Assess the Effect of Cucrumen in Histopathologcal Changes on the Cerebral Cortex of Offspring Rats Toxicity Induced By Fried Foods

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Abstract: Acrylamide is an industrial chemical formed in food containing starch like chips, crisps and bread during heat processing and preparation of food. Acrylamide used in preparing polyacrylamide which is used in water purification from organic substance, paper, oil field industries and preparation of poly acrylamide gels using in laboratory searching. The present investigation shows the effect of dietary fried food on the histoarchitecture of the cerebral cortex, female Sprague-Dawley rats were feeding with fried potato chips or fried bread alone or combined at dose 15%, 30% supplemented basil diet before 6 weeks of gestation and 6 weeks during the gestation and lactation, the offspring's reaching 3 weeks old. Microscopic examination of sections of the cerebral cortex of offspring's maternally fed on fried potato (G2) showing some cells appeared with distorted deeply stain ,malformed in pia mater with loss of density in plexus nerve fibers and dilatation blood capillary in piamater with many necrotic cells, Cerebral cortex of (G ,3,4) showed rupture piamater layer, with infiltrated inflammatory cells in molecular layer, The most prominent alterations in external granular such as most nuclei in external granular cell shrunken surrounded by spaces and dilated congested blood capillary in piamater and molecular layer with loss of density in plexus in molecular layer(G ,5,6 &7). The using of curcumen showing ameliorative cerebral tissue, represented in low doses of acrylamide (fried potato 15%%, fried bread 15% mixed fried bread & potato 15%),) groups: indicated the external granular cell appeared nearly normal, with moderate ameliorative. On the other side, the groups feds on high dose of acrylamide (fried potato 30%, fried bread 30% mixed fried bread & potato 30%), showed remarkable changes, represented necrotic cells& dilated blood capillary, inflammatory tricked in pia matter and loss of plexus, necrotic cells & dilated blood capillary.

[Ismail, N.H. **Assess the Effect of Cucrumen in Histopathologcal Changes on the Cerebral Cortex of Offspring Rats Toxicity Induced By Fried Foods**. *J Am Sci* 2012;8(8):215-221]. (ISSN: 1545-1003).
http://www.jofamericanscience.org.33

Key words: Cucrumen; Histopathologcal; Cerebral Cortex; Offspring Rat; Toxicity; Fried Foods

1. Introduction

Recently high levels…. were unexpectedly detected in widely consumed food items notably French fries, potato crisps, bread **(WHO, 2002)**. French fries and potato chips are common parts of to children's menus fast in fast food restaurant, over the past35 years ; these familiar food contain high levels of toxic and carcinogenic by products not found in the uncooked foods **(Mitka, 2002, Madbouly,2006)**. Acrylamide can be generated during the heating of specific foodstuffs as a result of Maillared reaction between amino acids and sugar **(Stadler,2002, Mottram,2002)**..The 64th Joint FAO/WHO Expert Committee on Food Additives concluded that an intake of 1 g/kg body weight/day of ACR could be taken to represent the average for the general population (**FHO/IPCS,2006**) .However ,infants and small children may be more highly exposed to ACR due to their lower body-weights and high consumption of snacks, so that their relative ACR intake is estimated to b 2 to 3-fold higher than in adults (**FHO/IPCS,2006**).The potential for exposure to ACR through human milk has been demonstrated in a study conducted with two women **(Soergel *et al.*, 2002).**

Other early studies demonstrated that ACR induces cumulative neurotoxicity linked to nerve terminal damage in the CNS and PNS where distal axon swelling and subsequent to be the hallmark degeneration were considered morphological features of this toxic axonopathy **(Miller and Spencer, 1985 and Lehning *et al.*, 1998).** At the molecular level, it has been postulated by **Carlson and Weaver, 1985** that covalent binding of ACR to CNS proteins may play an important role in ACR toxicity, resulting in inhibition of a number of enzymes and essential compounds.

Many previous studies on ACR induced toxicity during the developmental stages were conducted with the focus on behavioral endpoints ,but detailed assessment of changes in target organs tissues has been scarce. In the present study ,we thereby performed a histopathological assessment of the frontal cortex of brain of rat offspring maternally fed on fried potato chips and fried bread during the gestation and lactation period.

In the present study, to investigated the protective effects of the well-known antioxidant curcumin on ACR induced histological changes in brain.

