Prenatal Methamphetamine Hydrochloride Exposure Leads to Signal Transduction Alteration and Cell Death in the Prefrontal Cortex and Amygdala of Male and Female Rats’ Offspring

Nayereh Zare1 · Nader Maghsoudi2 · Seyed Hamidreza Mirbehbahani2,3 · Forough Foolad4 · Shahrzad Khakpour5 · Zahra Mansouri2,3 · Fariba Khodagholi3 · Batool Ghorbani Yekta5,6

Received: 22 June 2022 / Accepted: 23 August 2022 / Published online: 3 September 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract
In the last decade, there has been a great increase in methamphetamine hydrochloride (METH) abuse by pregnant women that exposes fetus and human offspring to a wide variety of developmental impairments that may be the underlying causes of future psychosocial issues. Herein, we investigated whether prenatal METH exposure with different doses (2 and 5 mg/kg) could influence neuronal cell death and antioxidant level in the different brain regions of adult male and female offspring. Adult male and female Wistar rats prenatally exposed to METH (2 or 5 mg/kg) and/or saline was used in this study. At week 12, adult rats’ offspring were decapitated to collect different brain region tissues including amygdala (AMY) and prefrontal cortices (PFC). Western blot analysis was performed to evaluate the apoptosis- and autophagy-related markers, and enzymatic assay was used to measure the level of catalase and also reduced glutathione (GSH). Our results showed that METH exposure during pregnancy increased the level of apoptosis (BAX/Bcl-2 and Caspase-3) and autophagy (Beclin-1 and LC3II/LC3I) in the PFC and AMY areas of both male and female offspring’s brain. Also, we found an elevation in the GSH content of all both mentioned brain areas and catalase activity of PFC in the offspring’s brain. These changes were more significant in female offspring. Being prenatally exposed to METH increased cell death at least partly via apoptosis and autophagy in AMY and PFC of male and female offspring’s brain, while the antioxidant system tried to protect cells in these regions.

Keywords Methamphetamine · Prenatal exposure · Apoptosis · Autophagy · Brain regions

Introduction
The illicit abuse of methamphetamines (METH) has become an international public health problem with an estimated 15 to 16 million users worldwide (Pyae). METH is known to be stimulant drug, which has a very broad effect on the user’s body especially on the central nervous system (CNS) (Yasaei and Saadabadi 2018). The molecular mechanisms underlying the action of METH in the CNS are not fully understood; however, there is ample evidence that this psycho-stimulant is a potent neurotoxin that causes alteration in release and activity of monoaminergic neurotransmitters (Riddle et al. 2006). In addition, several pathways such as oxidative stress, mitochondrial dysfunction, apoptosis, and autophagy have been reported as the important players in the CNS impairment during METH abuse (Yang et al. 2018).

In the last decade, there has been a great increase in METH use by pregnant women (Gabriel et al. 2021). This
growing tendency towards pregnancy METH abuse exposes fetus and human offspring to a wide variety of developmental impairments that may be the underlying causes of future psychosocial issues (Preller et al. 2014; Šlamberová et al. 2014). Besides, investigations showed that METH abuse during pregnancy could influence both mental and physical health in infants. Prenatal METH exposure not only increases stress but also reduces quality of movement in them (Smith et al. 2008).

Different adverse effects of the prepartum METH abuse have been reported during different gestation trimesters. Moore and colleagues revealed that METH abuse during the first and third trimesters causes long-term impairment of dopaminergic and serotonergic systems (Moore et al. 2011). Moreover, METH induces maternal depression and anxiety which cause fetal developmental impairment (Moore et al. 2011). It can cause life-threatening hyperthermia which negatively affects fetal development (Freedman et al. 2005). Also, METH reduces placental blood flow which makes the fetus susceptible to a chronic hypoxic status (Stek et al. 1995).

As CNS develops very fast in the gestational period, it is extremely fragile against damages caused by this neurotoxin (Dubois et al. 2014). Enhanced oxidative stress by METH promotes impairments to fetal DNA, protein, and lipid and causes signaling transduction alteration and cellular death (Wells et al. 2009). Previous reports (Pessoa 2010; Roussotte et al. 2012; Diaz et al. 2014; Roos et al. 2014; Yip et al. 2014; Warton et al. 2018; Friedman and Robbins 2022) have shown that the effects of prenatal exposure to METH on children increase cognitive disorders, stress, and problems in working memory; on the other hand, MRI studies have shown a decrease in the volume of the prefrontal cortex (PFC) and amygdala (AMY) following exposure to methamphetamine in the fetal period in children. Both areas are crucial regions in stress circuit and act as detector and responder to stress. So, herein, we investigated whether prenatal METH exposure could influence apoptosis, autophagy, and antioxidant levels in the PFC and AMY of adult male and female offspring’s brain.

