Adverse Outcomes of Repeated Chlorpyrifos- Ethyl and Methyl Exposure in Rats: The Ameliorating Role of N-Acetylcysteine

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ABSTRACT

The ameliorating effect of 150 mg/kg b.w. of N-acetylcysteine (NAC) against the oral administration of 7.88 (1/25 LD_{50}) or 202.07 (1/10 LD_{50}) mg/kg/day for 14 days of chlorpyrifos- ethyl (CPF-E) and chlorpyrifos-methyl (CPF-M), respectively, was investigated using neurobehavioral and biochemical markers for this toxicity. Neurobehavioral tests; open field test (OFT), hole-board test (HBT), light/dark box test (LDBT) and elevated plus maze (EPM) showed increase frequency of exploration, low level of anxiety and locomotor in rats treated with either CPE-E or CPF-M, while the co-administration of NAC to treated rats attenuated neurobehavioral parameters. Biomarkers such as acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), paraoxonase (PON) and adenosine 5'-triphosphatase, (ATP-ase) showed declining in their activities, while calcium (Ca^{+2}) levels in brain were increased. However, the administration of NAC following the intoxification of CPF-E or CPF-M attenuated the values of these biomarkers. It can be concluded that NAC can be used to ameliorate the toxicity of certain organophosphorus compounds such as CPF-E and CPF-M and considered it as a choice for the prevention and treatment of either CPF-E or CPF-M -induced toxicity.

Keywords:- Chlorpyrifos, Rat, Neurobehavioral, Biochemical, N-acetylcysteine, Attenuation.

INTRODUCTION

Organophosphorus compounds (OPs) are the most extensively used group of pesticides to control pests in agriculture and public health. The OPs exert their toxic effects by inhibiting acetylcholinesterase (AChE) leading to the accumulation of acetylcholine (ACh) at synapses and neuromuscular junctions (Franjesevic *et al.,* 2019), followed by hyperactivation of the receptors resulting in neurological dysfunctions and firing of neurons and finally death (Mishra *et al.,* 2015). Chlorpyrifos ethyl (CPF-E) and chlorpyrifos methyl (CPF-M) are organophosphorus compounds that widely used to control of Coleoptera, Diptera, Homoptera and Lepidoptera in soil or on foliage in many crops and also employed in disease vector control programs (Tomlin, 2002). The exposure to either CPF-E or CPF-M results in a variety of cellular alterations such as reduction of synaptogenesis, abnormal cell differentiation, problems in gene transcription and DNA synthesis, modifications of the expression of transcription factors, widening of the DNA grooves and destruction of the hydrated layer, which enhance DNA degradation, alteration of phosphorylation of Ca^{+2}/cAMP response element binding protein, and alterations in signaling of adenylyl cyclase (Slotkin, 2004; Braquenier *et al.,* 2010). Also, Anxiety-like behavior and emotional disturbances were commonly reported following exposure to OPs that attributed to the inhibition of AChE enzyme and accumulation of acetylcholine, ACh (Ahmed *et al.,* 2013).Therefore, neurobehavioral examinations of the nervous system are complementary components of basic research and toxicity testing of environmental chemicals such as Ops because behavior is the integrated sum of activities mediated by the nervous system, and functional tests used for neurotoxicity testing (Moser, 2011).

N-acetylcysteine (NAC) is a precursor to the amino acid L-cysteine and consequently the antioxidant glutathione (GSH) (Pieralisi *et al.,* 2016) and most notably found in plants of the Allium species, especially in the onion (Diniz *et al.,* 2006). It is a small molecule containing cysteinyl thiol group which is converted into cysteine inside body, and increases glutathione (GSH) production which has antioxidant properties and can scavenge reactive oxygen species, ROS (Balahoroğlu *et al.,* 2008). NAC is also used in toxicology for the elimination of certain metals through chelation which is directly related to the –SH groups exist in its structure (Abu El-Saad and Elgerbed, 2010). Unlike GSH itself, NAC has better oral and topical bioavailability (Kang *et al.,* 2003; Schmitt *et al.,* 2015) and commercially accessible since long-time ago (Youssef *et al.,* 2006). It has been used as a beneficial drug treatment for some disorders such as polycystic ovary syndrome patients with clomiphene citrate resistance, preterm birth, acetaminophen toxicity, chronic bronchitis, ulcerative colitis, liver cancer, muscle performance, hemodialysis, asthma, Alzheimer and Parkinson (Stey *et al.,* 2000; Amin *et al.,* 2008; Crowell *et al.,* 2008; Millea, 2009;

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Shahin, *et al.,* 2009; Sekhon *et al.,* 2010; Mokhtari *et al.,* 2017).

