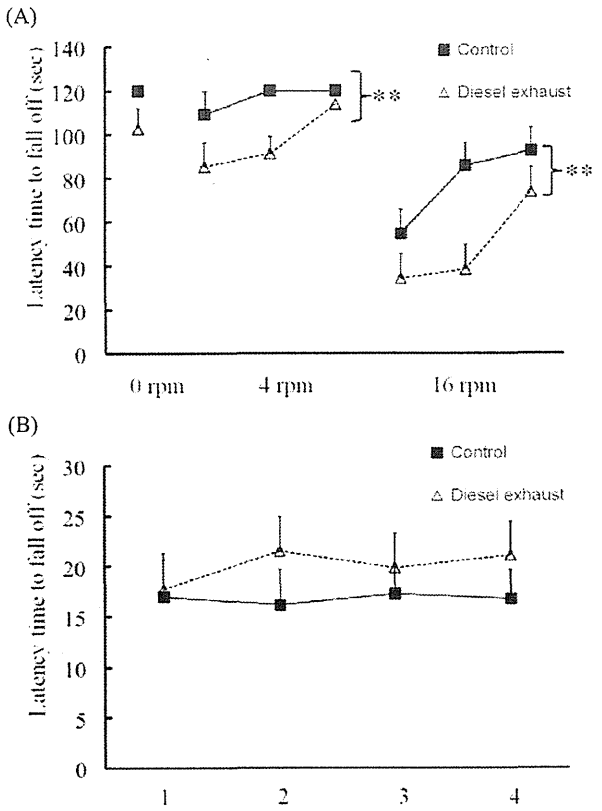

Fig. 1. Evaluation of motor function in the rotating rod test and the hanging test. (A) Retention time of control and maternally exposed diesel exhaust groups on the rotating rod at speed 0 rpm, 4 rpm, and 16 rpm. Mice that were maternally exposed to diesel showed decreased time on the rotating rod at 4 rpm and 16 rpm. The data represents time course changes in control and the maternally exposed diesel exhaust group. (B) Hanging time of control and maternally exposed diesel exhaust groups. No differences were detected between the two groups. Solid squares and triangles represent control and maternally exposed diesel exhaust mice (n = 15), respectively. Values are mean ± S.E. (*P < 0.05, **P < 0.01).

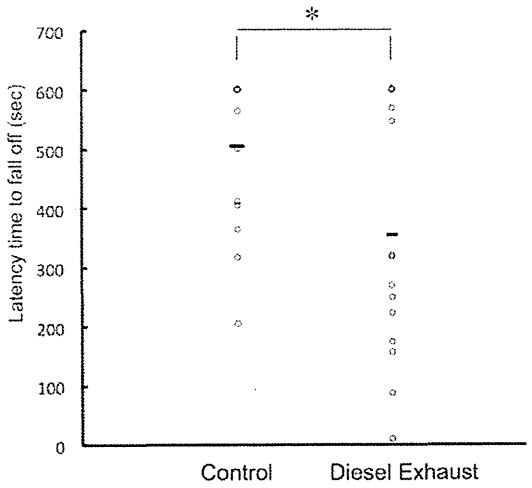

Fig. 2. Evaluation of impulsive behavior in the cliff avoidance test. Maternally exposed disesel exhaust mice tended to explore the corner of the inverted beaker which resulted in jumping off the inverted beaker. Significant differences were detected in cliff avoidance behavior between control and maternally exposed diesel exhaust mice. The data were expressed as scatter plot of latency to jump off within 10 min in control and diesel exhaust exposed groups. Mice that stayed on the inverted glass beaker were shown as 600 sec. Each black bar represents the mean latency to jump off the inverted glass beaker (n = 15; *P < 0.05 vs. control group).

ergic system. DA and a DA metabolite, 3-MT, were decreased in the prefrontal cortex in DE-exposed mice at three weeks of age (DA; P = 0.034, 3-MT; P = 0.041, Fig. 5A), but not changed at six weeks of age (Fig. 5B). In contrast, we found that DA levels were increased in DE-exposed mice at six weeks of age in the amygdala, and its metabolites were also increased at both three and six weeks of age (DA; P = 0.028, DOPAC; P = 0.008, HVA; P = 0.011, 3-MT; P = 0.023, Fig. 5C) (DOPAC; P = 0.012, Fig. 5D).