Materials and Methods

Reagents

METH was synthesized and analyzed by the Central Research Laboratories of Shahid Beheshti University of Medical Sciences (Tehran, Iran). Antibodies directed against caspase-3, Bax, Bcl-2, Microtubule-associated protein light chain 3B (LC3B), Beclin-1, and β-actin were purchased from Cell Signaling Technology (Beverly, MA, USA). Electrochemiluminescence (ECL) kit was obtained from Amersham Biosciences (Piscataway, NJ, USA). 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) was purchased from Sigma-Aldrich (St. Louis, MO, USA).

Animals and Experimental Design

Adult male and female Wistar rats, weighing 200–250 g, were obtained from Pasteur Institute (Tehran, Iran). The Ethics Committee of Shahid Beheshti University of Medical Sciences approved all the experimental procedures of this research. This research has received ratification by the Neuroscience Research Center Ethics Board (IR. SBMU.PHNS.REC.1396.112). All animals were treated in a moral way that obeyed the guidelines of the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80–23, revised 1996). All rats had free access to food and water and were housed at the standard condition with 12-h light/12-h dark cycle and a permanent temperature (22 ± 2 °C).

After the acclimation period, mating pair was planned to achieve pareunia (Šlamberová et al. 2005a, b). Vaginal plaque, Papanicolaou smears were done as the postpareunia monitoring in order to detect the pregnant female rats (Ajayi and Akhigbe 2020). Then, the pregnant rats were randomly assigned to three groups: saline group, which received normal saline intraperitoneally (i.p.); METH 2 mg and METH 5 mg, which received METH either 2 mg/kg or 5 mg/kg i.p. (Inoue et al. 2004; Bagheri et al. 2017; Jalayeri-Darbandi et al. 2018).

All pregnant rats were injected with METH and/or saline from the 10th gestational day to the parturition time. Three weeks weaning after the labor, the pups were separated by sex. They were left undisturbed until adulthood. Based on prenatal treatment, adult offspring were divided into six experimental groups: saline group, which was prenatally exposed to normal saline injection; and two MA groups, which were prenatally exposed to either 2 mg/kg or 5 mg/kg METH injection. This grouping was done in both sexes (n = 4/group) of offspring (Scheme 1).

Brain Tissue Collection

At week 12, adult rats’ offspring were decapitated to collect different brain region tissues. AMY and PFC were extracted according to the Paxinos and Watson atlas (The Rat Brain in Stereotaxic Coordinates, 2013) and immediately frozen in the liquid nitrogen and were kept at – 80 °C until use.

Western Blot Assay

The tissues were homogenated in lysis buffer including complete protease inhibitor cocktail. Protein supernatants were yielded through centrifugation and protein concentration
was measured by Bradford method (Bradford 1976). The protein were electrophoresed and transferred onto the polyvinylidene difluoride membranes. Afterward, blots were blocked and incubated with primary antibodies and the horseradish peroxidase–conjugated secondary antibody. Finally, immunoreactivity was detected with electrochemiluminescence kit and recorded by Kodak x-ray films. Relative density of the protein bands was quantified with ImageJ software 1.41o.

**Catalase Activity Assay**

Catalase activity was evaluated according to the method described by Goth (Goth 1991). Hydrogen peroxide 65 mM (in potassium phosphate buffer pH 7.4) was added to protein lysate. After 4 min of incubation at 25 °C, ammonium molybdate was added and the concentration of yellow color was recorded at 405 nm.

**Reduced Glutathione (GSH) Measurement**

Reduced glutathione content was determined according to the method of Ellman using DTNB (Ellman 1959). The absorbance was recorded at 412 nm.

**Statistical Analysis**

All data were depicted as mean±SEM and were analyzed using GraphPad Prism® 6.07. Results were processed with two-way analysis of variance (ANOVA) followed by multiple comparisons via Tukey’s post hoc test to find out any sex and dose dependency by METH. \( P < 0.05 \) was considered as significant difference.

