

**INVESTIGATION OF THE EFFECTS OF 4(3H)QUINAZOLINONE-2-ETHYL-2-PHENYL ETHYL  
(QEPE) ON THE CENTRAL NERVIUS SYSTEM (BRAIN) OF NEWBORN BALB/C MICE**

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**Summary**

This study aim to investigate effects of 4(3H)quinazlonones-2-ethyl-2-phenyl ethyl (QEPE) as a new quinazolinone on brain development of newborn Balb/C mice. Pregnant Balb/C mice (n=8) were divided into 3 groups of control, receiving distilled water, sham,treated with 0.05% methyl cellulose (the solvent)and experimental group, receiving one of the most effective dose of 100mg/kg/body weight of 4(3H)quinazlonones-2-ethyl-2-phenyl ethyl (QEPE), by IP injections on days 8<sup>th</sup> to 15<sup>th</sup> of gestation. After anesthetizing, brains of 5-day old newborn Balb/C mice were removed and prepared for histopathological studies. Data demonstrated an increase in the number of astrocytes of cerebral cortex and medulla of newborn mice of treated groups. Confirming the results, statistical studies showed no significant differences between the morphology of newborn mice of control, sham and treated groups'astrocytes, but there were significant differences in the number of astrocytes of newborn mice of group treated with QEPE. In conclusion, astrocyte hyperplasia decreases toxic effects of QEPE by passing through blood-brain barrier.

**Keywords:** 4(3H)quinazlonones-2-ethyl-2-phenyl ethyl (QEPE), Brain, Balb/C mice.

### Introduction

During the past few decades, it has become increasingly evident that human and animal embryos are subjected to a variety of environmental influences and drugs that could have deleterious effects on their development (1-3). Since the thalidomide tragedy, attention has been focused on drugs or chemicals as potential teratogen, to which pregnant women might be exposed (4-6). Quinazolinones are heterocyclic and water insoluble compounds (7), with various pharmacological; antimicrobial, antifungal, antitumor, anticonvulsant, anti-inflammatory, antiallergy, antimalaria (8-14). They are more efficient than other chemicals in inhibiting HIV and cancer (15, 16). The mechanism of the effects of quinazolinones on the embryonic cells is not clear yet, but there are quite a few reports showing its toxic characteristics. They inhibit polymerization of tubulin (17) and pass through placental barriers (18), so there is a possibility that it has some sort of toxic and teratogenic effects on embryos. Previous studies at the Department of Zoology, Faculty of Biological Science, University of Shahid-Beheshti, 4(3H)quinazlonones-2-ethyl-2-phenyl ethyl (QEPE) can cause morphological, skeletal and histological abnormalities in Balb/C mice embryos. In the present study we interested that whether treatments pregnant mice with QEPE would affect the brain development of Balb/C mouse fetuses.

### Materials and Methods

Balb/C mice were housed in  $24 \pm 1^{\circ} \text{C}$ ,  $65 \pm 0.5\%$  humidity and lighted controlled room (12h light-dark), provided with lab chow (pellets) and tap water. They were originally obtained from Razi Institute (Tehran, Iran); Random breedings were implemented in our local facility, animal room, with breeding, operation and maintenance sections. Males mated virgin females at overnight, observing vaginal plugs presented day zero of pregnancy. The new derivative of qunazolinones: 4(3H)quinazlonones-2-ethyl-2-phenyl ethyl (QEPE), synthesized at Department of Chemistry,

