THE EFFECTS OF 4(3)QUINAZOLINONE-2-PROPYL-2-PHENYL ETHYL ON BRAIN DEVELOPMENT OF NEWBORN BALB/C MICE

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Summary

Quinazolinones, water insoluble heterocyclic compounds, have various biological and pharmacological properties (anti-bacterial, anti-inflammation, sedation and anti-depression) are also used for the treatments of cancer and HIV. Our previous results proved that new derivative of quinazolinones is toxogenic and teratogenic in mouse. 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)quinazolinone-2- propyl-2-phenyl ethyl (QPPE) by IP injections on days 8^{th} to 15^{th} of gestation. After anesthetizing, brains of 5-day old newborn Balb/C mice were removed and prepared for histopathological studies. Pathological observations 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 QPPE. In conclusion, astrocyte hyperplasia decreases toxic effects of QPPE by passing through blood-brain barrier.

Keywords: 4(3H)quinazolinone-2- propyl-2-phenyl ethyl (QPPE), Brain dvevelopment, Balb/C mice.

Introduction

More than 40 alkaloid composed of 4(3H) – quinazolinones moiety were isolated from nautralsources (1, 2). Quinazolinones,frequently encountering heterocycles in medical chemistry(3),with two conjoined aromatic rings incorporating two nitrogen atoms and one of the carbons oxidized with a keto oxygen,have wide applications,and are extensively used in treatments of prevalent diseases(4-6).They belong to hyponic chemicals,are immunopathological and anti-tumor agents, inhibitores of tubulin polymerization, DNA repair enzyme Poly(ADP-ribose) polymerase (PARP), mixed lineage kinases, mammalian aspartate transcarbamylase, HIV reverse transcriptase , some proteins and enzymes such as PgP(Pglycoprotein), MRP(multidrug resistance associated protein),PARP(poly ADP-ribose polymerase), polymerization of tubuline, decrease midbrain dopamine unit activity,causing stress, anti-inflammatory activity,active in synthesis and reduction of prostaglandin E2 production, antagonists of CXCR3, and acting strongly to inhibit human immunodeficiency viruses and other activities mentioned in previous papers (7-22).They pass through placental barriers,which make them chemicals of interest for research and there is a high possibility that they will create toxic and teratogenic effects on embryos and newborns as a whole. In the present study we interested that whether treatments pregnant mice with QPPE would affect the brain development of Balb/C mouse fetuses.

Materials and Methods

Balb/C mice were housed in 24±1° C ,65 ± 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)quinazolinone-2- propyl-2-phenyl ethyl (QPPE), 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 QPPE (most effective dose), respectively, by IP injection, on days 8th to 15th 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

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

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 QPPE increased these factors in the brain of experimental group.

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

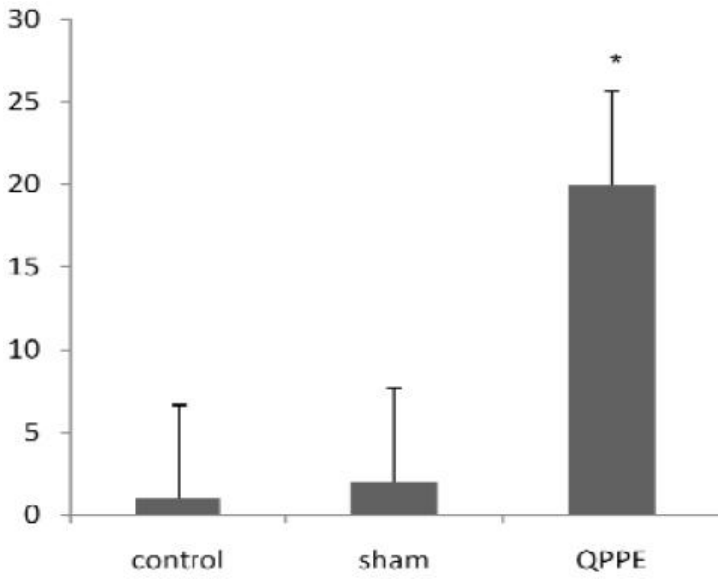


Figure 2: Effect of QPPE on the number of abnormal myelin sheaths of newborn Balb/C mice. (P<0.05).

