Toxicology Letters 280 (2017) 247–258

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Hippocampal-dependent memory deficit induced by perinatal exposure to polutted eels in middle-aged offspring mice: Sex differential effects

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ARTICLE INFO

Keywords:
Cognitive deficit
Early-life exposure
Microglia
Inflammation
Later-life
Polluted eels
Long-term memory

ABSTRACT

The effects of perinatal exposure to low, intermediate, or highly polluted eels on neonatal, postnatal, adult and middle-aged brain inflammation, and on cognitive performances of middle-aged offspring mice were compared to those of offspring controls. Inflammatory markers in microglia were assessed in offspring on the postnatal days–PNDs 1, 21, 100 and 330. Activated p38MAPK, ERK-1/2 and p65, and acetylcholine levels were assessed in the middle-aged hippocampus. Plasma myeloperoxidase and corticosterone levels were evaluated at PND 330. Learning and its retention, and working memory in middle-aged offspring were assessed using the Morris water maze, and Y-maze. Our results showed enhanced microglia production of inflammatory markers across the lifespan of male as well as female exposed offspring. Inflammation and increased p38 MAPK activation were detected in the exposed middle-aged hippocampus of both exposed sexes. Significant levels of MPO, but not corticosterone, were found in middle-aged males and females perinatally exposed to eels. However, decreases in ERK1/2 and p65 activation, and acetylcholine levels were only detected in female hippocampus exposed to either intermediately or highly polluted eels. Sex selective effects were also detected with regard to memory, the only altered cognitive function. Thus, middle-aged females, but not males, perinatally exposed to either intermediately or highly polluted eels take longer to locate the escape platform, spend considerably less time in the platform and perform less visit to the platform in the retention test. Our results suggest perinatal programming of hippocampal-dependent memory deficit by inflammation in middle-aged offspring, in sex and dose dependent manner.

1. Introduction

Accumulating evidence indicates that physiology or pathophysiology associated to health or diseases throughout our lifespan may depend on the course of brain development, if remaining normal or rather becoming altered (De Luca et al., 2016; Soualeh et al., 2017; Spencer, 2013a,b; Spencer and Tilbrook, 2009). Brain development trajectory may be incredibly influenced by early-life events including immune challenges (Bilbo and Schwarz, 2009; Marques et al., 2013; Spencer, 2013a). In addition to infections, maternal conditions including elevated body weight, obesity, unhealthy diet such as high-fat or polluted fish-containing diets, trauma or stress and diseases, such as diabetes may constitute factors favoring pro-inflammatory responses (Bolton and Bilbo, 2014; Hale et al., 2014; Marques et al., 2013; Soualeh et al., 2017; Spencer, 2013a,b). Such conditions result in an enhanced cytokine production, which may have maternal, placental, fetal and/or postnatal origin (Hagberg et al., 2015; Hale et al., 2014; Hava et al., 2006), mediating a bi-directional communication between the nervous and immune regulatory systems (ThyagaRajan and Priyanka, 2012; Wilson et al., 2002). The timing of the early challenge is critical since developing brain presents several sensitive time points during neurodevelopment (Ingber and Pohl, 2016; Spencer, 2013b; Spencer et al., 2007, 2006; Viggiano, 2008). Recently, a particular interest is given to maternal diet, as besides healthy and nutritious components, maternal diet may also contain detrimental ingredients such as persistent organic pollutants—POPs—and mercury, which is the case of fatty fishes including eels, sardines, salmon, mackerel, tuna and trout (SACN, 2004; Soualeh et al., 2017). POPs and heavy metals (or their metabolites) can cross the protective barriers, such as placenta, intestinal as well as blood-brain barrier, and further be available in breast milk (Bouayed et al., 2009; Elnar et al., 2012; Li et al., 2013; Marques et al., 2013), thereby eliciting brain programming via early-life inflammation (Soualeh et al., 2017). However, besides inflammation, diet constituents may also influence developmental programming via other mechanisms, e.g. owing to their ability to promote modulations in the offspring gut microbiome, which in turn belongs to the brain-gut-enteric microbiota axis (Borre et al., 2014; Marques et al., 2013; Spencer, 2013a). Therefore, maternal diet can be the

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http://dx.doi.org/10.1016/j.toxlet.2017.08.019
Received 2 May 2017; Received in revised form 20 August 2017; Accepted 21 August 2017
Available online 25 August 2017
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conditioning factor of several late effects across our lifespan, including alterations in behavioral and cognitive functions (Hale et al., 2014; Marques et al., 2013; Spencer, 2013a,b).