**Results**

**Prenatal METH Exposure Increased Apoptosis System in the Different Brain Regions of Adult Rats’ Offspring**

All the stimuli that induce apoptotic cascade increase mitochondrial permeability, and eventually release pro-apoptotic molecules such as cytochrome c from them. This pathway is closely linked to a group of proteins belonging to the Bcl-2 family: pro-apoptotic proteins (Bax family) and anti-apoptotic (Bcl-2). The ratio of Bax and Bcl-2 proteins influenced the activation of caspase-3, which is the protein activating the nuclear damage (Pisani et al. 2020). As observed in Fig. 1B, C, in PFC of male offspring, there was a significant increase in METH-exposed rats by about 2.79 (\( p < 0.0001 \)) and 2.63-fold (\( p < 0.0001 \)) in the ratio of Bax/Bcl-2 and 1.57 (\( p = 0.013 \)) and 2.57 (\( p < 0.0001 \)) fold in the caspase-3 cleavage of the 2 and 5 mg/kg groups. The elevation of cleaved caspase-3 in 5 mg/kg treated rats was about 1.63-fold compared to 2 mg/kg dose group (\( p < 0.0001 \)). Also, in PFC of female offspring, there was a significant elevation by about 2.57 (\( p < 0.0001 \)) and 2.32 (\( p < 0.0001 \)) fold for the Bax/Bcl-2 ratio and 1.72 (\( p < 0.0001 \)) and 1.25 (\( p = 0.0058 \)) fold for cleaved caspase-3 in the METH 2 and 5 mg/kg groups compared to saline group. Comparison between different doses showed a significant change by about 27% (\( p < 0.0001 \)). Moreover, as shown in Fig. 1E, F, similar trend of changes in the AMY region was observed. In male offspring, Bax/Bcl-2 ratio and cleaved caspase-3 level were elevated due to prenatal METH exposure by about 1.57 (\( p < 0.0001 \)) and 1.44 (\( p = 0.0160 \)) fold for the Bax/Bcl-2 ratio and 1.72 (\( p < 0.0001 \)) and 1.25 (\( p = 0.0058 \)) fold for cleaved caspase-3 in the METH 2 and 5 mg/kg groups compared to saline group. Also, statistical analysis
of caspase-3 expression between different dose exposure indicated a dose-dependent increase by about 1.3 ($p=0.0071$) and 1.2 ($p=0.0236$) fold in male and female offspring. Sex-dependent analysis showed an elevation in caspase-3 level of both doses in female offspring's PFC and AMY ($p<0.0001$ and $p<0.0001$ for 2 mg/kg; $p=0.0421$ and $p=0.0002$ for 5 mg/kg, respectively).

**Prenatal METH Exposure Enhanced Autophagy System in the Different Brain Regions of Adult Rats’ Offspring**

Autophagy influences cell survival through maintenance of cell bioenergetics and clearance of protein aggregates and damaged organelles. LC3B and Beclin-1 are specific marker proteins of autophagy, as well as important regulators of autophagy (Doherty and Baehrecke 2018).

As demonstrated in Fig. 2C, Beclin-1 was significantly upregulated in the PFC of both sexes' offspring of METH (2 mg and 5 mg/kg) Statistical analysis showed an increase by about 2.22 ($p<0.0001$) and 2.34 ($p<0.0001$) fold in male group (2 and 5 mg/kg), and 1.5 ($p=0.0002$) and 1.67 ($p<0.0001$) fold in female offspring (2 and 5 mg/kg) when compared to saline. Moreover, as evidenced in Fig. 2B, in the PFC of male and female offspring, the lipidation of LC3I to LC3II increased in both METH doses compared to the saline group. This ratio rise by about 1.74 ($p<0.0001$) and
2.15 ($p < 0.0001$) fold in male group (2 and 5 mg/kg), and 1.6 ($p = 0.001$) and 1.71 ($p < 0.0001$) fold in female offspring (2 and 5 mg/kg) related to saline. In addition, dose-dependent comparison revealed a significant increase by about 1.23 fold ($p = 0.0150$) in the level of LC3II/LC3I in male groups.

Our result revealed that in AMY area of male and female offspring, Beclin-1 level was remarkably elevated by about 1.58 ($p = 0.001$) and 1.61 ($p < 0.0001$) fold in the male METH 2 and 5 mg/kg groups, and about 1.33 ($p = 0.0243$) and 2.12 ($p < 0.0001$) fold in the female METH 2 and 5 mg/kg groups in comparison with the saline group (Fig. 2E).

Five mg/kg exposure to METH increased the level of Beclin-1 in female rats by about 1.6-fold ($p < 0.0001$) compared to 2 mg/kg dose. Besides as shown in Fig. 2F, there was a significant elevation in the LC3II/LC3I ratio after METH exposure in AMY of both sexes. This elevation was about 1.99-fold ($p < 0.0001$) in the male 5 mg/kg group and about 1.65 ($p < 0.0001$) and 1.71 ($p < 0.0001$) fold in the female 2 and 5 mg/kg relative to controls. Different dose exposure significantly altered the level of LC3II/LC3I in male ($p < 0.0001$), while it did not show any changes in female groups. In addition, analysis between different sexes of offspring revealed an increase in Beclin-1 protein of female 5 mg/kg groups in both PFC and AMY areas ($p = 0.0382$ and $p = 0.012$, respectively), and LC3II/ LC3I ratio of female 2 mg/kg group in AMY ($p < 0.0001$).
Prenatal METH Exposure Aﬀected Endogenous Antioxidant System in the Diﬀerent Brain Regions of Adult Rats’ Offspring

Reactive oxygen species (ROS) are normally detoxiﬁed by an antioxidation system, consisted with non-enzyme antioxidation system and antioxidase. Catalase, a special antioxidase, converts hydrogen peroxide into water simultaneously with GSH-Px that use GSH as its substrate to remove redundant free radicals and peroxidase (Wu et al. 2010).