In the serotonergic system, we found that prenatal exposure to DE increased 5-HT and 5-HIAA levels in the amygdala at three weeks of age (Table 2). At six weeks of age, an increase was detected in the prenatal DE exposure group in 5-HT and 5-HIAA concentrations in the prefrontal cortex and hypothalamus, respectively (Table 3).

DISCUSSION

The results of the present study indicate for the first time that maternal exposure to DE affects motor coordination and impulsive behavior in mice. In addition, this study demonstrates neurochemical alterations in specific brain regions related to these behavioral deficits. In the present study, DE concentrations were approximately 10 times higher than realistic concentrations. However, the DE concentrations were not so high when lifespan is taken into account, given that mice were only exposed in the fetal period. Only male offspring mice were used in this study due to the variations associated with hormonal imbalance during the estrous cycle seen in female mice.

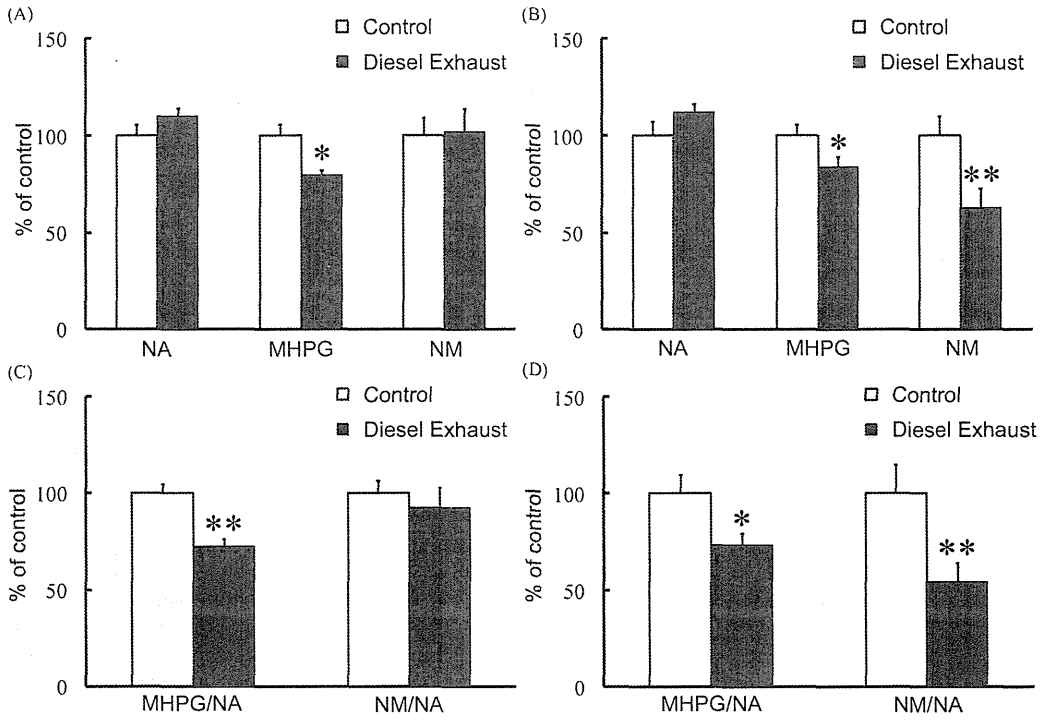

Fig. 3. Levels of noradrenaline and its metabolites in the cerebellum. (A, B) Levels of NA and its metabolites in the cerebellum at (A) three and (B) six weeks old of age. The data were expressed as a percentage of the value in control mice. Each column represents the mean ± S.E. of nine mice ($^{*}P < 0.05$, $^{**}P < 0.01$ vs. control group). (C, D) Measurement of NA turnover in the cerebellum at (C) three and (D) six weeks old of age. The data were expressed as a percentage of the value in control mice. Each column represents the mean ± S.E. of nine mice ($^{*}P < 0.05$, $^{**}P < 0.01$ vs. control group). Abbreviations: NA, noradrenaline; MHPG, 4-hydroxy-3-methoxyphenylglycol hemipiperazinium; NM, normetanephrine hydrochloride.

