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THE EFFECT OF VITAMIN C ON THE CEREBRAL CORTEX NEURONS OF RATS EXPOSED BY PRENATAL NOISE STRESS

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Abstract– The development of cerebral cortex neurons is important due to the complexity of synaptogenesis. Various stressors including prenatal noise exposure may have adverse effect on this process. Vitamin C has been reported to act as an antioxidant in the brain that could function as a reactive oxygen species scavenger and a neuromodulator. Here we investigate the protective effect of vitamin C on the cerebral cortex neurons of the rat offspring exposed by prenatal noise. Twenty-four rat offspring age 0 from 32 pregnant *Wista rmothers* were divided into 4 groups equally: K1 (distilled water), K2 (vitamin C), P1 (distilled water + noise), P2 (vitamin C + noise). Vitamin C was administered orally 150 mg/kg of body weight, once daily from day 1 of pregnancy until delivery. Prenatal noise exposure was a white noise given 4 hours daily at 95 dB (from day 15 to delivery). The number of neurons from both hemisphere was counted in duplicate from slides stained with hematoxylin-eosin; 4 ì in thickness, parasagittal sliced, 400x of magnification under a light microscope. Data from 4 groups were then analysed using ANOVA and LSD post-test with significance level of $p<0.05$. The neuron number of P1 is significantly lower compared to the control groups ($p=0.006$). When compared to P1, the number of the neurons in P2 is significantly higher ($p=0.006$). From the current study, vitamin c may protect the cerebral cortex from the adverse effect of prenatal noise during pregnancy in rats.

INTRODUCTION

The cerebral cortex is the neural tissue in cerebral hemispheres containing mostly of grey matter. The cerebral cortex plays a key role in memory, attention, perceptual awareness, thought language, and consciousness. The cerebral cortex of adult mammals is composed of six layers with nerve cell bodies, dendritic arborisations and synaptic interconnections (Crossman and Neary, 2015). The development of cerebral cortex begins in the gestation stage and continues to the postnatal period (Dobbing and Sands, 1979). The development of fetal brain during the prenatal period is influenced by environmental factors, such as sound (Hayashi *et al.*,1998). Prenatal exposure to comfortable music of 65 dB for 1 hour enhances the brain development of the fetus, improves spatial learning and spatial memory capability in rat offspring (Kim *et al.*, 2013; Kim *et al.*, 2006). However, there is evidence that prenatal noise exposure above 80 dB can decrease the neurogenesis in the hippocampus and the medial prefrontal cortex of rats. One of proposed pathophysiology is the cell death via stress oxidative, that noise exposure during pregnancy might raise the levels of malondialdehyde (MDA). This pathology may result in synaptic alteration and impairment of memory (Manikandan*et al.*, 2006; Wang *et al.*, 2016).

Vitamin C is a water-soluble antioxidant that has numerous functions, including reactive oxygen scavenging, neuromodulation and involves in angiogenesis in the brain (Hansen *et al.*, 2014). In Guinea pig, vitamin C deficiency was shown to cause a reduced number of the neurons in the

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hippocampus hence altered the spatial memory (Tveden-Nyborg *et al.*, 2009).

In this study we would like to determine the potential protective effect of oral vitamin C on the developing cerebral cortex of the offspring rat brain after prenatal noise exposures.

MATERIALS AND METHODS

This study has an ethical clearance from The Faculty of Veterinary Medicine, UniversitasAirlangga, Surabaya, Indonesia (no. 2.KE.041.03.2018).

Animals and Treatments

Twenty-four male and female offspring from 32 female *Wistar* rats were divided equally into 4 groups: K1 (distilled water), K2 (vitamin C), P1 (distilled water + noise), P2 (vitamin C + noise). The pregnant rats were given vitamin C (IPI, Indonesia) 150 mg/kg of body weight or distilled water orally (given once daily from day 1 of pregnancy until delivery, at 9 am). P1 and P2 mothers were exposed to a noise stressor for 4 hours of white noise 95 dB from a Real-time analyzer software version 5.2.0 (Yoshimasa Electronic Inc., Japan) connected to a loudspeaker (Sony SRS XB30, Japan), at 10 a.m. to 14 p.m. daily from day 15 to delivery). The loudspeaker was located 30 cm above the rat home cages. The intensity of the sound was measured by a sound level meter (Krisbow, Indonesia). K1 and K2 mothers were kept in a chamber without noise exposures in a different room during the experiment as control groups. After birth, the offspring (n=6 in each group) were sacrificed and brains were carefully taken, except in P2 where only 5 offspring could be harvested due to damaged brain tissue during process.

Tissue preparation and quantification of cerebral cortex neurons

The brain of the newborn rats was harvested after decapitation, then fixed in 10% formalin-PBL solution. Both hemispheres were paraffinated and sliced at 4 ì parasagittaly. Slides were stained with hematoxylin-eosin and observed under a light microscope (Olympus, Japan). The number of cerebral cortex neurons were counted using Image Raster 3 software (Mikonos Transdata Nusantara, Indonesia) and done twice independently at 400x of magnification (6-10 visual fields/animal).

Data analysis

Data were analysed using one way ANOVA with LSD post-test after done the Saphiro Wilks normality test and Levene test of homogenity (SPSS 17, USA). Level of significance is $p<0.05$.