As shown in Table 1, catalase activity elevated in PFC of adult offspring that were prenatally exposed to METH. This elevation was about 2.74 (p = 0.0013) and 3.22 (p < 0.0001) fold for the 2 mg/kg and 5 mg/kg groups of male offspring.

Also, our results indicated that the catalase activity in the AMY did not alter in male and female offspring of METH (2 and 5 mg/kg) as compared with saline group (Table 1).

Moreover, statistical analysis indicated that GSH level was more aﬀected by prenatal exposure to METH. The GSH content increased in PFC of female offspring by about 2.15 (p = 0.0011) and 2.08 (p = 0.0019) fold; however, there was a non-signiﬁcant elevation in male offspring (p > 0.05) (Table 2). Also, it rises in AMY region of male rats’ brain by about 1.44 (p = 0.0017) and 1.35 (p = 0.0114) fold in the 2 and 5 mg/kg groups and 1.52-fold in the AMY of female brain of the 5 mg/kg group (p = 0.0002).

Dose comparison between groups showed an elevation about 1.32-fold (p = 0.0091) in 5 mg/kg group of female in AMY region compared to 2 mg/kg dose. On the other hand, sex comparison between diﬀerent groups revealed a signiﬁcant increase of catalase and GSH in both groups of PFC region (p = 0.0363 and p = 0.0269 in catalase and p = 0.0116 and p = 0.0091 in GSH for 2 and 5 mg/kg, respectively).

Discussion

The data from our experiment showed that METH exposure during pregnancy did not aﬀect oﬀspring growth and weight (data not shown), while it increased the level of apoptosis and autophagy in the PFC and AMY areas of both male and female oﬀspring’s brain. Also, we found an elevation in the GSH content of both mentioned brain areas (PFC and AMY) and catalase activity of PFC in the oﬀspring’s brain.

METH-induced neuropathological changes have been observed in various brain areas of users including the prefrontal cortex (PFC) and hippocampus (Proebstl et al. 2018). In addition, investigations revealed alteration in the structure and function of diﬀerent brain regions of rats (Thanos et al. 2016). Administration of METH is associated with ROS production, and consequently apoptosis, autophagy, and DNA damage (Li and Trush 1993; Nopparat et al. 2010). Our results revealed that METH exposure during pregnancy leads to substantial alterations in the diﬀerent brain regions of oﬀspring, and the mentioned alterations were detectable in adulthood. Protein assessment showed an increased level of Bax/Bcl2 and caspase-3 in the PFC and AMY of oﬀspring that were prenatally exposed to METH. This elevation was same as molecular changes reported in the hippocampal neurons of maternally exposed animals to METH during pregnancy and lactation period (Bagheri et al. 2017).

An elevation in Bax/Bcl-2 ratio in the PFC and AMY areas indicated the onset of apoptosis in these areas, and with an increase in the cleaved caspase-3 level as an important executive agent in apoptosis pathway, cell death is observed in oﬀspring exposed to METH during gestation. It is important to note that brain AMY and PFC are involved in cognitive processes such as anxiety, stress learning, and memory. Consistent with our ﬁndings, some studies have shown that cognitive processes are disrupted following prenatal METH exposure (Acuff-Smith et al. 1996; Bubenikova-Valesova et al. 2009; Dong et al. 2018). Also, a brain imaging study in children with prenatal METH exposure indicated less connectivity in frontal and limbic hubs over time compared to healthy control children (Roos et al. 2020).

