. In addition, the potential anti-inflammatory and antioxidant properties of chrysin have been reported in several researches. **Anand et al., (2012)** showed that CR reduces the disturbances of redox status, named superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione in liver, kidney, and brain tissues of rats treated with D-galactose. Moreover, chrysin significantly improves memory impairment and neuronal cell apoptosis induced by chronic cerebral hypoperfusion in rats. It decreased lipid peroxide, reduced the increased activities of superoxide dismutase, and attenuated the activities of glutathione peroxidase in these rats **(He et al., 2012 and Yao et al., 2014). Pushpavalli et al. (2010)** showed that chrysin acts as a hepato-protective and antioxidant agent against d-galactosamine-induced hepatotoxicity.

The results of this work was also supported by **Benkovic et al. (2008) and Ozgur et al. (2016).**

In conclusion, the present study demonstrated the anti-inflammatory and antioxidant protective effects of chrysin, which reversed the oxidative stress in rats exposed to acrylamide and radiation. Adding radiation to ACR and chrysin carrying no significant differences regarding all the parameters except BDNF compared to ACR and chrysin. Therefore, chrysin might be used as a supportive treatment for those frequently exposed to ingested acrylamide and/or radiation. Further studies are required to clarify the effects and mechanisms of action of chrysin on hazards of brain radiation.

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تأثيرات الحماية العصبية لعقار الكريسين على تسمم الجرذان الذكور البيضاء البالغة المتعرضة للأكريلاميد والإشعاع

ليلى أحمد راشد ـ حنان فتحي السعيد* ـ محمد محمد الشوا*

قسم الكيمياء الحيوية ـ كلية الطب ـ جامعة القاهرة
قسم الفسيولوجيا ـ كلية الطب (بنات) ـ جامعة الأزهر*

خلفية البحث: الأكريلاميد مادة صناعية سامة معروفة جداً تؤدي الي تسمم الخلايا العصبية الذى يتميز بتآكل الخلايا العصبية. بالإضافة إلي ذلك، فإن إصابات المخ الناجمة عن الإشعاع تعد من الآثار الجانبية البارزة للعلاج الإشعاعي للمخ. يعتبر الكريسين من المواد الطبيعية النشطة بيولوجياً وله خصائص مضادة للأكسدة وذات طبيعة علاجية للأعصاب.

الهدف من البحث: تحديد التأثيرات العصبية العلاجية لعقار الكريسين على نسيج مخ ذكور الجرذان البيضاء المتعرضة للتسمم بالأكريلاميد والإشعاع.

مواد وطرق البحث: إستخدم في هذا البحث سبعون من ذكور الجرذان البيضاء البالغة من سلالة محلية تتراوح أوزانها بين ١٤٠-١٦٠جراماً. وقد تم تقسيم الجرذان إلى سبع مجموعات متساوية: المجموعة الضابطة، مجموعة الأكريلاميد، مجموعة الإشعاع، مجموعة الأكريلاميد والإشعاع، مجموعة الأكريلاميد والكريسين، مجموعة الإشعاع والكريسين، مجموعة الأكريلاميد والإشعاع والكريسين. وفي نهاية فترة التجربة (٤ أسابيع) تم جمع عينات الدم لقياس عامل نخر الورم والعامِل التغذويّ العصبيّ المُشتقّ من الدِّماغ. وقد تم استخراج المخ لكل فأر بعناية لقياس محتوياته من حامض جاما أمينو بيوتريك و المالونداايالدهيد والجلوتاثيون.

النتائج: أدى استعمال مادة الكريسين في الجرذان التي تلقت أكريلاميد إلى إرتفاع مستوى الجلوتاثيون وإنخفاض مستوى المالونداايالدهيد وعامل نخر الورم. إضافة إلى ذلك، إرتفع العامِلَ التغذويّ العصبيّ المُشتقّ من الدِّماغ وإنخفض حامض جاما أمينو بيوتريك. على الجانب الآخر: عند إضافة الإشعاع: لم تقل التأثيرات العلاجية لمادة الكريسين لكل القياسات بإستثناء العامِلِ التغذويّ العصبيّ المُشتقّ من الدِّماغ.

الإستنتاج: عكس الكريسين آثار كلا من الإجهاد التأكسدي والحالة المنشطة للإلتهابات في الجرذان المعرضة للأكريلاميد والإشعاع. ولذلك يمكن إستخدام الكريسين كعلاج داعم عند التعرض لهذه الأخطار البيئية.