The present study was carried out to assess the effects of CPF-E and CPF-M in rats using different tools such as biochemical and neurobehavioral tests. The biochemical tests included acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), paraoxonase (PON), adenosine 5'-triphosphatase, (ATP-ase) and calcium (Ca^{+2}), while the neurobehavioural tests included open field test (OFT), hole-board test (HBT), light/dark box test (LDBT) and elevated plus maze (EPM). Also, the purpose of this study was to ascertain whether NAC administration could attenuate the neurobeavoiral and biochemical insults induced by CPF-E and CPF-M in the male rats.

MATERIALS AND METHODS

2.1. Animals and treatment

Healthy adult male Wistar Albino rats weighing 180–200 gm (6-8 weeks old) were obtained from the animal house in Institute of Graduate Studies and Research, Alexandria University, Egypt. Animals were randomly housed in plastic cages at temperature of 25±2 ◦C, 50-70 % humidity and 12 h light: 12 h dark cycle. The animals were allowed to acclimatize for 2 weeks before starting the study.

2.2. Chemicals

Chlorpyrifos-ethyl(O,O-diethylO-(3,5,6-trichloro-2-pyridinyl) phosphorothioate) and chlorpyrifos-methyl (O,O-dimethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate) with purity of 97% were obtained from Agro-chem Company (Egypt), while N-acetycysteine (600 mg as effervescent instant) was obtained from Sedico Pharmaceuticals Company, Egypt; other chemicals used in this study were of the highest purified grades available purchased from Sigma and Merck Chemical Companies.

2.3. Toxicity studies

The median fatal doses (LD_{50} Values) and their confidence limits of CPF-E and CPF-M on rats were calculated according to Weil (1952) by administrating different doses of CPF-E and CPF-M in corn oil directly into the stomach of mice via needle oral gavage (5 rats for each dose). The number of dead animals and symptoms of acute toxicity in the treated groups were recorded.

2.4. Experiment design

Animals were randomly divided into 7 groups (8 rats per each). Animals in each group were received a single daily dose from either CPF-E, CPF-M and NAC alone or NAC combined with either CPF-E or CPF-M for 14 consecutive days. The first and second groups were treated orally with distilled water and corn oil, respectively and kept as negative controls. The third and fourth groups were orally treated with 7.88 and 202.07 mg/kg b.w. of CPF-E and CPF-M in corn oil, respectively for 14 days. The fifth, six and seven groups were orally treated for 14 days with 150 mg/kg b.w. of NAC alone in distilled water, 7.88 mg/kg of CPF-E plus 150 mg/kg of NAC and 202.07 mg/kg of CPF-M plus 150 mg/kg of NAC, respectively. The volume used for oral administration (gavage) was standardized, to be 1ml/100 gm of rat weight. The usual recommended loading dose of NAC that used in the present study was selected on the basis of previously published reports and the oral administration is the preferred route for NAC therapy (Cankayali *et al.,* 2005; Oksay *et al.,* 2013).

All experimental procedures were carried out according to the local committee for care and use of laboratory animals. The experimental protocols were reviewed and approved by the Animal Care Committee of the University of Alexandria, Egypt.

2.5. Neurobehavioral Tests

Neurobehavioral assays such as open field test (OFT), hole-board test (HBT), light/dark box test (LDBT) and elevated plus maze (EPM) apparatus tests evaluated at the end of the experiment to investigate the integrated sum of activities mediated by the nervous system of rats following treatment with the tested compounds. OFT and EPM tests were carried out according to (Brown *et al.,* 1999)**.** OFT was scored as line crossing frequency, center square entries frequency, rearing frequency and grooming, while EPM scored as open arm entries, open arm time, closed arm entries and the letter is used as an evaluation of locomotor activity in addition to closed arm time. HBT was investigated and scored according to (Brown and Nemes, 2008) as following: head-dip, edge sniffing and rearing, while LDBT was carried out according to (Arrant *et al.,* 2013) and behaviors were scored as following, movements into the light compartment, movements into the dark compartment as well the time in the light or dark compartment.