Furthermore, there is a complex interaction between autophagy and apoptosis molecular pathways. Autophagy acts as a double-edge sword and it has been shown to protect

Table 1 The eﬀect of prenatal METH (2 and 5 mg/kg) exposure on catalase activity of the prefrontal cortex and amygdala of adult rats’ brain

| Brain Region  | Saline   | METH 2 mg/kg | METH 5 mg/kg |
|---------------|----------|--------------|--------------|
| Male          | 0.3 ± 0.05 | 0.83 ± 0.05 ** | 0.98 ± 0.18 **** |
| Female        | 0.32 ± 0.02 | 0.41 ± 0.01 ^ | 0.54 ± 0.03 ^  |
| Amygdala      | 0.35 ± 0.02 | 0.38 ± 0.03 | 0.37 ± 0.01   |
| Female        | 0.38 ± 0.05 | 0.39 ± 0.07 | 0.4 ± 0.05    |

Values are presented as mean ± SEM (U/mg pr). (N = 4; *, #, and ^ different from the control, METH 2 mg/kg and sex; *p < 0.05; **p < 0.01; ****p < 0.0001)

Table 2 The eﬀect of prenatal METH (2 and 5 mg/kg) exposure on GSH content of the prefrontal cortex and amygdala of adult rats’ brain

| Brain Region  | Saline   | METH 2 mg/kg | METH 5 mg/kg |
|---------------|----------|--------------|--------------|
| Prefrontal cortex |          |              |              |
| Male          | 2.84 ± 0.35 | 3.57 ± 0.28 | 3.24 ± 0.21  |
| Female        | 3.18 ± 0.56 | 6.8 ± 0.83 ** ^ | 6.6 ± 0.57 ** ^  |
| Amygdala      | 3.4 ± 0.17 | 4.9 ± 0.15 ** | 4.6 ± 0.2 *  |
| Female        | 3.65 ± 0.28 | 4.2 ± 0.23 | 5.5 ± 0.28 *** ### |

Values are presented as mean ± SEM (nmol/mg pr). (N = 4; *, #, and ^ different from the control, METH 2 mg/kg and sex; *p < 0.05; **p < 0.01; ***p < 0.0001)
against apoptosis, as an anti-apoptotic pathway to reduce cell death, or, pro-apoptosis, as a combined or dependent mechanism for modulation of cell death. However, the precise tendency to death or controlling the fate of neurons in response to METH exposure is not well understood. Xu et al. showed that METH abuse, at least in part, caused premature autophagy before apoptosis in a time-dependent manner, dominated the pathophysiological process earlier, and then gradually progressed to apoptosis. As we found that prenatal METH exposure influenced Beclin-1 level, Xu and colleagues observed an expression-regulated expression of Beclin-1 in METH-exposed animals, indicating a representative of active autophagy (Xu et al. 2018). Subsequently, our result showed the accumulation of autophagosomes (LC3-I to LC3-II), which may cause cytotoxicity (Button et al. 2017) and induce apoptotic signals by increasing cleaved caspase expression. Beclin-1 as an essential mediator of autophagy interacts with Bcl-2 and can influence apoptosis level by activating proapoptotic proteins of the Bcl-2 family and increase the permeabilizing of the mitochondrial membrane. On the other hand, liberating Beclin-1 from its inhibition by Bcl-2 at the level of the endoplasmic reticulum modulates via these Bcl-2 family members and activates autophagy. Also, some studies have shown that binding of Beclin-1 to Bcl-2 leads to release of cytochrome c into the cytosol and activation of caspases-3/-9 by cleavage of them (Huang et al. 2014). Although the process of autophagy may initially be activated to prevent apoptosis, it could not prevent cell death due to apoptosis, and finally the process of apoptosis recruit autophagy to proceed neuronal cell death (Xu et al. 2018). So, METH abuse not only can cause neuronal apoptosis and autophagy in several areas of the brain, including the striatum, cortex, hippocampus, and olfactory bulb (Deng et al. 2002, 2007; Krasnova and Cadet 2009; Subu et al. 2020), but also could influence neuronal cell death in the brain PFC and AMY of next generation if used in pregnancy period.

One of the important endogenous defense mechanisms against oxidative stress that can defeat neuronal cell death is antioxidant system. Oxidative stress leads to direct or indirect damage by ROS to nucleic acids, proteins, and lipids (Ray et al. 2012). It was found that elevated oxidative damage by METH in embryonic and fetal brain causes long-term postnatal neurodevelopmental deficits. These impairments have no relation to dopaminergic neurotoxicity (Jeng et al. 2005). In addition, ROS activation by METH self-administration has been shown (Jang et al. 2017) The enzymatic–nonenzymatic antioxidant cellular defense system including catalase and GSH plays a key role in protecting cells from oxidative stress by regulating the production of free radicals and their metabolites (Patlevič et al. 2016). Our results indicated an increased activity of catalase in the PFC, as well as the amount of GSH in all studied areas of offspring’s brain.