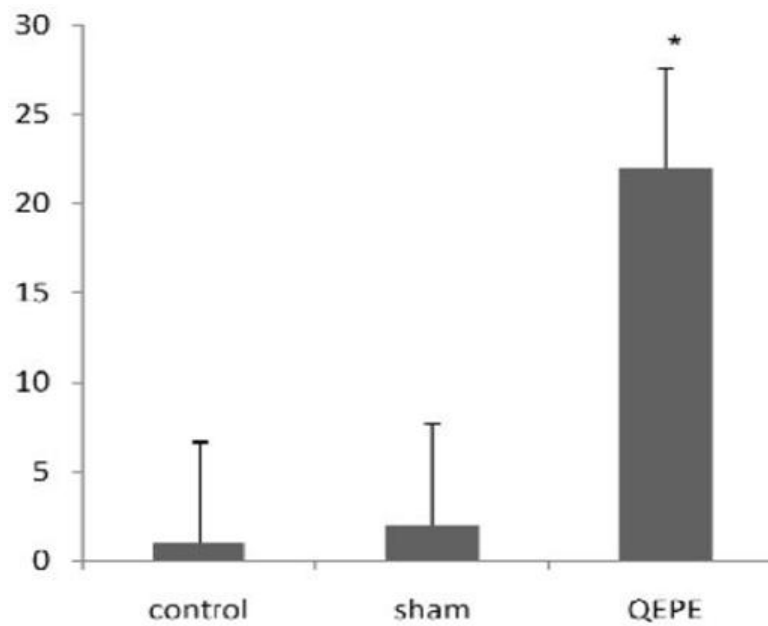
Faculty of Science, University of Shahid-Beheshti, Tehran, Iran were used for IP injection. So, pregnant mice were divided into 3 groups (n=10) of control, sham, and experimental, received distilled water (10ml/kg), methyl cellulose %0.05 (10ml/kg) (the solvent of quinazolinones) and 100 mg/kg Balb/C body weight of QEPE (most effective dose), respectively, by IP injection, on days 8<sup>th</sup> to 15<sup>th</sup> of gestation. 5day old newborns were killed by cervical dislocation. The brain was excised from each mouse and measured in weight. Then they were fixed in formalin %10, stained with H&E (Hematoxilin & Eosine) for histological and pathological studies under compound microscope. Data were analyzed with statistical packages for social sciences (SPSS,version 12.0). Mean and standard error of mean [SEM] were calculated and the significance of difference was analyzed by applying One-Way ANOVA. Level of significance difference was  $P<0.05$ .

### **Results:**

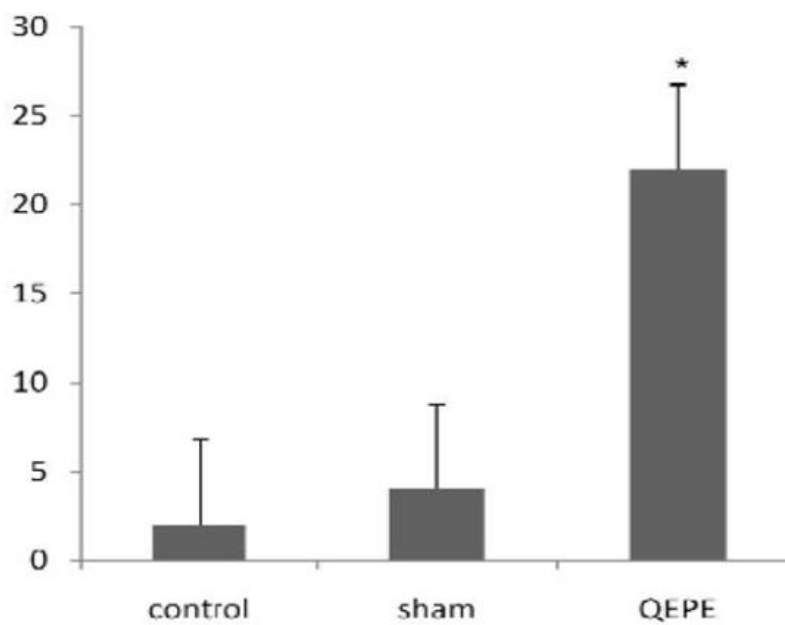
Results showed increase in the diameters of cerebral microglia of newborn Balb/C mice brains of mothers treated with QEPE. Abnormal myelin sheaths were observed in newborn Balb/C mice of mothers treated with QEPE.

Statistical analysis showed significant differences ( $P<0.05$ ) between the number of astrocytes of newborn Balb/C mice cerebral cortex and medulla of 3 different groups and QEPE increased these factors in the brain of experimental group.