2.6. Biochemical Assays

Twenty four hours after the last treatment, animals were dissected and brain tissue was immediately removed, washed with ice-cold saline and homogenized (10% w/v) in phosphate buffer (0.1 M, pH 8) for determination of AChE and BuChE activities, in 1.15% ice-cold KCl for determination of PON activity, in 0.9% cold saline for determination of Ca^{+2} level and in TSE Buffer (10 mM Tris, 0.32 M sucrose and 0.001 M EDTA, pH 7.5) for determination of ATP-ase activity. Homogenate was centrifuged at 5000 xg for 30 min at 4 ^{o}C using (MSE Hi-Spin 21 centrifuge). The resultant supernatant was used for biochemical assays. AChE and BuChE activities were measured spectrophotometrically

according to Ellman *et al.* (1961) using acetyl- and butryl- thiocholine iodide as substrates, respectively. Paraoxanase (PON), adenosine triphosphatase (ATP-ase) and calcium (Ca^{+2}) level were measured according to Furlong *et al.* (1988); Koch, (1969); Kessler and Wolfman (1964), respectively. The total protein content was determined by the method of Lowry *et al.* (1951) using bovine serum albumin as the standard.

2.7. Statistical data analysis

Data were analyzed by analysis of variance (ANOVA) using Costat version, 6.4 software. LSD multiple comparisons test was used to identify differences between groups if means were considered significantly different at $P < 0.05$.

RESULTS AND DISCUSSION

3.1. Toxicity of CPF-E and CPF-M in male rats

The LD_{50} values of CPF-E and CPF-M are 197.04 and 2020.73 mg/kg b.w., respectively and the ethyl analogue is more toxic than and the methyl one by 10.26 folds (Table 1). The *in vivo* effect of sub-lethal doses of 7.88 and 202.07 mg/kg b.w./day of CPF-E and CPF-M for 14 days on some neurobehavioral parameters and biomarkers are illustrated in the following data.

3.2. Neurobehavioral effects of CPF-E and CPF-M and role of NAC

OFT is a tool to obtain some parameters such as line square frequency, center square frequency and grooming (Bagi *et al.,* 2017). The present results illustrated that there were non-significant differences between animals treated with distillated water or corn oil regarding either the neurobehavioral parameters or biochemical analysis. The effects of CPF-E and CPF-M on locomotors and exploratory activities, as well as grooming behavior in the open field revealed that CPF-E and CPF-M- exposed rats had a significant decrease in all tested parameters than non-exposed rats (Table 2). Also, the results showed that CPF-E in the most cases was more potent to change these parameters than CPF-M. Reduction in locomotor and exploratory activities may derive from reduced excitability of the central nervous system due likely to central depression (Okoli *et al.,* 2010). However, the supplementation of NAC to rats treated either with CPF-E or CPF-M attenuated the reduction in locomotors and exploratory activities in addition to grooming behavior. Also, rats treated with NAC and CPF-M were more recovered than rats treated with CPF-E and NAC. Results of the present work agree with that found by N'Go *et al.* (2013) who reported that treatment with malathion revealed significant decline of spontaneous locomotors activities of rats with high decrease in number of squares crossed. Also, CPF-E in the drinking water showed significant decrease in locomotors activity at the age of 8 days of chicks (Al-Baggou, 2014).

Repeated head dipping in HBT may reflect either the factors activity and/ or exploration (File and Wardill, 1975). The poking nose into a hole is a normal behavior of the rat indicating curiosity and was utilized as a measure of exploratory behavior (Terçariol and Godinho, 2011). The present study investigated the potential effect of NAC supplementation in rats subjected either to CPF-E or CPF- M intoxication (Table 2). Animals treated with CPF-E and CPF- M had a significant increase in the number of head-dip and rearing, while head-sniffing frequency was significantly decreased compared to control animals. However, administration of NAC combined with CPF-E or CPF-M ameliorated the significant changes in parameters of HBT compared to CPF-E and CPF- M groups. These findings are in agreement with those reported by (Gómez-Giménez *et al.,* 2018) who showed that the treatment with 0.5 mg/kg/day of endosulfan for 5 days in male rats caused a significant decrease in number of head dipping in the HBT compared to control group. Arrant *et al.* (2013) stated that time in the light compartment and latency to emerge into the light compartment can be used as measures of anxiety-like behavior, while time in the dark compartment is considered as indices of locomotor activity. The results of CPF-E or CPF- M exposure on dark/light box and the effect of NAC are illustrated in (Table 2).