After data analysis, we found that METH exposure during pregnancy affects male and female offspring differently. METH exposure had more impact on female offspring than males in evaluated markers of apoptosis, autophagy, and antioxidant pathways. However, sex-dependent reports of different studies regarding prenatal METH exposure are controversial. Some studies supporting our results showed more affected female offspring. More sensitivity of females to METH exposure demonstrated as behavioral alterations in cognitive function, learning ability and locomotion, and even as myocardial sensitivity to ischemic injury in different investigations (Schutová et al. 2013; Slamberová et al. 2013; Macúchová et al. 2014; Rorabaugh et al. 2016), whereas some experiments demonstrated more influence and enhanced neurotoxicity in dopaminergic nigrostriatal projection of male offspring (Heller et al. 2001). The reason of more susceptibility to prenatal METH exposure in female is unclear, but it is possible that the observed alterations are a result of sex differences in the expression of different types of adrenergic or dopaminergic receptors or their downstream signaling proteins in different regions of the brain in the male and female fetus (Rorabaugh et al. 2016). Although, there are other studies that reported no significant difference between the sexes in the expression of D1 and NMDA receptors due to METH exposure (Westbrook et al. 2020). Moreover, our investigation revealed a doses-dependent effect of METH exposure on different areas of the brain in male and female offspring, demonstrating that even exposure to lower dose of METH could exert destructive effect on CNS development and function.

### Conclusion

Taken together, we found that prenatal METH exposure increased apoptosis and autophagy in AMY and PFC of offspring’s brain of male and female rats. The increase of endogenous antioxidant system was not enough to protect against oxidative stress and neuronal cell death in mentioned brain regions (Scheme 1). Both sex and exposure doses could affect the alterations in mentioned pathways of mentioned areas. It is important to note that brain AMY and PFC are involved in cognitive processes such as anxiety, stress learning, and memory. So, the elevation of the apoptotic and autophagic pathways in mentioned areas may affect cognitive performance in the offspring that are prenatally exposed to METH.

### Author Contribution

NZ designed and performed the molecular experiments, analyzed the data, and wrote the manuscript. NM performed the conception, experimental design, supervision, and reviewed the manuscript. SHM performed the molecular experiments, analyzed the data, and wrote the manuscript. FF analyzed the data and reviewed the manuscript. SK contributed to design and reviewed the manuscript.
ZM performed the molecular experiment and analyzed the data. FK performed the conception, experimental design, and reviewed the manuscript. BGY performed the conception, experimental design, supervision, analysis, interpretation, and reviewed the manuscript. All authors read and approved the final manuscript.

Funding This work was supported by the research grant of Shahid Beheshti University of Medical Sciences (No. 13422–8–2).

Declarations

Ethical Approval This research has received ratification from the Neuroscience Research Center Ethics Board (IR.SBMU.PHNS.REC.1396.112).

Informed Consent Not applicable.

Conflict of Interest The authors declare no competing interests.

References

Acuff-Smith KD, Schilling MA, Fisher JE, Vorhees CV (1996) Stage-specific effects of prenatal d-methamphetamine exposure on behavioral and eye development in rats. Neurotoxicol Teratol 18(2):199–215

Ajayi AF, Akhigbe RE (2020) Staging of the estrous cycle and induction of estrus in experimental rodents: an update. Fertil Res Pract 6(1):1–15

Bagheri J, Rajabzadeh A, Baei F, Jalayeri Z, Ebrahimzadeh-Bideskan A (2017) The effect of maternal exposure to methamphetamine during pregnancy and lactation period on hippocampal neurons apoptosis in rat offspring. Toxins Rev 36(3):194–203

Bradford MM (1976) A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 72(1–2):248–254

Bubeníková-Valesová V, Kacer P, Syslova K, Rambousek L, Janovsky J, Pisani C, Ramella M, Boldorini R, Loi G, Billia M, Boccafoschi F, Gabrhelík R, Skurtveit S, Nechanská B, Handal M, Mahic M, Mravčík M, A (2017) The effect of maternal exposure to the drug. J Pharmacol Exp Ther 298(2):769–779

Bax, Caspases 3/9, Bcl-2, p53 and Ki-67 in prostate cancer after 12 Gy single-dose. Sci Rep 10(1):1–10

Ellman GL (1959) Tissue sulfhydryl groups. Arch Biochem Biophys 82(1):70–77

Freedman RR, Johanson C-E, Tancer ME (2005) Thermoregulatory effects of 3, 4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology 183(2):248–256

Friedman NP, Robbins TW (2022) The role of prefrontal cortex in cognitive control and executive function. Neuropsychopharmacolgy 47(1):72–89

Gabrhelík R, Skurtveit S, Nechanská B, Handal M, Mahic M, Mravčík M, A (2017) Prenatal methamphetamine exposure and adverse neonatal outcomes: a nationwide cohort study. Eur Addict Res 27(2):97–106

Goth L (1991) A simple method for determination of serum catalase activity and revision of reference range. Clin Chim Acta 196(2–3):143–151