The purpose of this study is to evaluate late effects of perinatal exposure to polluted eels on cognitive function of offspring mice, considering sex. Our previous results have showed that early-life exposure to polluted eels resulted in differential sex alterations in neonatal, postnatal and adult brain inflammatory responses (Soualeh et al., 2017), and in behavior of offspring mice including activity (Dridi et al., 2017) and resignation (Soualeh et al., 2017). Given that the life stages of offspring mice e.g. mature adult (3–6 months), middle (10–15 months) and old (≥18 months) ages, which are equivalent in human years to 22–30, 39–48 and ≥57, respectively (Flurkey et al., 2007), may be determinant for the onset of impairments induced by early-life pollutant exposure (Andersen, 2003; Cauli et al., 2012; Dridi et al., 2017), this study was carried out at middle age, although no effects were found on spatial cognitive performances in juvenile (postnatal day–PND 38, age analogues to periadolescence period in human) and adult (PNDs 120–123) offspring mice (Dridi et al., 2014). Thus, cognitive performances of male and female middle-aged offspring mice perinatally exposed to polluted eels were assessed using the Morris water maze spatial navigation task to evaluate both spatial learning and memory retention, and the Y-maze to evaluate immediate working memory. In addition, inflammation was assessed in microglia isolated from neonatal (PND 1), postnatal (PND 21), adult (PND 100) and middle-aged (PND 330) brains by assessing the levels of interleukin (IL)-1β, IL4, IL10, IL6, tumor necrosis factor alpha (TNFα), transforming growth factor beta (TGFβ), interferon gamma (IFNγ) and nitric oxide (NO). Owing to the role of the hippocampus in learning and memory processes (Broadbent et al., 2004; Karabeg et al., 2013; Miller and Spencer, 2014; Squire, 1992, 1993), the levels of IL1β, IL4, IL6, TNFα, activated p38 mitogen-activated protein kinases (p38MAPK), activated extracellular signal-regulated kinases (ERK)-1/2, activated nuclear factor NF-kappa-B p65 subunit (p65), and acetylcholine were assessed in the middle-aged hippocampus. Moreover, corticosterone, a stress marker, and myeloperoxidase (MPO), an inflammatory enzyme, were assessed in plasma of middle-aged offspring mice at PND 330. Due to the potential role of maternal inflammation on offspring programming, the plasma levels of IL1β, IL6, TNFα, and MPO were therefore evaluated in mothers.

2. Materials and methods

2.1. Animals

Forty pregnant CD1 mice (Charles River, France), obtained after a mating session in our laboratory as detailed in our previous study (Bouayed et al., 2009), were used in this study. The presence of a vaginal plug was designated as the first gestational day (G1). Pregnant females were housed individually in standard cages with ad libitum access to water and food pellets (SDS Dietex, St Gratien, France) and they were maintained on a standard 12-h light/dark cycle (lights "on" starting at 8:00 p.m.), temperature-controlled conditions (22 ± 2 °C), and a relative humidity of 55 ± 10%. The parturition day was considered to be postnatal day (PND) 1. All litters (n = 13–18) were randomly equalized to have n = 10 pups/litter, 5 pups/sex to prevent litter size bias. In regard to the remaining pups (i.e., at PND 1), only one pup/litter was randomly selected and sacrificed as described below in the section for Biochemical analyses. On PND 21 (i.e., at weaning), male and female offspring mice were separated from their mothers and housed in two different rooms (n = 5/cage: 21 × 37 × 15 cm) to exclude the effects of sexual pheromones on behavior at adult age. Efforts were made to have a relevant number of females (> 150 females) in the same room in order to develop a lengthened estrous cycle, which is a phenomenon obtained by the effects of the all-female environment (crowded females) leading to the suppression of estrus due to a prolonged diestrum (Marsden and Bronson, 1965; Whitten, 1959). Although our strategy aimed to obtain synchronized females, it should be noted that from 8 months age, Swiss albino mice are marked by irregular estrous cycle showing prolonged cycles due to extended diestrus (Kaur, 1994).