Table 1. Toxicity of CPF-E and CPF-M in male rats

Compounds	LD_{50} (mg/kg b.w.)	M.W	95% Confidence limits		◊ MLD_{50}
			Lower	Upper	
Chlorpyrifos-ethyl (CPF-E)	197.04	350.6	134.28	289.13	0.56
Chlorpyrifos-methyl (CPF-M)	2020.73	322.5	1249.67	3267.53	6.27

◊ MLD_{50} means molar median lethal doses.
MLD_{50} = LD_{50} value / molecular weight (m.w) of the compound

Table 2: *In vivo* effect of CPF-E, CPF-M, NAC and/or their combination on neurobehavioral activities of male rats after 14 daily doses

Treatment	Open field test				Elevated plus maze				Light/dark box test				Hole-board test		
	Locomotor activity		Exploratory activity												
	Line crossing	Center square entries	Rearing	Grooming	Open arm time	Close arm time	Open arm entry	Close arm entry	Light time	Dark time	Light entry	Dark entry	Head dips	Head sniffing	Rearing
Control	12.38± 0.65 a	1.05± 0.42 a	5.50± 0.78 a	1.55± 0.37 a	47.35± 0.83c	43.83± 1.05 c	41.74± 5.80 bc	54.09± 9.61b	31.42± 1.47 d	64.29± 1.31 b	47.52± 6.99 a	10.76± 2.01 c	11.46± 1.14 bc	2.71± 0.88 a	5.33± 0.87 c
CPF-E	9.80± 0.74 c	0.78± 0.31 abc	2.30± 0.65 e	0.30± 0.15 cd	27.25± 1.07e	59.75± 0.96 a	38.66± 7.26 c	61.34± 7.24 a	39.38± 1.08 b	59.79± 0.97 c	45.75± 3.65 a	14.08± 0.71 a	14.67± 1.71 a	1.13± 0.69 b	9.38± 1.60 a
CPF-M	10.88± 1.23 b	0.83± 0.23 abc	3.20± 0.59 d	0.23± 0.07 d	34.04 ±1.26d	57.13± 0.92 b	47.25± 3.98 b	52.75± 3.98 b	48.46± 1.66 a	48.29± 1.33 e	43.72± 7.87 a	10.04± 1.54 c	14.17± 1.89 a	1.38± 0.65 b	7.50± 1.15 b
NAC	12.00± 1.00 a	1.03± 0.29 ab	4.70± 0.61 b	1.08± 0.24 b	47.81± 1.06 c	40.25± 0.75 e	73.08 ±6.57 a	26.92± 6.57 c	29.21± 1.75 e	67.08± 2.10 a	48.68± 4.35 a	11.63± 1.43 bc	10.21± 1.48 c	1.17± 0.59 b	5.79± 1.18 c
CPF-E+NAC	10.75± 0.85 b	0.73± 0.32 bc	4.03± 0.45 c	0.25± 0.09 d	51.62± 1.29 b	41.38± 1.10 d	67.39 ±8.13 a	32.61± 8.10 c	37.50± 1.41 c	59.75± 1.38 c	47.21± 6.39 a	13.62± 1.82 a	14.13± 1.61 a	2.42± 0.58 a	6.08± 1.19 c
CPF-M+NAC	12.75± 0.72 a	0.65± 0.30 c	4.25± 0.51 bc	0.50± 0.21 c	55.12± 1.19 a	41.13± 0.91de	70.42 ±5.70 a	29.58± 5.72 c	39.96± 0.74 b	56.75± 2.05 d	45.57± 6.41 a	12.53± 1.67 ab	12.25± 1.18 b	2.46± 0.71 a	5.67± 1.13 c

Results are expressed as Mean ± SD.

Values in the same column with different small letters are significantly differ ($p<0.05$).