Heller A, Bubula N, Lew R, Heller B, Won L (2001) Gender-dependent enhanced adult neurotoxic response to methamphetamine following fetal exposure to the drug. J Pharmacol Exp Ther 298(2):769–779

Huang X, Qi Q, Hua X, Li X, Zhang W, Sun H, Li S, Wang X, Li B (2014) Beclin 1, an autophagy-related gene, augments apoptosis in U87 glioblastoma cells. Oncol Rep 31(4):1761–1767

Inoue H, Nakatome M, Terada M, Mizuno M, Ono R, Ino M, Ino Y, Ogura Y, Kuroki H, Matoba R (2004) Maternal methamphetamine administration during pregnancy influences on fetal rat heart development. Life Sci 74(12):1529–1540

Jalayeri-Darbandi Z, Rabajzadeh A, Hosseini M, Beheshti F, Ebrahimzadeh-Bideskan A (2018) The effect of methamphetamine exposure during pregnancy and lactation on hippocampal doublecortin expression, learning and memory of rat offspring. Anat Sci Int 93(3):351–363

Jiang Y, Yang CH, Hedges DM, Kim SP, Lee JY, Ekins TG, Garcia BT, Kim HY, Nelson AC, Kim NJ (2017) The role of reactive oxygen species in methamphetamine self-administration and dopamine release in the nucleus accumbens. Addict Biol 22(5):1304–1315

Jeng W, Wong AW, Ting-A-Kee R, Wells PG (2005) Methamphetamine-enhanced embryonic oxidative DNA damage and neurodevelopmental deficits. Free Radical Biol Med 39(3):317–326

Krasnova IN, Cadet JL (2009) Methamphetamine toxicity and messengers of death. Brain Res Rev 60(2):379–407

Li Y, Trush MA (1993) DNA damage resulting from the oxidation of hydroquinone by copper: role for a Cu (II)/Cu (I) redox cycle and reactive oxygen generation. Carcinogenesis 14(7):1303–1311

Macúchová E, Nohejlová K, Slamberová R (2014) Gender differences in the effect of adult amphetamine on cognitive functions of rats prenatally exposed to methamphetamine. Behav Brain Res 270:8–17

Moore D, Turner J, Goodwin J, Fulton S, Singer L, Parrott A (2011) Alcohol, drugs and medication in pregnancy: the long term outcome for the child

Nopparat C, Porter JE, Ebadi M, Govitrapong P (2010) The mechanism for the neuroprotective effect of melatonin against methamphetamine-induced autoagy. J Pineal Res 49(4):382–389

Patlevič P, Vašková J, Švorc P Jr, Vaško L, Švorc P (2016) Reactive oxygen species and antioxidant defense in human gastrointestinal diseases. Integr Med Res 5(4):250–258

Pessoa L (2010) Emotion and cognition and the amygdala: from “what is it?” to “what’s to be done?” Neuropsychologia 48(12):3416–3429

Pisani C, Ramella M, Boldorini R, Loi G, Billia M, Boccafoschi F, Volpe A, Krengli M (2020) Apoptotic and predictive factors by Bax, Caspases 3/9, Bcl-2, p53 and Ki-67 in prostate cancer after 12 Gy single-dose. Sci Rep 10(1):1–10
Preble KH, Hulka LM, Vonmoos M, Jenni D, Baumgartner MR, Seifritz E, Dziobek I, Quednow BB (2014) Impaired emotional empathy and related social network deficits in cocaine users. Addict Biol 19(3):452–466

Probstl L, Kamp F, Koller G, Soya M (2018) Cognitive deficits in methamphetamine users: how strong is the evidence? Pharmacopsychiatry 51(6):243–250

Pyae YYP The United Nations office of drugs and crime. https://www.unodc.org/

Ray PD, Huang B-W, Tsuji Y (2012) Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. Cell Signal 24(5):981–990

Riddle EL, Fleckenstein AE, Hanson GR (2006) Mechanisms of methamphetamine-induced dopaminergic neurotoxicity. AAPS J 8(2):E413–E418

Roos A, Fouche JP, du Toit S, Plessis S, Stein DJ, Donald KA (2020) Structural brain network development in children following prenatal methamphetamine exposure. J Comp Neurol 528(11):1856–1863

Roos A, Jones G, Howells FM, Stein DJ, Donald KA (2014) Structural brain changes in prenatal methamphetamine-exposed children. Metab Brain Dis 29(3):341–349

Rorabaugh BR, Seeley SL, Bui AD, Sprague L, D’Souza MS (2016) Prenatal methamphetamine differentially alters myocardial sensitivity to ischemic injury in male and female adult hearts. Am J Physiol Heart Circ Physiol 310(4):H516–H523