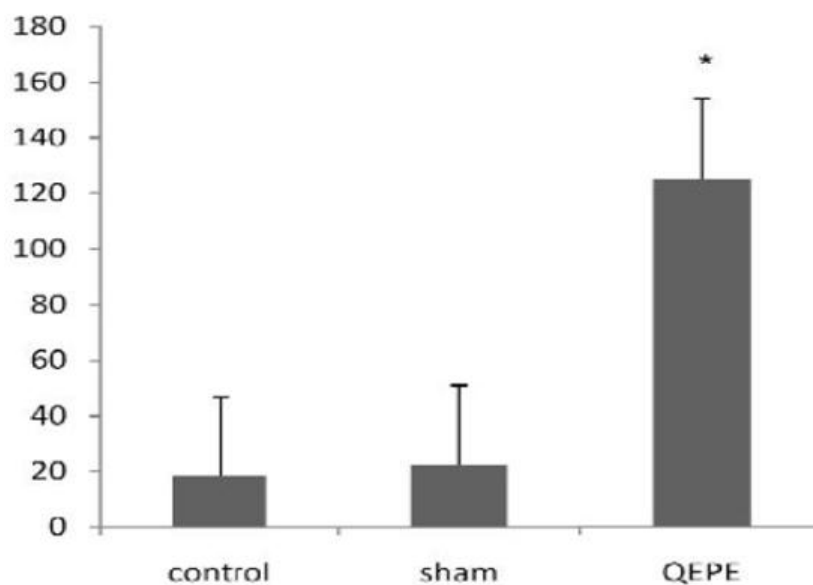
**Figure 1:** Effect of QEPE in diameters of cerebral microglia of newborn Balb/C mice. ( $P < 0.05$ ).



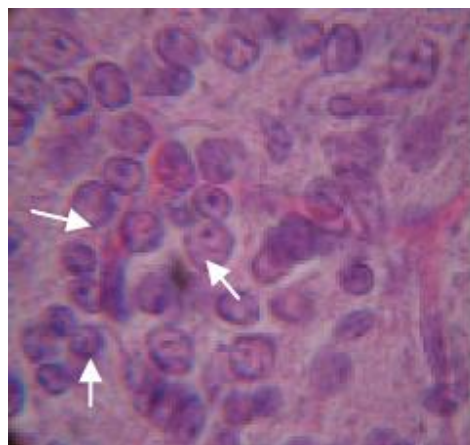
**Figure 2:** Effect of QEPE on the number of abnormal myelin sheaths of newborn Balb/C mice. ( $P < 0.05$ ).



**Figure 3:** Effect of QEPE on the mean number of astrocytes of newborn Balb/C. ( $P < 0.05$ ).



**Figure 4:** Increase in the mean number of astrocytes of newborn Balb/C treated with QEPE. . ( $P < 0.05$ ).



### Discussion

Quinazolinones are heterocyclic, water insoluble and lipophilic compounds, with various pharmacological characteristics; (antimicrobial, antifungal, antismoothing, Parkinson and etc.) (7-14).

They are more efficient than other chemicals in inhibiting HIV and cancer (15-17). They enter circulatory system and passes through placental barrier (18). In current study, there was no significant difference between brain of control and sham groups, indicating methyl cellulose 0/05% (the solvent) had no teratogenic effects on newborn mice. Results of this investigation proved that quinazolinones pass through placenta barrier, affecting brain and other organs. In response to QEPE treatments, astrocytic hyperplasia was observed in the brains of newborn Balb/C mice, so that their processes, surrounding synapses with efficient uptake systems, removed excitotoxins; There are growing evidences suggesting that astrocytes play critical role in the regulation of excitotoxicity and inflammatory processes during evolution of Alzheimer's disease (19). Neurons are not injured because of astrocytes' involvement in homeostasis of CNS, regulating ionic and water balances, anti-oxidant concentrations, uptake and metabolism of neurotransmitters, and sequestration of potential neurotoxins(ammonia, heavy metals, and excitatory amino acid neurotransmitters such as glutamate and aspartate) (20, 21). Previous investigations indicated that IL-6, released from astrocytes, corresponded with gliosis, inducing FGF from astrocytes (22, 23). On the other hand, QEPE enters the brain as antigen, causing release of chemotaxics from macrophages. Thereafter, macrophages produce lysozymal enzymes, chemical mediators and free radicals which would not bring about severe swellings, however, as in our experiments, brain could repair itself (24).

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