At the end of experiment, the mean percent number of light entry was decreased in CPF-E and CPF-M- treated rats, while the mean percent number of dark entry was decreased in CPF-M group but in CPF-E was increased. On the other hand, the mean of percent number of light time was increased in CPF-E and CPF-M- exposed rats and vice versa in the mean percent number of dark time. NAC treatment in combined with CPF-E or CPF-M attenuated the significant alterations in these parameters when compared to CPF-E and CPF- M groups. The present results are in consistent with many studies (Grabovska and Salyha, 2015), where 15 mg/kg/day of CPF-E induced in rats significant neurobehavioral changes regarding the number of peeks out of the hole between dark and light compartment. Braquenier *et al.* (2010) showed that the oral administration of CPF-E at doses 0.2, 1, or 5 mg/kg/ day increased the anxiety level in rats with a maximum effect at 1 mg/kg/day in light/dark box test. Venerosi *et al.* (2010) determined the the light /dark exploration in CD-1 mice exposed to CPF-E at dose of 6 mg/kg b.w. for 14 – 17 of gestational days. They found that the treatment with CPF-E increased anxiety levels in female mice and the lower latency to enter in the dark compartment. The total entries and time spent in both open and closed arms using EPM provide a measure of anxiety or fear-induced inhibition of normal exploratory activity (Terçariol and Godinho, 2011). The present experiment investigated neurobehavioral changes due CPF-E and CPF- M treatments on elevated EPM (Table 2). The percentage of time spent in open arm showed a significantly decrease than control values, the percentage of time spent in close arm revealed a significantly increase compared to control after two weeks of treatment with CPF-E or CPF-M. The second measure of anxiety level was the proportion of entries in the open or close arms. The percentage of open arm entries was lower in CPF-E and vice versa in CPF-M-treated group where, an increase in open arm activity (duration and/or entries) reflects anti-anxiety behavior (Walf and Frye, 2007). Also, the results showed that the percentages close arm entries were higher in CPF-E and vice versa in CPF-M-treated group. A decrease time and entries into the open arms related to increased anxiety in the EPM and vice versa were observed (Riebe and Wotjak, 2012). However, similar observations were found by Sánchez-Amate *et al.* (2001), who reported that, CPF-E at doses 166 and 250 mg/kg, s.c induced neurobehavioral changes in male rats included significant decrease in the percentage of time spent and percentage of entries into open arms in the EPM and these changes were dose-dependent. However, López-Crespo *et al.* (2009) found an increase in the percentage of open-arm entries and time when rats treated with CPF-E. Also, the time spent in closed arms was significantly higher in the malathion treated animals, while the percentage of open arm entries was slightly smaller in the exposed group, whereas the percentage of closed arm entries was slightly higher compared to control group (Hashjin *et al.,* 2013). In the present experiment, the supplementation of NAC to rat treated either with CPF-E or CPF-M resulted in mitigating the significant alteration in the percentage of close/open arm entries and times.

3.3. Biochemical studies

3.3.1. Effect on AChE

AChE is mainly found at neuromuscular junctions and cholinergic synapses in the central nervous system to terminate synaptic transmission, preventing continuous nerve firings at nerve endings (Blotnick-Rubin and Anglister, 2018). The inhibition of AChE leads to accumulation of the neurotransmitter ACh in neuronal synapses that due to prolonged over-stimulation of cholinergic receptors and resulting cholinergic toxicity. Therefore, AChE is considered as a specific molecular target of OPs and recognized as biological marker of pesticide poisoning (Lionetto *et al.,* 2013). The present study investigated the effect of NAC supplementation to rat subjected to CPF-E or CPF-M intoxication (Table 3). Brain AChE activity showed significant decreases ($P<0.05$) by 43.94% and 30.29% after 14 doses of either CPF-E or CPF-M, respectively. CPF-E was more potent to inhibit AChE than CPF-M. The present results confirmed the previous reports of Aly and El-Gendy (2015) and Fereidounni and Dhawan (2018), who reported that parathion and chlorpyrifos induced significant decreases in the activities of brain AChE of rabbits and rats, and the toxicological effects of CPF-E are pounced than CPF-M with increasing period (El-Tawil, 2014). Repeated doses of 6 mg/kg b.w. for 28 days of CPF-E caused prolonged inhibition of AChE activities in blood and brain tissues (Barski and Spodniewska, 2018), while, powdered feed containing 50 ppm of CPF-M caused significant reduction in serum AChE activity in rats when treated for 65 days (Zidan, 2009). On the contrary, Kopjar *et al.* (2018) found that treatment of male Wistar rats with 0.010 mg/kg b.w./day of CPF-E for 4 weeks showed non- significant differences in AChE activity in plasma and brain tissue compared to control values. In the present study, the co-administration of NAC to rats treated with either CPF-E or CPF-M increased brain AChE activity by 25.74 and 12.24% in rats, respectively. Shadnia et al. (2007) demonstrated that administration of NAC in male rats treated subchronicaly with diazinon have useful effects in the reactivation of AChE and reversed the oxidative stress damage. Pena-Llopis *et al.* (2003) the effectiveness of NAC as a protective agent against