Curcumin (diferuloylmethane) is a natural compound present in turmeric, a rhizome of the plant *Curcuma longa Lin* Plant material in the human diet contains a large number of natural compounds, which may be of benefit . In protecting the body. one of the plants with constituents reputed to possess antioxidant properties was curcumin . It is extensively used as a dietary spice and pigment in Asian cooking and also as an herbal medicine for inflammatory diseases. Curcumin is the principal curcuminoid found in turmeric and is generally considered as its most active constituent **(Duvoix *et al.*, 2005; Sharma *et al.*, 2005).** Turmeric exhibits anti-tumor, anti-inflammatory and anti-infectious activities with low toxicity **(Cohly *et al.*, 1998, Mathuria and Verma, 2008)**.) .Furthermore, the present study aims to evaluate the histological effects in the cerebral cortex of offsprings maternaly female rats fed on diet containing fried potato and bread and investigate the possible protective effect of curcumin .

In the previous literature regarding detailed histological change in acrylamide induced neurotoxicity is lacking. Thus the present study was aimed to investigate the histological changes in the cerebral cortex of offsprirings.

2. Materials and Methods

Experimental Animals

The present study was carried out on 80 mature virgin females and 26 fertile males of Wistar albino rats weighing 120 -150 g. were obtained from Hellwan Animal Breeding Farm, Ministry of Health, Cairo, Egypt and used for experimentation. Rats were housed in individual cages and maintained in a room with good ventilation at 23 ºC. The housing room was maintained on a 12:12 h light: dark cycle Standard diet composed of 20% casein, 15% corn oil, 55% corn starch, 5% salt mixture and 5% vitaminzed starch (Egyptian Company of Oils and Soap Kafr-Elzayat Egypt). Daily examination of virgin smear of each virgin female was carried out to determine the estrous cycle. Mating was induced by housing proestrous females with untreated male at the ratio of 3 females with 1 male for 12 hour between 8 P.M till 8 A.M. In the next morning, the presence of sperm in vaginal smear determined the zero day of gestation. During the experiment, the animal groups were fed with diets and water ad labium.

The doses

Female rats feed with varied concentrations potatoes chips, fried bread alone ,ancompinedat doses(15% ,30%) supplemented basil diet 6 weeks before gestation and 6 weeks during the gestation and lactation periods , offspring until reaching 3 weeks old from parturition. This doses is low if compared to the doses used by **(Hassan *et al.*, (2011)**, which was 50%.

Curcumin supplementation:

Powder curcumin was obtained from the market and mixed with basil diet at concentration of 2% and supplied for feeding during experimental period **(Young *et al.*, 2004).**animals were fed on diet containing 0.2g/100g curcumin powder.

The offspring rats were arranged into 14 groups each was composed of 5 pregnant rats as follows:

Control offspring rats fed basil diet(G1). *

Fried potato chips 15% for 3 months. (G2)*

*Fried bread 15% for 3 months. (G3)

*Mixture of fried potato and fried bread (7.5% + 7.5%) for 3 months(G4).

*Fried potato chips 30% for 3 months(G5).

*Fried bread 30% for 3 months.

*Fried potato and fried bread mixed at (15% + 15%) at 3 months.

The same previous groups were repeated with 2% curcumin.

The offspring rats aging 3 weeks, experimental groups were sacrificed , and. brain of offspring was removed, fixed in 10% formal saline, dehydrated, cleared and embedded in paraffin wax. Sections were cut at 5-7µ thickness and stained with haematoxylin and eosin.

3.Result:

Microscopic examination of sections of the cerebral cortex of the offspring of control rats showed the layer of the cerebral cortex, the molecular layer covered with piamater, the external granular, external pyramidal, internal granular, internal pyramidal and polymorphic layer (Fig.1).The molecular layer was thick and contained dense plexus of nerve fibers with few cells. Whereas, the external granular & external pyramidal contained numerous granular cells and pyramidal cells.

Several histophathological alterations were seen in the sections of cerebral cortex of the offspring of each group. Examination of sections of frontal cortex of offspring's maternally fed on fried potato (G1) showing some cells appeared with distorted deeply stain ,malformed in pia mater with loss of density in plexus nerve fibers and dilatation blood capillary in piamater with many necrotic cells fig (2). Cerebral cortex of group (3) showed rupture pia mater layer, with infiltrated inflammatory cells in molecular layer (Fig.3)

Inspected Cerebral cortex sections obtained from group(4) revealed dilated congestion blood vessels with fibrosis epithelial layer in pia- matter and . Loss of

density in plexus nerve fibers resulted to reduced nerve cells (Fig.4).