RESULTS

The number of the neuron in P1 was lowest compared to the other groups (Table 1).

Table 1. The results of the number of cerebral cortex neuron in each group

Groups	Number of cerebral cortex neurons
K1 (n=6)	1136.64 ± 95.76[a]
K2 (n=6)	1087.60 ± 15.72[a]
P1 (n=6)	804.79 ± 41.39
P2 (n=5)	1234.81 ± 69.03[a]

Data are expressed as mean ± standard error of the mean.
[a] P1 vs. K1, K2, P2

When compared to the other groups, the number of the neuron in P1 was significantly lower ($p=0.006$). In figure 1, the representative pictures of cerebral cortex of K1, K2, P1 and P2 were shown.

DISCUSSION

From this study, we reported a significant decrease in the neuron number of the cerebral cortex after a prenatal noise exposure of 95dB compared to controls. Prenatal stress causes psychological and psychosomatic problem in mothers, thus decreased newborn body weight, induces stillbirths, fetal teratogenesis, and abortion (Kim *et al.*, 2013; Rehm and Jensen, 1978). Prenatal noise stressor could activate the maternal hypothalamus-hypophysis-adrenal axis hormones, sympathetic endocrine, and inflammation interaction. Prenatal noise stress also reduces the expression and activity of 11â-HSD2 in the placenta. Down-regulation of placental 11â-HSD2 activity increases glucocorticoid exposure of the placenta and the fetus. Stress-induced glucocorticoids may change the neurogenesis thus brain morphology (Charil *et al.*, 2010). The placenta could be a key source of the oxidative stress metabolites due to high metabolic rate and level mitochondria activity during pregnancy. Prenatal stress generates excessive free radicals that may lead into a neurodegeneration that could result in changes of cognitive function (Miller *et al.*, 2012).

The neuron number of the P2 was significantly higher when compared to the P1 in this study.

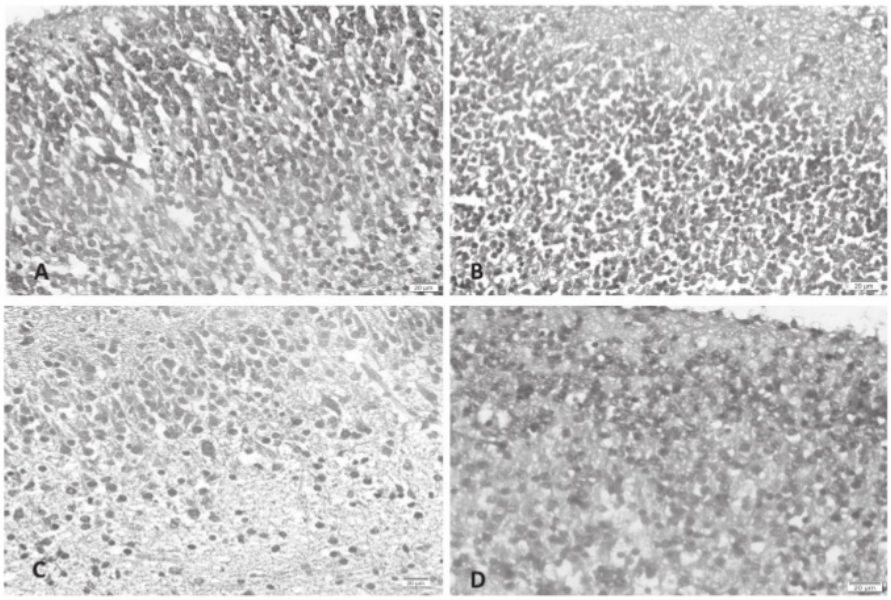

Fig. 1. Brain tissue of the newborn rat cerebral cortex of K1, K2, P1 and P2 at 400x magnification with hematoxylin-eosin staining (A = K1, B = group K2, C = group P1, D = group P2). Scale bar 20 µ. Numbers of neuron in P1 were decreased significantly after a prenatal noise-stress exposure compared to control groups (K1 and K2) or to P2 group ($p<0.05$).

Vitamin C is essential nutrients and may act as an electron donor, thereby preventing other agents from becoming oxidized and quenching an overproduction of free radicals(Agus*et al.*, 1997). Previous study reported that the administration of vitamin C may decrease the levels of MDA in rat dentate gyrus exposed by 0.2% lead acetate-orally (Karamian *et al.*, 2015). Ibrahim *et al.* reported that an administration of oral vitamin C in pregnant rats exposed with formaldehyde may increase the total antioxidant capacity of the offspring (Ibrahim *et al.*, 2016). In other study, 7-day-olds newborn mice injected with ethanol and vitamin C subcutaneously, and it was reported that vitamin C can prevent a neurodegeneration due to apoptosis occurred in the cerebral cortex (Naseer *et al.*, 2009). In human studies, certain plasma concentration of vitamin C has been reported to be positively correlated to better cognitive performance and significantly reduced risk of dementia in elderly people (Hansen *et al.*, 2014).

CONCLUSION

In this study, oral vitamin C could enhance the neurogenesis thus protect the developing brain tissue from the adverse effect of prenatal noise stressor.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4