dichlorvos in european eel (*Anguilla Anguilla*) at concentrate 0.17 mg/l for 96 hrs. They observed NAC concentration ameliorated muscular GSH depletion and the inhibition of brain AChE activity. Also, the treatment rats with malathion in the presence of NAC resulted in significant attenuation in liver AChE activity (Aboubakr *et al.,* 2019). Improvement of AChE activity of rats may be attributed to the ability of NAC to facilitate rapid elimination of toxic malathion metabolites from the body and diminishing its action (Lasram *et al.,* 2014).

3.3.2. Effect on BuChE

BuChE is a major human cholinesterase, (also known as pseudo cholinesterase and nonspecific cholinesterase), is found in plasma as well as liver and other tissues (Singh and Dixit, 2014). It hydrolyzed the serine that catalyses the hydrolysis of esters of choline, including butyrylcholine, succinylcholine and acetylcholine (Darvesh et al., 2003). Data in Table (3) show the activity of brain BuChE following treatment with CPF-E, CPF-M or their combination with NAC. The enzyme activity revealed significant inhibition ($P<0.05$) by 31.97 and 27.13% after 14 days of CPF-E and CPFM treatment, respectively and CPF-E still was more potent to inhibit BuChE than CPF-M. These results are in coincide with results of many investigators who indicated that dichlorvos (Kose *et al.,* 2010), methamidophos (Araoud *et al.,* 2016) and malathion (Abdel-Salam *et al.,* 2018) exhibited significant inhibition of BuChE activity of rats. However, the supplementation of NAC to either CPF-E or CPF-M treated rats attenuated brain BuChE activity, where the % of inhibition decreased from 31.97% to 22.10% and from 27.13 to 13.30%, respectively, 14 days after treatment. John *et al.* (2019) demonstrated that when male mice exposed to phosphorofluoridate (DFP) and then to NAC in the presence of atropine and 2-PAM, the activity of plasma BuChE was restored to the normal values.

3.3.3. Effect on PON

PON is a calcium-dependent esterase that hydrolyzes the active metabolites (oxons) of several OPs including parathion, chlorpyrifos and diazinon (Abdel-Salam *et al.,* 2016). PON plays a role in inflammation and oxidative stress (Aviram and Rosenblat, 2004). The effects of NAC on brain PON activities of male rats treated with CPF-E and CPF-M for 14 consecutive days are illustrated in Table (3). Brain PON activities declined by 10.85 and 14.73% in rats treated with CPF-E or CPF-M, respectively. These findings are in parallel with previous studies, where rats treated with malathion and methamidophos showed significant inhibition in the activities of PON in different organs (Abdel-Salam *et al.,* 2018; Araoud *et al.,* 2016). On the contrary, when rats treated with dichlorvos, significant increase in serum PON activity was recorded (Kose *et al.,* 2010). In the present study NAC administration to CPF-E or CPF-M treated rats, brain PON activities were slightly restored by 4.35% and 8.18%, respectively. When rainbow trout treated with cypermethrin at dose of 2.05×10^{-3} mg/L for 96 hours then treated with NAC, PON activity in the blood was ameliorated (Uçar *et al.,* 2019).