Roussotte FF, Rudie JD, Smith L, O’Connor MJ, Bookheimer SY, Narr KL, Sowell ER (2012) Frontostrriatal connectivity in children during working memory and the effects of prenatal methamphetamine, alcohol, and polydrug exposure. Dev Neurosci 34(1):43–57

Schutová B, Hrubá L, Rokyta R (2013) Gender differences in behavioral changes elicited by prenatal methamphetamine exposure and application of the same drug in adulthood. Dev Psychobiol 55(3):232–242

Šlamberová R, Charousová P, Pometlová M (2005a) Maternal behavior is impaired by methamphetamine administered during pre-mating, gestation and lactation. Reprod Toxicol 20(1):103–110

Šlamberová R, Charousová P, Pometlová M (2005b) Methamphetamine administration during gestation impairs maternal behavior. Dev Psychobiol J Int Soc Dev Psychobiol 46(1):57–65

Šlamberová R, Macúchová E, Nohejllová-Deykun K, Schutová B, Hrubá L, Roktya R (2013) Gender differences in the effect of prenatal methamphetamine exposure and challenge dose of other drugs on behavior of adult rats. Physiol Res 62(Suppl 1):S99–s108

Šlamberová R, Vrajová M, Schutová B, Mertlová M, Macúchová E, Nohejlová K, Hrubá L, Puskárčiková J, Bubeníková-Valešová V, Yamamotová A (2014) Prenatal methamphetamine exposure induces long-lasting alterations in memory and development of NMDA receptors in the hippocampus. Physiol Res 63

Smith LM, LaGasse LL, Derauf C, Grant P, Shah R, Arria A, Huestis M, Haning W, Strauss A, Della Grotta S (2008) Prenatal methamphetamine use and neonatal neurobehavioral outcome. Neurotoxicol Teratol 30(1):20–28

Stek AM, Baker RS, Fisher BK, Lang U, Clark KE (1995) Fetal responses to maternal and fetal methamphetamine administration in sheep. Am J Obstet Gynecol 173(5):1592–1598

Subu R, Jayanthi S, Cadet JL (2020) Compulsive methamphetamine taking induces autophagic and apoptotic markers in the rat dorsal striatum. Arch Toxicol 94(10):3515–3526

Thanos PK, Kim R, Delis F, Ananth M, Chachati G, Rocco MJ, Masad I, Muniz JA, Grant SC, Gold MS (2016) Chronic methamphetamine effects on brain structure and function in rats. PLoS ONE 11(6):e0155457

Warton FL, Taylor PA, Warton CMR, Molteno CD, Wintermark P, Lindinger NM, Zöllle L, van der Kouwe A, Jacobson JL, Jacobson SW, Meintjes EM (2018) Prenatal methamphetamine exposure is associated with corticostriatal white matter changes in neonates. Metab Brain Dis 33(2):507–522

Wells PG, McCallum GP, Chen CS, Henderson JT, Lee CJ, Persijn J, Preston TJ, Wiley MJ, Wong AW (2009) Oxidative stress in developmental origins of disease: teratogenesis, neurodevelopmental deficits, and cancer. Toxicol Sci 108(1):4–18

Westbrook SR, Dwyer MR, Cortes LR, Gulley JM (2020) Extended access self-administration of methamphetamine is associated with age-and sex-dependent differences in drug taking behavior and recognition memory in rats. Behav Brain Res 390:112659

Wu Y-L, Yang Y-Z, Jin X-J, Lian L-H, Piao J-Y, Wan Y, Jin H-R, Lee JJ, Nan J-X (2010) Acanthoic acid, a diterpene in Acanthopanax koreanum, protects acetaminophen-induced hepatic toxicity in mice. Phytomedicine 17(6):475–479

Xu X, Huang E, Luo B, Cai D, Zhao X, Luo Q, Jin Y, Chen L, Wang Q, Liu C (2018) Methamphetamine exposure triggers apoptosis and autophagy in neuronal cells by activating the C/EBPβ-related signaling pathway. FASEB J 32(12):6737–6759

Yang X, Wang Y, Li Q, Zhong Y, Chen L, Du Y, He J, Liao L, Xiong K, Yi C-X (2018) The main molecular mechanisms underlying methamphetamine-induced neurotoxicity and implications for pharmacological treatment. Front Mol Neurosci 11:186

Yasaee R, Saadabadi A (2018) Methamphetamine

Yip SW, Potenza EB, Balodis IM, Lacadie CM, Sinha R, Mayes LC, Potenza MN (2014) Prenatal cocaine exposure and adolescent neural responses to appetitive and stressful stimuli. Neuropsychopharmacology 39(12):2824–2834

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.