Different alterations in the architecture of cerebral cortex sections for group (5).The most prominent alterations in external granular such as most nuclei in external granular cell shrunken surrounded by spaces and dilated congested blood capillary in piamater and molecular layer with loss of density in plexus in molecular layer. Cerebral cortex sections of group (6) revealed necrosis in external granular neurocytes and some appeared shrunken pyknotic nuclei, these cells are surrounded by unstained areas (Fig.6).Group (7) sections of cerebral cortex showed that completely degenerative areas of cerebral tissue and enlargement of blood capillary and some necrosis cells are seen. Figure (8) related to the same group exhibited cells in external granular showing necrosis of cells, pyknotic nuclei, and unstained area surrounded some cells. The using of curcumen showing amolirative cerebral tissue, represented in fried potato (15%) fried bread (15%) groups: indicated the external granular cell appeared nearly normal, with moderat amolirative in group fed with mixed fried bread & potato (15%).

On the other side, the groups feds on fried potato (30%), fried bread (30%) Mixed fried bread & potato (30%), showed remarkable changes, represented necrotic cells& dilated blood capillary (12), inflammatory thicked in pia matter and loss of plexus (13), necrotic cells & dilated blood

The average number and the percentage of embryos of different groups are shown in Table (1),

the treated groups with low doses recorded decreasing in their percentage in G2,G3 and G4 with respect to the control group. However the treated groups with high doses recorded decreasing in their percentage in G5,G6 and G7 with respect to the control group and groups with low doses. Curcumin improved decreasing in the percentage especially group G11.

Table (1): Showing the average number and the percentage of embryos of different groups,

Group without curcromin			Group with curcromin		
Group	Average ±SD	Percentage	Group	Average ±SD	Percentage
G1	8.8 ± 0.8		G8	9.2 ± 0.8	5
G2	6.4 ± 0.5	-27	G9	6.2 ± 0.8	-30
G3	6.2 ±0.4	-30	G10	6.2 ± 0.8	-30
G4	6 ± 0.7	-32	G11	6.4 ± 1.1	-27
G5	4.6 ± 0.5	-48	G12	4.6 ±0.5	-48
G6	4 ± 0.7	-55	G13	4.8 ± 1.1	45
G7	4.4 ± 0.5	-50	G14	4.6 ± 1.1	-48

4. Discussion:

The literature contain little information concerning the possible histopathological effects of feeding of fried potato chips and fried bread on brain tissue of both pregnant rats and their offspring's ,that is why it was particularly chosen in the current work. The present investigation showed that the alterations in neurological cells were defined by very characteristic changes in the cerebral tissue of offsprings maternally feed with fried potato chips and fried bread including necrosis of several sings of constituent nerve cell .Variable degree of degeneration were noticed in the cell undergoing pyknosis and necrosis. Also , there were various vascular changes which including marked dilated, congested blood capilla ry with fibrosis epithelial layer. The present findings revealed that the brain is sensitive to the cytotoxicity of feeding on fried potatoes chips and fried bread during both gestation and lactation periods . Cell necrosis may be due to inhibition of the synthesis of DNA needed for growth and maturation of the cell (**Scott,1971**). Moreover, animals administration acrylamide orally or fed a diet high in fried foods **(Tarek ,2000)** had higher levels of hemoglobin DAN adduct compared to unexposed animals. It has been demonstrated that reproductive toxicity is not only induced by ACR, but also by its metabolite glycidamide (GA) (**Adler, 2000, Doerge ,2007).**

In addition, acryl amide binds to dietary proteins under intestinal conditions. Although acryl amide monomers readily diffuse through Caco-2 minelayers, acryl amide uptake from food in the human intestine may differ from these experimental conditions , acryl amide contains a reactive terminal double bond, which may interact with food ingredients, mainly proteins, DNA, and RNA . we concider that acryl amide is most likely bound covalently to glutathione via Micheal addition of cysteine residues to yhe reactive terminal double bond ,However .also a binding to the primary amino group cannot be excluded . **(Godin, *et al.,* 2002).**

This suggests that acrylamide may occur during heating of these foods at high temperatures. Many studes observation of acrylamide formation in starchy foods as a result of heating at higher than 120 ^{0}C revealed the results that temperatures higher than 100 ^{0}C is enough for acrylamide formation , **(Stadler,2002,**

Mottram,2002); Yaylatan, and Stadler, 2005,WeiBhaar, and Gutsche,2002).