3.3.4. Effect on ATP-ase

Na^+-/K^+-ATP-ase is identified as a key transmembrane enzyme of the central nervous system vital for regulation of intracellular pH, cell volume and calcium concentration. Excessive reduction in Na^+/K^+ ATP-ase activity may have been associated with neuronal damage caused by excessive reactive oxygen spices (ROS) generated (Adefegha *et al.,* 2016). The decrease in Na^+/K^+ATP-ase activity causes energy deficiency, which is commonly observed in neurodegenerative diseases (Kinoshita *et al.,* 2016). The present study investigated the role of NAC supplementation in rat subjected to CPF-E or CPF-M intoxication (Table 3). Brain ATP-ase activity showed significant decrease ($P<0.05$) by 14.66 and 17.03% after 14 doses with CPF-E or CPF-M, respectively. The present results are in consistent with many studies, where CPF-E and parathion were found to inhibit brain ATP-ase of male Wistar rats (Mehta *et al.,* 2005) and New Zealand rabbits (Aly and El-Gendy, 2015). Also, the inhibition of ATP-ase activities in blood, brain and liver of male rats after daily exposed to anilofos were recorded (Hazarika and Sarkar, 2001). On the contrary, membrane bound ATP-ase of rats was not significantly influenced by malathion exposure (Bhatti *et al.,* 2013). However, the supplementation of NAC to treated rats with CPF-E or CPF-M resulted in slight recovery of ATP-ase activities by 3.52 and 9.47%, respectively. Kamboj *et al.* (2006) investigated the protective role of NAC (200 mg/kg b.w.) in attenuating the toxicity induced by carbofuran at a dose of 1 mg/kg b.w. in male rat brain for 28 days. It was found that NAC administration ameliorated the effects of carbofuran induced alterations in lipid composition and restoring the activity of Na^+-/K^+-ATP-ase and Ca^{2+}-ATP-ase to normal values.

Table 3: *In vivo* effect of CPF-E, CPF-M, NAC and/or their combination on brain AChE, BuChE, ATP-ase and PON activities and Ca^{+2} Level of male rats after 14 daily doses

Treatment	Brain Specific Activity				Brain Ca^{+2} Level (mg/gm tissue)
	AChE [1]	BuChE [2]	ATPase [3]	PON [4]	
Control	8.20 ± 0.56 a	44.90±0.62 a	154.28±2.25 a	1.29±0.02 a	57.34±0.35 e
CPF-E	4.59 ± 0.37 d	30.55±0.62 d	131.66±2.53 d	1.15±0.02 c	72.20±0.28 a
CPF-M	5.71 ± 0.35 c	32.72±0.54 c	128.01±1.71 e	1.10±0.02 d	63.53±0.36 c
NAC	8.58 ± 0.44 a	45.36±0.81 a	154.11±2.43 a	1.28±0.03 a	54.26±0.31 f
CPF-E+NAC	5.78 ± 0.38 c	37.30±0.72 b	136.30±3.22 c	1.20±0.01 b	67.21±0.43 b
CPF-M+NAC	6.41 ± 0.49 b	37.07±0.89 b	140.13±2.09 b	1.19±0.02 b	60.99±0.39 d

Results are expressed as Mean ± SD.
Values in the same column with different small letters are significantly differ ($p<0.05$).
[1] Activity is expressed as µmole acetylcholine iodide hydrolyzed /min/mg protein.
[2] Activity is expressed as µmole butyrylcholine iodide hydrolyzed /min/mg protein.
[3] Activity is expressed as µmole phosphorus inorganic liberated /min/mg protein.
[4] Activity is expressed as µmole paraoxon hydrolyzed /min/mg protein.

3.3.5. Effect on Ca^{+2}

Ca^{+2} homeostasis plays an important role in numerous cell functions, such as neuronal cell signaling, neuronal development and gene expression (Leclerc *et al.,* 2011). Therefore, any alternations in free intracellular Ca^{+2} reflects neurotoxic damage (Raheja and Gill, 2002). The effects of CPF-E and CPF-M on the Ca^{+2} levels of brain rats and the effect of NAC are illustrated in Table (3). The results revealed that Ca^{+2} levels in brain tissues exhibited significant increases ($P<0.05$) by 25.91and 10.80% in case of CPF-E and CPF-M, respectively, after 14 days of successive treatments. Based on the data obtained in this study, these findings are in agreement with that reported by many investigators who stated that OPs induced significant increase in the levels of intra-synaptosomal Ca^{+2} (Raheja and Gill, 2002; Lasram *et al.,* 2014). However, the supplementation of NAC to either CPF-E or CPF-M treated groups slightly restored the percentages of change of calcium by 6.90% and 4.00%, respectively. The accumulation of Ca^{+2} reveals development of distinct patterns of neurodegeneration associated with a variety of neuropathological conditions. Intracellular Ca^{+2} can be increased through many pathways such as increase in depolarization-induced Ca^{+2} uptake or failure of Ca^{+2} expelling system (Kaur and Gill, 2005).