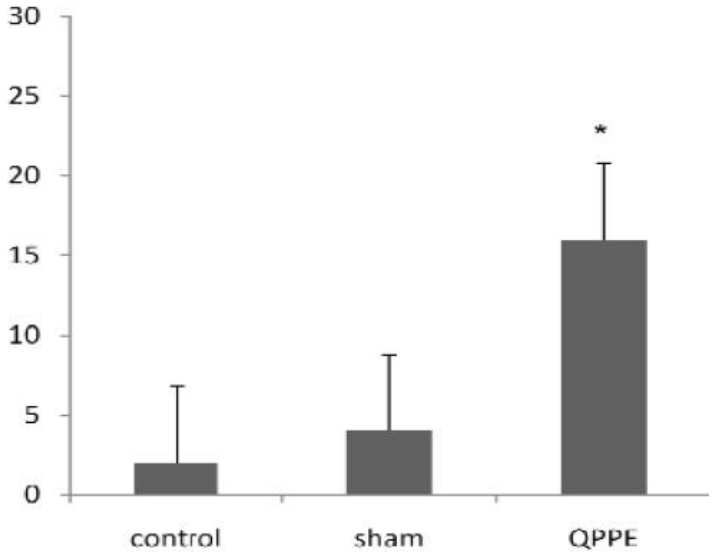


Figure 3: Effect of QPPE on the mean number of astrocytes of newborn Balb/C. (P<0.05).

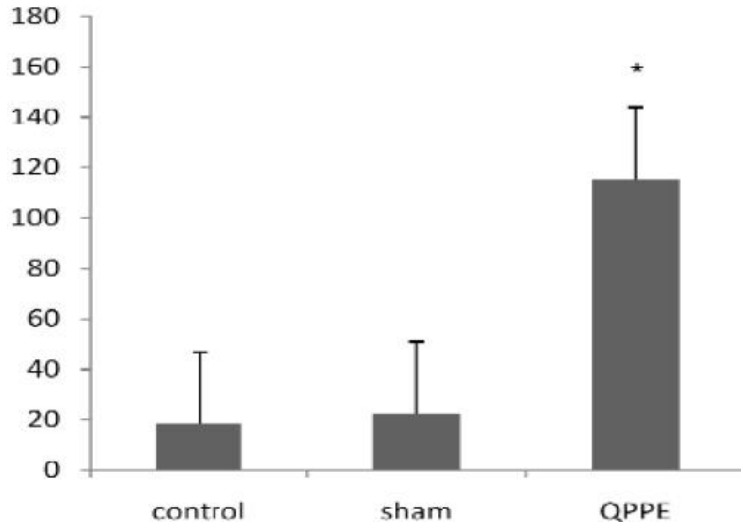
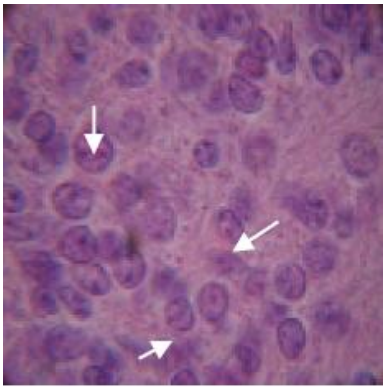


Figure 4: Histopathological studies of brain in group treated with QPPE. Increase in the mean number of astrocytes of newborn Balb/C. . (P<0.05).



Discussion

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 QPPE treatments, astrocytic hyperplasia was observed in the brains of newborn Balb/C mice, so that their processes, surrounding synapses with efficient uptake systems, removed excitatoxins; There are growing evidences suggesting that astrocytes play critical role in the regulation of excitatoxicity and inflammatory processes during evolution of Alzheimer's disease (23). 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 aspirate) (24, 25). Since astrocytes are responsible for major part of glutamate uptake and this turns glutamate from an excitatory neurotransmitter to a powerful neurotoxin. On the other hand, astrocytic factors down regulate the expression of major histocompatibility complex-class-II and intercellular adhesion molecule-1 on human monocytes **,** which modulate inflammatory events in CNS and function as antigen presenting cells (APC) upon expression of class-II major histocompatibility complex (MHC) antigens,in response to QPPE . They also secrete growth factors and extracellular matrix molecules which play roles not only in development but also in repairing CNS. Increase in the number of astrocytes (astrocytosis), in response to IL-1 (released from microglia) leads to the secretion of FGF, IGF, IL-6 and TGF (endocrine and paracrine) from astrocytes, maintaining extracellular matrix and homeostasis of functioning neurons (26, 27). Previous investigations indicated that IL-6, released from astrocytes, corresponded with gliosis, inducing FGF from astrocytes (28, 29). On the other hand, QPPE enters the brain as antigen, causing release of chemotaxics from macrophages. Thereafter, macrophages produce lysozymal enzymes, chemical mediatores and free radicals which would not bring about severe swellings, however, as in our experiments, brain could repair itself (30).

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