During the dark phase (1 h after lights "off") of the light/dark cycle, tests on animals were performed in a silent and isolated room, under dim red lighting for a maximum of 4 h per day of experimentation (i.e., experiments were finished at 5 h after lights "off" to avoid circadian cycle bias). All animal procedures were performed in accordance with the relevant European Union regulations (Directive 2010/63/EU) and were approved by the institutional ethics committee of the University of Lorraine (authorization number CELMEA-2013-0010).

2.2. Perinatal diet manipulation

2.2.1. Eel matrix and pollutant quantification

A permit to fish for eels was obtained from the Ministry of the Walloon region, Belgium (authorization number DNF/DCP/CD705.1/Sortie 2007: 31416). Five river yellow eels (la Meuse, Belgium) were stunned and caught with a dip net in the spring of 2011. Additionally, 10 reared yellow eels were purchased from Zon-Aquafarming (Helmond, The Netherlands). Biologists from the University of Liège (ULg) identified both the river and the reared eels as *Anguilla anguilla* L. during the autopsy process. Eel muscle was then sampled, separated into two pools according to their origin, freeze-dried, mixed, and stored at −20 °C until paste preparation. Levels of pollutants including polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins/dibenzofurans (PCDD/Fs), polycyclic aromatic hydrocarbons (PAHs), polybrominated diphenyl ethers (BDEs), organochlorine pesticides and metals such as mercury and lead were reported in both reared and river muscle eels, as described in the Table 1 (Soualeh et al., 2017). It is worth noting that eel matrices may contain other unspecified chemicals (antibiotics, estrogen, etc.). Thus, in this study, river and reared eels were considered to be highly and lowly polluted eels, respectively. In addition, an artificial eel matrix obtained by mixing reared and river eels, at a ratio of 2:1, was used in order to assess the effects of an intermediate level of pollution i.e., intermediately polluted eels (Soualeh et al., 2017).

2.2.2. Eel paste preparation

The contaminated food (paste consisting of eels and chow) was prepared daily for a group of mothers (n = 10) by mixing 10 g of powdered food pellets (SDS Dietex, St Gratien, France) with 10 ml of water, 0.5 ml of sweet syrup, and 1 ml of corn oil and 320 mg of lyophilized eels (i.e., low, intermediate, or highly polluted eels) with a household kitchen blender (Robot monofonction Seb Valentin 8553, France) to obtain a homogenous paste (i.e., a mother weighing 40 g ingested 32 mg-dw of eels that corresponded to 0.8 g-dw of eel per kg of body weight (bw) of the mouse). Vigorous mixing was employed to ensure complete mixing, following protocols that were established in earlier investigations (Soualeh et al., 2017; Dridi et al., 2014, 2017). On the following day, the obtained homogenous paste was cut into smaller pieces based on the weight of the pregnant and nursing females (40–70 g) in order to be delivered as 0.8 g-dw of eel muscle/kg-bw/day to the mice. For control pregnant and lactating mice (n = 10), the paste was prepared with the same ingredients cited above but without adding eels, as no unpolluted eels (e.g. no PCB-free eels) could be sourced.

2.2.3. Perinatal exposure to polluted eels

Pregnant females were allocated to the four experimental groups by stratified randomization; 40 dams ingested the standard diet (food pellets, SDS Dietex, St Gratien, France) plus paste with or without eels on a daily basis from gestational day (GD) 6 until PND 21 (i.e. weaning). The appropriate pastes were placed into each female's cage on a daily basis during the exposure period. The paste was completely

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