CONCLUSION

In the present study, the role of NAC against the oral toxicity of 7.88 of CPF-E or 202.07 of CPF-M mg/kg/day for 14 days was investigated in male rats using neurobehavioral and biochemical markers. The usual recommended loading dose of 150 mg/kg NAC was used by oral administration as the preferred route for NAC therapy. Reduction in locomotor, exploratory activities, anxiety-like behavior and emotional disturbances were commonly reported following exposure to CPF-E or CPF-M may derive from reduced excitability of the central nervous system due likely to central depression and inhibition of AChE. Brain AChE activity revealed significant decreases by 14 days after treatment with CPF-E or CPF-M, and the ethyl analogue was more potent to inhibit AChE than the methyl one. Also, PON and Na^{+}-/K^{+}-ATP-ase showed excessive reduction which is commonly observed in neurodegenerative diseases. The present results revealed that Ca^{+2} levels in brain tissues exhibited significant increases when rats treated for 14 days with either CPF-E or CPF-M. Because Ca^{+2} homeostasis plays an important role in neuronal cell signaling and neuronal, therefore, any alternations in the levels of Ca^{+2} reflects neurotoxic damage of brain. However, the supplementation of NAC to rats treated either with CPF-E or CPF-M attenuated the reduction in neurobehavioral parameters and significantly restored the levels of tested biomarkers. It can be concluded that NAC can be used to ameliorate the toxicity of certain OPs such as CPF-E and CPF-M and considered it as a choice for the prevention and treatment of CPF-E or CPF-M induced toxicity.

Conflict of interest statement

No conflict of interest.

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الملخص العربي

التأثيرات الضارة جراء التعرض المتكرر لمركبى الكلوربيريفوس- إيثيل وميثايل فى الجرذان: الدور المخفف لمركب ن- أسيتايل سيستئين

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تم دراسة التأثير المخفف لمركب ن- أسيتايل سيستئين بجرعة قدرها ١٥٠ مجم/كجم ضد التأثير السام لمركبى الكلوربيريفوس- إيثايل والكلوربيريفوس- ميثايل عند معاملة ذكور الجرذان بجرعات فمية قدرها ٧,٨٨ و٢٠٢,٠٧ مجم/كجم، على التوالى لمدة ١٤ يوم وذلك بعد قياس بعض المؤشرات السلوكية العصبية والبيوكيميائية. أظهرت نتائج السلوك العصبي وجود زيادة فى نسبة الاستكشاف ومستوى منخفض للخوف والنشاط الحركى فى الجرذان المعاملة بكلا المركبين موضع الدراسة، وأن خلط مركب ن- أسيتايل سيستئين مع المركبين أدى إلى تخفيف التغيرات الحادثة في المؤشرات السلوكية العصبية. أيضاً أظهرت النتائج أن المعاملة بمركبي الكلوربيريفوس- إيثايل وميثايل أدى إلى تثبيط النشاط الأنزيمي لكل من الأسيتايل كولين إستريز، البيوتريل كولين إستريز، الباراأوكسينيز والانزيم المحلل للأدينوسين ثلاثي الفوسفات الموجودة بمخ الجرذان، بينما أدت المعاملة بالمركبين إلى حدوث زيادة معنوية فى مستوى الكالسيوم فى مخ الحيوانات المعاملة. من ناحية أخرى أدت المعاملة المشتركة لمركب ن- أسيتايل سيستئين مع المركبين أدى إلى تحسين قيم التغيرات الحادثة في المؤشرات البيوكيميائية.

ويمكن القول أن المعاملة بمركب ن- أسيتايل سيستئين قد أظهر تحسناً وتأثيراً علاجياً ضد التأثيرات السامة لمركبي الكلوربيريفوس- إيثايل والكلوربيريفوس- ميثايل وأن هذا المركب يمكن إستخدامه فى تخفيف السمية الناتجة عن بعض مركبات الفسفور العضوية مثل الكلوربيريفوس ايثايل والكلوربيريفوس- ميثايل ويعتبر إختياراً جيداً فى محاولة لمنع وتقليل حدة سمية المركبين موضع الدراسة.