First, we found that prenatal DE exposure decreased the time latency to fall off in the rotating rod test, but did not alter the time latency to fall off in the hanging test. The cerebellum is important for regulation of motor coordination; higher order motor function (Shimizu *et al.*, 2002). It is possible that prenatal exposure to DE affected motor coordination that was specific to parts of the CNS such as the cerebellum, but not components of the periphery such as the skeletal muscle. The results indicated that the concentration of NA metabolites and NA turnover in the cerebellum were decreased by the matenal exposure to DE at three and six weeks of age. The cerebellum, especially Purkinje cells, is important to the modulation of motor coordination and motor learning tasks regulated by gamma aminobutyric acid (GABA) neuron activity (Mitoma and Konishi, 1999). Previous studies indicate that the cerebellum receives widespread nerve terminal projections from noradrenergic neurons (Watson and McElligott, 1984). GABAergic neurons in the Purkinje cells are stimulated by NA neurons to elicit a prolonged inhibition of Purkinje cell activity (Mitoma and Konishi, 1999). A previous study showed that the number of caspase 3 positive cells in the Purkinje cells were significantly increased in maternally DE exposed mice (Sugamata *et al.*, 2006b). In addition, it was reported that vincristine caused massive apoptosis in the cerebellum with caspase 3-like protease activation, which was associated with motor dysfunction in the rotating rod test (Shimizu *et al.*, 2002). It was quite possible that the impairment seen in the rotating rod test following maternal DE exposure may be caused by a reduction in the activity of noradrenergic systems in the cerebellum.

The cliff avoidance test showed that maternal exposure to DE affected impulsive behavior of offspring under novel environmental stress. Impulsive behavior is related to various psychological factors such as social and environmental stress (Matsuoka *et al.*, 2005). In addition, prenatal exposure to DE also affected the concentration of NA

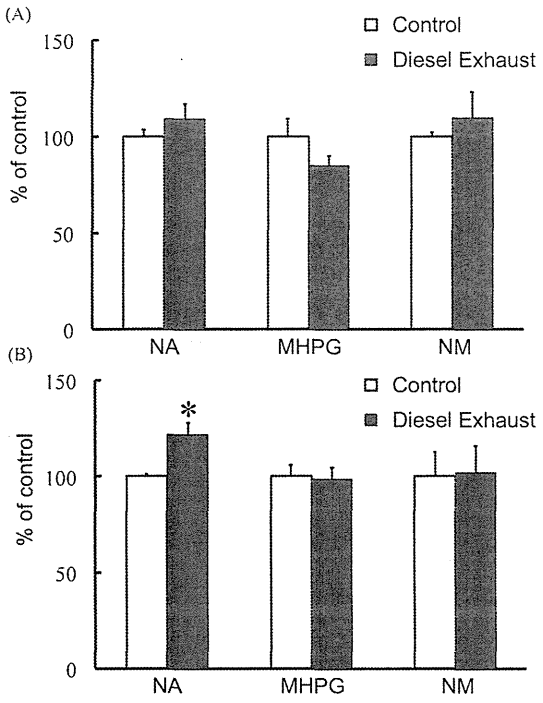

Fig. 4. Levels of noradrenaline and its metabolites in the hypothalamus. (A, B) Levels of NA and its metabolites in the hypothalamus at (A) three and (B) six weeks of age. The data were expressed as a percentage of the value in control mice. Each column represents the mean ± S.E. of nine mice (*P < 0.05 vs. control group). Abbreviations: NA, noradrenaline; MHPG, 4-hydroxy-3-methoxyphenylglycol hemipiperazinium; NM, normetanephrine hydrochloride.

in the hypothalamus, and these results suggest that DE may represent a stressor when exposed to mouse fetuses. The hypothalamus receives rich noradrenergic innervation from the brainstem, and secretes adrenocorticotropic hormone due to the noradrenergic input (Szafarczyk *et al.*, 1987, 1988). Moreover, intracerebral administration of NA into the paraventricular nucleus, a part of the hypothalamus, also results in an activation of the stress axis (Itoi *et al.*, 1994). On the contrary, noradrenergic antagonists can block stress axis activation. These findings confirm the importance of NA in stimulating corticotropin releasing hormone neurons, which stimulate corticosterone secretion from the adrenal gland into blood (Handa *et al.*, 1994). It was previously reported that prenatal exposure to endocrine disrupting compounds during development affects the hypothalamo-pituitary-adrenal (HPA) axis (Diamanti-Kandarakis *et al.*, 2009). Furthermore, DE and DEP were also reported to elicit hormone-like activity (Takeda *et al.*, 2004). Therefore, the alteration of impulsive behavior in the prenatal DE exposure group may be mediated by hypothalamic impairment, which is induced by HPA axis activation as well as hormone-like reactions of some DE components.