The studies performed in order to understand how acrylamide is formed in fried or roasted foods showed it occurs a result of Maillard Reaction between carbonyl group of reduced sugars (glucose, factose) during treatment with heat and amino group of amino acids especially aspagrine amino acid **(Stadler,2002, Mottram ,2002),**ACR occurs at medium level (5-50 µg/kg) as a result of cooking foods rich in protein and at higher levels (150-40000µg/kg) as a result of cooking foods rich in carbohydrate such as potatoes and cereals**,(Mendel, 2003.).** Asparagines' constitutes 14% of total free amino acid in wheat flour,18% of total free amino acid in ray, and 40% of total amino acid content of potatoes used in production of potato chips is asparagine **(Martin, and Ames, 2001.)** .

The observation recorded in the present work that damage in cerebral cortex of brain rats , mightily reflect and support the toxic of acrylamide formed during cooking of vegetable foods such as potatoes and cereals on nervous tissues.

The obtained result may be attributed to the increased level of ACR in the blood of treated mother as well as in the umbilical cord blood of neonates as a result of its higher affinity of forming N-terminal haemoglobin adducts . In view of the shorter life spam of neonatal erythrocytes and the lower body weight of newborn infants ,the relative internal dose of ACR adducts in neonates (in microgram's /Kg body weight) must be assumed to be at least equal to that of the mother .Because of the high cell-replication rates during fetus development, trans-placental exposure of neonates to ACR might raise concerns **(Schettgen *et al.,* 2004)**. It has been suggested that ACR manifested toxicity principally toward growth and development **(Garey *et al.,* 2005, Wang *et al.,* 2010). FHO/IPCS, (2006)** reported that toxicity studies of in ACR have hitherto mainly been performed using adult animals to mimic occupational exposure ,the dada for effects during fetal, infantile and pubertal periods are rather limited Therefore ,it is important for risk assessment of ACR exposure in human to evaluate toxicity taking into account physiological differences between adults and fetuses infants that might influence sensitivit. It is a evident that ACR is a developmental toxicant in rodents, because suppression of offspring body weight results from maternal exposure **(Garey *et al.,*2005).**

Soergel *et al.* (2002) found that from 10 to 50% of dietary ACR in pregnant women was transferred via blood through the placenta to the fetus. Breast milk was found to contain up to 18.8/mg/L of ACR. Because water soluble ACR can pass both placental and blood brain barriers, the authors suggested that to protect fetuses' pregnant women should not consume high-ACR food .

Park, *et al.* (2010) found that elevated intracellular levels of reactive oxygen species were involved in ACR-mediated cytotoxicity. Interestingly, the administration of ACR to young mice resulted in a significant decrease in the number of newly generated cells in the dentate gyrus of the hippocampus, suggesting an impairment of adult neurogenesis. These results suggest that ACR's deleterious effects on the central nervous system are due to the death of neural progenitor cells and impaired adult neurogenesis. There is evedince that ACR may affecet the covalent binding of ACR to CNS proteins may play an important role in ACR toxicity, resulting in inhibition of a number of enzymes and essential compounds by **Carlson and Weaver, 1985 ,** More recent studies demonstrated that this presynaptic toxicity appears to be mediated by the formation of sulfhydryl adducts on the cysteine residues of many proteins **(Barber & LoPachin, 2004 and LoPachin *et al.,* 2007) .** Quantitative analyse of whole-brain synaptosomes isolated from ACR intoxicated rats revealed an accumulation of the cysteine adduct, S-(2-carboxyethyl)-cysteine (CEC) that was closely correlated to the development of neurotoxicity **(Barber and LoPachin, 2004) ,**also it has been reported to induce varieties of symptoms in both the central and peripheral nervous systems**(LoPachin, 2004) .**

