

Quercetin, a Natural Flavonoid, Mitigates Fenthion Induced Locomotor Impairments and Brain Acetylcholinesterase Inhibition in Male Wistar Rat

Imed Eddine Bouhali, Hakima Tayaa and Abdelkrim Tahraoui

Applied Neuroendocrinology Laboratory, Department of Biology,
Faculty of Science, University Badji Mokhtar 23000, Annaba, Algeria

Abstract: Exposure to organophosphorus is thought to evoke behavioral and physical impairments. In our work exposure to fenthion, organophosphorus pesticide, during ten consecutive days in males Wistar rat altered locomotion, exploratory behavior and brain acetylcholinesterase activity. Besides, pretreatment with quercetin enhances these abnormalities. Notably, Quercetin intake mainly for workers having contact with OP seems to be beneficial to minimize negative outcomes.

Key words: Organophosphorus • Fenthion • Quercetin • Locomotion • Rat

INTRODUCTION

Organophosphate (OP) insecticides which have largely replaced the organochlorine compounds are one of the most widely used estimated to account for about 50% of all insecticides used globally [1]. OP inhibits acetylcholinesterase (AChE) activity which causes accumulation of acetylcholine at cholinergic synapses leading to increased activation of nicotinic and muscarinic receptors [2]. Poor working conditions and unawareness of the potential hazards of OP lead to intoxication that evokes a consistent pattern of physical and neurobehavioral symptoms such as depression, anxiety and cognitive impairments [3]. Workers exposed to pesticides have been reported to manifest physical symptoms, neurobehavioral deficits and emotional disorders [4, 5]. Fenthion [O, O-dimethyl-O-(4-methylmercapto-3-5 ethylphenyl)-phosphorothioate] is one of the most well known OP and is a moderately toxic product [2-6]. As other OP, fenthion has been found to be a potent inhibitor of rat behavior [7]. Many approach have been carried out in order to modulate neurotoxicity related OP [8], nevertheless, the need for a powerful strategy remain persistent. Recently, a substantial attention was paid to flavonoid as molecules with therapeutic opportunities and prominent pharmacological effectiveness, among these plant molecules; quercetin is being increasingly used in experimental studies [9]. Quercetin (3,5,7,3',4'-pentahydroxyflavone) is a polyphenolic flavonol molecule that occurs in many fruits

and vegetables such as onions, apples, berries, peanuts, soybeans, potatoes, broccoli, grapes, citrus fruits and tea [10,11]. Moreover, several experimental investigations showed the potential of quercetin against behavioral deficits in various animal models [12, 13]. In this, we aimed to investigate whether fenthion affects exploratory behavior and locomotor capacities in males Wistar rat, as well as, potentialities of quercetin was evaluated.

MATERIAL AND METHODS

Experimental Protocol: Twenty-eight (28) male Wistar rats obtained from Pasteur Institute (Algiers, Algeria) were housed in transparent cages at a constant temperature (23±1 °C) with a 12 h/12 h light/dark cycle (Lights on at 07:30 a.m.). Rats had access to standard rodents chow and tap water *ad libitum* and weighing 250 ±10 g at the beginning of the experiment. Rats were randomly divided to four equal groups: group C; control rats received orally corn oil (1ml/kg) and intraperitoneally saline solution NaCl 0.9% (1ml/kg); group Q; received 60 mg/kg of quercetin (Quercetin dihydrate, 98% purity powder; Sigma Aldrich Co., Steinheim, Germany) dissolved in 1ml/kg of corn oil ; Group 03: received 20 mg/kg of fenthion (Lebaycid) intraperitoneally dissolved in 1ml/kg of saline solution; Group 04 received quercetin 30 min before fenthion. The dose of fenthion was selected from Virginia [7]. The treatment lasted for 10 consecutive days, then, battery of behavioral testing was done.

Behavioral Test

Open Field Test: The open field (OF) can be considered as a non-conditioned anxiety test based on the creation of a conflict between the exploratory drive of the rat and its innate fear of exposure to an open area [14]. The OF test was performed to measure changes in exploratory behavior and emotionality. Briefly, the apparatus, as previously described [15] consist of a gray square (70 cm x 70 cm x 40 cm) divided into 16 equal squares that had been drawn in the floor of the arena. Each rat was placed in the arena individually and allowed to freely explore it for 5 min. Upon completing the task, the rat was removed from the arena by the experimenter and returned to the home cage. After each test, the apparatus was cleaned with an alcoholic solution followed by wet and dry paper towels to avoid transfer of olfactory cues between animals. Traveled distance and rearings were measured.

Elevated Plus-Maze Test: The elevated plus-maze (EPM) test is a widely used paradigm to investigate anxiety-related behavior in rats and general locomotor activity [16]. The EPM was made of painted wood cross (Arms 50 cm long x 10 cm wide) elevated 50 cm above the floor. Two opposite arms were enclosed by walls (10 cm x 50 cm x 45 cm high) and two arms were open. The arms extended from a central platform (10 x 10 cm) [17]. The open arms in the maze that we use do not have a railing, but addition of a 3–5 mm high railing on the open arms of the plus maze has been used with success to increase open arm exploration. The rat was placed in the center of the apparatus facing one of the open arms, for a free exploration of 5 min. Entry into an arm was defined as the animal placing all four paws on the arm. After each test, the rat was returned to its home cage and the maze was cleaned with an alcoholic solution followed by wet and dry paper towels, prior to the next trial. Number of entries in open and closed arms was measured

AchE Activity: After behavioral testing, rats were decapitated and brain was removed to measure AchE activity according to Ellman *et al.* [18].