Understanding the critical periods associated with the effects of DE exposure on the CNS is very important. Previous studies indicate that stimulation or insult at critical phases of CNS development can result in long-term changes in brain structure and function due to neural plasticity via gene-environmental interactions. For instance, the serotonin system in the CNS is well known to be affected by perinatal environmental alterations (Van den Hove *et al.*, 2011). In the present study, we evaluated serotonergic systems of various brain regions in male offspring following maternal DE exposure. At three weeks of age, increased levels of 5-HT and 5-HIAA were observed in the amygdala, and increases in 5-HT and 5-HIAA levels were observed in the prefrontal cortex and hypothalmus at six weeks of age, respectively. Serotonin-based activity propagates from neurons located in the raphe nuclei of the brainstem, the most primitive part of the brain. Therefore, the serotonergic systems are involved in fundamental aspects of physiology including body temperature control, cardiovascular activity as well as respiration, and this system also regulates motor control as well as higher order behaviors, such as impulsive behavior and depressive like behavior (Chase and Murphy, 1973). The broad range of physiology and behavior asociated with the serotonin nerve systems can be attributed to the widespread distribution of serotonin-containing nerve fiber terminals that arise from the raphe nucei. Indeed, the branching of the serotonin network comprises the most expansive neurochemical system in the brain. In our previous study, we found that maternal exposure to DE increased serum testosterone levels in adulthood, which is related to aggressive behavior (Yoshida *et al.*, 2006). A strong relationship between serotonin and testosterone has also been reported in the literature (Birger *et al.*, 2003). The alteration of the serotonin nervous system by maternal exposure to DE may contribute changes in impulsive behavior. However, contradictory findings have been reported regarding the reduction in serotonin concentration and impulsive behavior such as aggression (Birger *et al.*, 2003). Therefore, further investigation is necessary to examine the effects of prenatal exposure to DE on the serotonergic systems and impulsive behavior.

In the present study, the dopaminergic system was investigated in prenatally DE-exposed mice at both three