The obtained results are in agreement with many investigators who studied the neurotoxicity of ACR. **Edwards *et al* .(1991)** reported that the manifestations of ACR intoxication was closely similar in human and experimental animals and were in the form of swollen axons and or decrease in numbers of large axons diameter, **Takahashi *et al.* (2008)** obtained similar results after studying the effect of ACR on rat offspring. In vivo and in vitro chronic treatment of rats with ACR was found to produce a substrate-dependent, toxicologically specific inhibition of brain mitochondrial respiration. This inhibition of mitochondrial energy production might play a role in the neurotoxin mechanisms of action for ACR **(Medrano and LoPachin, 1989).**Following administration ACR exposure was found to be linked to nerve terminal damage in the central nervous system and peripheral nervous system (**Lehning *et al.,* 2003 and LoPachin *et al.,* 2003).**

It was demonstrated that ACR can produce neurological toxicity in the absence of axonopathy; i.e. whereas equivalent neurotoxicity can be induced by intoxication over a wide range of daily dose-rates, axon degeneration in PNS and CNS occurred only during long-term exposure to lower ACR dose-rates **(LoPachin *et al.,* 2002; Lehning *et al.,* 2003**).

Recently, **Allam *et al.* (2011)** reported that prenatal and perinatal ACR disrupts the biochemical machinery, cause oxidative stress and induce structural

changes in the developing rat cerebellum..**Hassan *et al.* (2011)** reported that the feeding of fried potato chips during gestation caused histopathologecal changes on the development of retina in albino rat. **Saker,*et al.*(2011)** found the same results by using acrylamid, which suppoted the currnt study. This changes may be due the presence of acrylamide or its metabolite.

Recently, it was also reported that antioxidants could exert their beneficial effects by abstracting reactive free electrons from free radical intermediate postulated to be formed in the Maillard reaction **(Friedman, and Levin, 2008).**Curcumim which is a cheap available natural plant could a meliorate changes in brain . Antioxidants are the frontline of defense against free radicals **(Osawa and Kato, 2005)**. The antioxidant mechanism of curcumin is due to its specific conjugated structure of two methoxylated phenols and an enol form of diketone.

This structure is responsible for free radical trapping ability as a chain breaking antioxidant **(Masuda et al.,2001).** The ability of curcumin to chelate the toxic metals was shown by **Daniel *et al.* (2004).** They found that curcumin significantly protects against lipid peroxidation induced by heavy metals, lead and cadmium in the rat brain homogenate, as well as reduces lead-induced structural damage in the hippocampus. Curcumin prevents free radical generation by competing with peroxidant metals for cell binding sites, which decrease the possibility of free radical formation or by maintaining the activities of antioxidant enzymes like SOD and catalase (**Reddy and Lokesh, 1992). Huang *et al.*(2008)** reported that a single dose of curcumin (20 or 40 mg/kg, intraperitoneally) was effective in inhibiting the increase in glutamate level in the hypothalamus during lipopolysaccharide - induced systemic inflammation in rabbits.

Oxidative stress has been proven to be involved in mutation, chromosome aberration, tumor promotion, and cancer development and repeatedly addressed as an important mechanism of indirect genotoxicity **(Spit, *et al.*, 2002)**.

In principle, chemicals that give rise to excess ROS production and lipid peroxidation will cause different types of toxicity, including genotoxicity and cell death. These adverse effects can be suppressed by antioxidants, which can eliminate ROS **(Weisburger,2001)**. Curcumin, a polyphenol derived from the herbal remedy and dietary spice, turmeric, is well known for its antioxidant properties, because it is able to suppress the generation of ROS and decrease lipid peroxidation **(Chan, 2005)**, The present study revealed that slightly improvement in cerebral cortex alteration caused by acrylamide, this is may be its attributed to its antioxidant and free radical scavenging activities.

In addition, **Chen *et al.* ,(2010)** reported that a single intraperitoneal injection of curcumin (20 mg/kg) attenuated airway hyperreactivity induced by ischemia-reperfusion of the pancreas in rats.

Conclusion

Curcumin could prevent neurotoxicity of ARC in the rat's brain. If Hyperhomocysteinemia is one of the pathological reasons for neurodegenerative disorders such as sporadic AD or Parkinson's disease, curcumin may be an effective prophylactic agent in the prevention of oxidative stress by ACR. Furthermore, data of this study suggest that curcumin's mechanism for protection of the brain against the toxicity of ACR may be inhibition of brain lipid peroxidation and improvement of learning and memory deficits in rats. Further studies are required to reveal the exact mechanism of ACR in cell death process (apoptosis or necrosis) and the neuroprotective properties of curcumin must be studied in more detail. Curcumim which is a cheap available natural plant could a meliorate changes in brain.

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7/1/2012