Statistical Analysis: Mintab version 13 was used for statistical analysis. All data are presented as mean ± SEM. The data obtained were tested by ANOVA followed by Tukey's post-hoc multiple comparison test. $P < 0.05$ was considered statistically significant.

RESULTS

Effect on Traveled Distance: Figure 1 showed that fenthion inhibits significantly ($p < 0.001$) traveled distance. However, pretreatment with quercetin increase significantly ($p < 0.001$) traveled distance.

Effect on Number Rearing: Table 1 Showed that rats treated with fenthion decreased significantly ($p < 0.001$) number of rearings, however, pretreatment with quercetin significantly ($p < 0.05$) alleviated the numbers of rearings.

Effect on Number of Entries in Open and Closed Arms: number of entries in open and closed arms was significantly affected, interestingly; pretreatment with quercetin alleviates these changes

Effect on Brain Acetylcholinesterase Activity: Figure 2 Showed that rats treated with fenthion inhibits significantly ($p < 0.001$) AchE activity, however, pretreatment with quercetin increased significantly ($p < 0.01$) AchE activity.

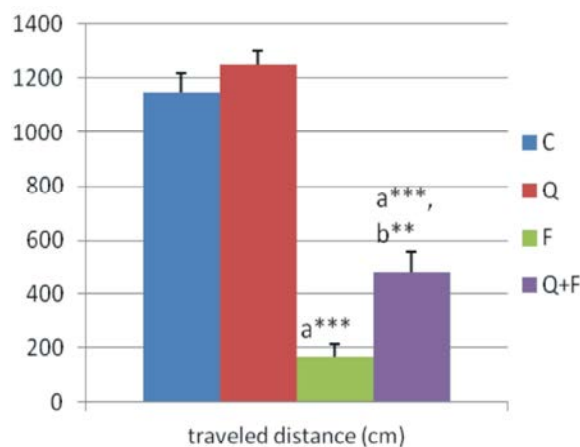


Fig. 1: Traveled distance (cm). (n=07, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$)

Table 1: Variations of the number of rearings and the numbers of entries

Parameters/Groups	C	Q	F	Q+F
Number of rearings	15,02±1	14,9±1.5	1,02±1.8 a***	4,23±1.2 a***, b*
Number of entries in open arms	5,43±1.02	5,71±0.75	0,57 ±0.53 A***	3,14±0.52 A**, b***
Number of entries in closed arms	5,57±0.97	5,71±0.8	1,42±1.00 a***	2,71±0.8 a**, b**

(n=07, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$)

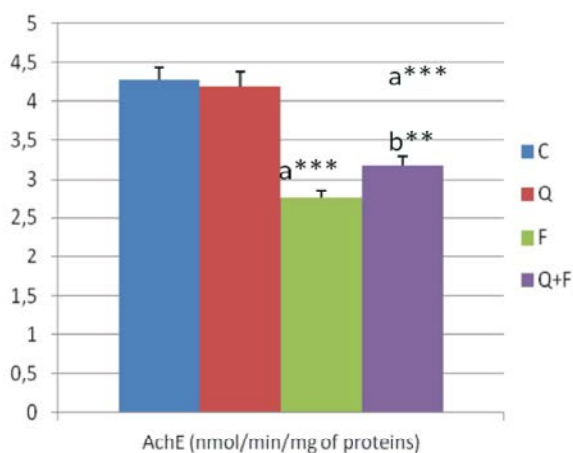


Fig. 2: Effect on brain acetylcholinesterase activity. (n=07, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$)

DISCUSSION

Our results showed that short term exposure to fenthion alters exploratory and locomotor behavior. These findings were supported by the decrease of traveled distance and number of entries in the arms. The number of entries in the arms in elevated plus maze device is superior in the rats of control group than in treated group with fenthion. The number of entries in the arms is usually described as an index of locomotion [19]. Acetylcholine intervenes in the control of the muscles through the neuromuscular ending. Excess made at the motor end plate, acetylcholine can inhibit muscle contractions resulting from nerve stimulation [20]. OP exerts its toxicity by setting its oxygen analogs on acetylcholinesterase (AChE), enzyme neuronal, causing accumulation of acetylcholine endogen in nervous tissue and effector organs [21]. In fact, accumulation of acetylcholine causes nicotinic syndromes that involve muscles fasciculations and cramps, asthenia and growing rapidly reached by the neuromuscular progressing to paralysis of skeletal muscles [22]. Our results were correlated with brain acetylcholinesterase inhibition. Inhibition of AChE by OP leads to an accumulation of acetylcholine and subsequent impairment of numerous body functions [23]. AChE inhibition was implicated with locomotor disruption as well as with mood disorders such as anxiety and depression [24]. Interestingly, pretreatment with quercetin alleviated AChE inhibition and behavioral changes. This point approves that modulation of AChE by quercetin play an important role in the appearance of locomotor pathologies. Recently, close link between AChE modulation by quercetin and amelioration in behavioral

status was determined [25]. In addition, efficiency of quercetin in the treatment of impairment of motor nerve function in rat was investigated [26].

CONCLUSION

In this work, exposure to fenthion during 10 consecutive days induced locomotor impairments and brain AChE inhibition, however, pretreatment with quercetin modulated these changes.

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