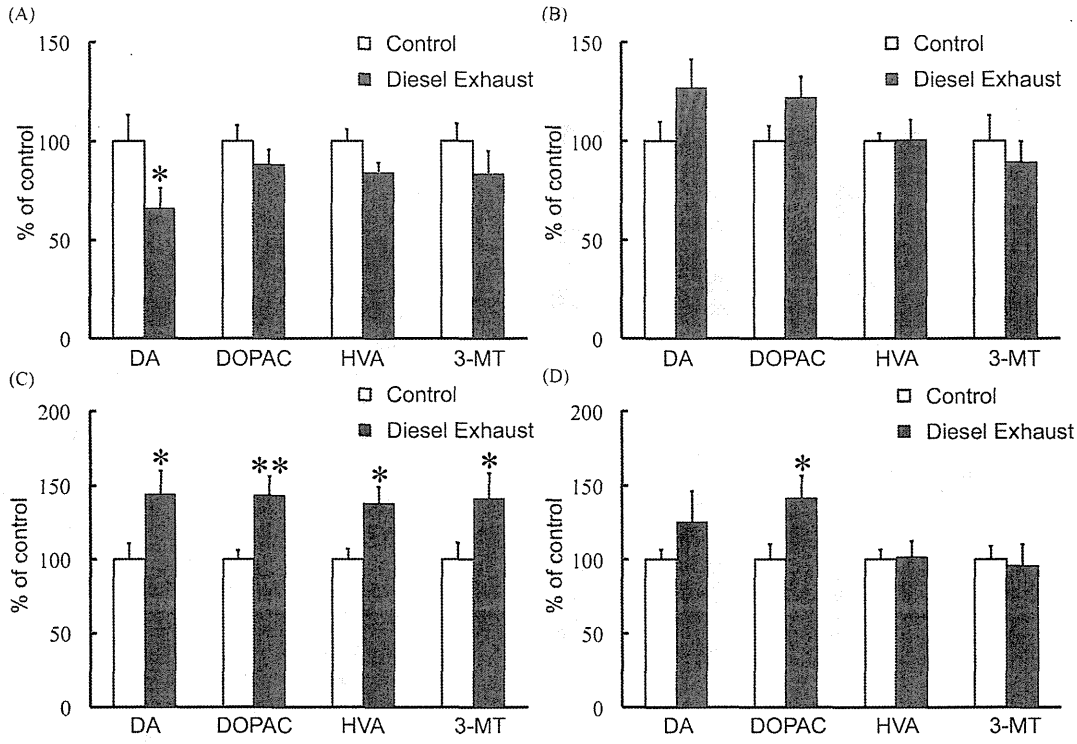

Fig. 5. Levels of dopamine and its metabolites in the prefrontal cortex and the amygdala. (A, B) Levels of DA and its metabolites in the prefrontal cortex at (A) three and (B) six weeks of age. The data were expressed as a percentage of the value in control mice. Each column represents the mean ± S.E. of nine mice (*P < 0.05 vs. control group). (C, D) Levels of DA and its metabolites in the amygdala at (C) three and (D) six weeks of age. The data were expressed as a percentage of the value in control mice. Each column represents the mean ± S.E. of nine mice (*P < 0.05 vs. control group). Abbreviations: DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid, 3-MT, 3-methoxytyramine hydrochloride.

and six weeks of age. We found a decrease in DA and its metabolite in the prefrontal cortex of DE-exposed mice (three-week-old), whereas we detected an increase in DA and its metabolite in the amygdala of DE-exposed mice (three- and six-week-old). We previously observed a distribution of DEP in the prefrontal cortex and striatum in adult offspring mice in adulthood (Sugamata *et al.*, 2006a). The direct toxicity of DEP on the DA neuron was reported in an *in vitro* study that demonstrated that DEP induces DA neuron damage (Block *et al.*, 2004). These findings suggest that inhaled DEP entered the fetal brain accumulating in the prefrontal cortex and striatum, ultimately resulting in DA neuron damage in these brain regions and a reduction in DA and its metabolites. However, DEP accumulation was not detected in the amygdala of offspring mice that were prenatally-exposed to DE. These findings suggest that the mechanism of toxicity associated with maternally inhaled DE may be due to direct or indirect action of DEP. Our unpublished data showed that prenatal exposure to DE affected the CNS more seriously than that of filtered DE, which removes small nano-sized DEP from the exhaust with a filter. We previously reported that the inhalation toxicity of DE on androgenesis during the fetal period was reduced by filtering and cutting off DEP (Ono *et al.*, 2008). These observations suggest the possibility that surface chemical compounds such as PAH and estrogen around the DEP may affect the CNS of offspring mice. Further investigation will be required to trace DEP in order to identify the various neural cells that incorporate DEP. This study would lead to a better understanding of the precise mechanism associated with how DEP affects motor coordination and impulsive behavior.

In conclusion, in the present study, we showed that prenatal exposure to DE affected motor coordination and impulsive behavior of male offspring mice. In addition,

Table 2. Maternal exposure to diesel exhaust changes serotonergic systems in offsprings at three weeks of age

Brain region	Group	Concentration (pg/mg protein)		Turnover
		5-HT	5-HIAA	5-HIAA/5-HT
Prefrontal cortex	Control	6692 ± 543	3520 ± 243	0.54 ± 0.03
	Exposed	6711 ± 561	3509 ± 225	0.53 ± 0.02
Striatum	Control	6110 ± 320	6384 ± 162	1.07 ± 0.05
	Exposed	6830 ± 403	7035 ± 278	1.05 ± 0.04
Hippocampus	Control	4910 ± 167	5507 ± 228	1.12 ± 0.03
	Exposed	4733 ± 286	5120 ± 292	1.10 ± 0.04
Amygdala	Control	10888 ± 490	5654 ± 168	0.52 ± 0.02
	Exposed	15426 ± 863**	7568 ± 466**	0.49 ± 0.01
Hypothalamus	Control	16168 ± 547	9625 ± 291	0.60 ± 0.01
	Exposed	18831 ± 1251	11458 ± 712	0.61 ± 0.02
Cerebellum	Control	1448 ± 138	1633 ± 102	1.17 ± 0.07
	Exposed	1988 ± 421	1691 ± 95	1.01 ± 0.09
Brainstem	Control	15369 ± 573	10437 ± 400	0.68 ± 0.02
	Exposed	16126 ± 724	10948 ± 336	0.68 ± 0.02

The data were presented as the mean ± S.E. of nine mice (*P < 0.05, **P < 0.01 vs. control group).

Table 3. Maternal exposure to diesel exhaust changes serotonergic systems in offsprings at six weeks of age

Brain region	Group	Concentration (pg/mg protein)		Turnover
		5-HT	5-HIAA	5-HIAA/5-HT
Prefrontal cortex	Control	6630 ± 426	2973 ± 150	0.45 ± 0.01
	Exposed	8686 ± 516*	3493 ± 223	0.41 ± 0.03
Striatum	Control	8530 ± 382	7309 ± 667	0.86 ± 0.07
	Exposed	8615 ± 346	6376 ± 636	0.74 ± 0.07
Hippocampus	Control	8096 ± 496	8061 ± 653	0.99 ± 0.05
	Exposed	8315 ± 551	9022 ± 625	1.09 ± 0.04
Amygdala	Control	11861 ± 948	5381 ± 476	0.45 ± 0.01
	Exposed	11020 ± 307	5136 ± 153	0.47 ± 0.02
Hypothalamus	Control	17518 ± 410	8544 ± 355	0.49 ± 0.01
	Exposed	19143 ± 731	11559 ± 697**	0.61 ± 0.04*
Cerebellum	Control	3470 ± 533	2165 ± 303	0.64 ± 0.04
	Exposed	2736 ± 431	1960 ± 166	0.79 ± 0.07
Brainstem	Control	13395 ± 435	8517 ± 538	0.63 ± 0.03
	Exposed	14436 ± 466	9092 ± 518	0.63 ± 0.03

The data were presented as the mean± S.E. of nine mice (*P < 0.05, **P < 0.01 vs. control group).

we found that maternal DE exposure altered the monoaminergic systems in various brain regions in male offspring at both three and six weeks of age. The monoaminergic system plays an important role in regulating behavior and maintenance of the CNS. These results provide novel and significant information regarding the health effects of DE and DEP, and further confirm the need to remove DEP from the environment in order to avoid the risk of exposure.

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REFERENCES

Ball, J.C., Straccia, A.M., Young, W.C. and Aust, A.E. (2000): The formation of reactive oxygen species catalyzed by neutral, aqueous extracts of NIST ambient particulate matter and diesel engine particles. J. Air Waste Manag. Assoc., **50**, 1897-1903.

Birger, M., Swartz, M., Cohen, D., Alesh, Y., Grishpan, C. and Kotelr, M. (2003): Aggression: the testosterone-serotonin link. Isr. Med. Assoc. J., **5**, 653-658.

Block, M.L. and Calderón-Garcidueñas, L. (2009): Air pollution: mechanisms of neuroinflammation and CNS disease. Trends. Neurosci., **32**, 506-516.

Block, M.L., Wu, X., Pei, Z., Li, G., Wang, T., Qin, L., Wilson, B., Yang, J., Hong, J.S. and Veronesi, B. (2004): Nanometer size diesel exhaust particles are selectively toxic to dopaminergic neurons: the role of microglia, phagocytosis, and NADPH oxidase. FASEB. J., **18**, 1618-1620.

Calderón-Garcidueñas, L., Azzarelli, B., Acuna, H., Garcia, R., Gambling, T.M., Osnaya, N., Monroy, S., DEL Tizapantzi, M.R., Carson, J.L., Villarreal-Calderon, A. and Rewcastle, B. (2002): Air pollution and brain damage. Toxicol. Pathol., **30**, 373-389.

Campen, M.J., Lund, A.K., Knuckles, T.L., Conklin, D.J., Bishop, B., Young, D., Seilkop, S., Seagrave, J., Reed, M.D. and McDonald, J.D. (2010): Inhaled diesel emissions alter atherosclerotic plaque composition in ApoE(-/-) mice. Toxicol. Appl. Pharmacol., **242**, 310-317.

Chase, T.N. and Murphy, D.L. (1973): Serotonin and central nervous system function. Annu. Rev. Pharmacol., **13**, 181-197.

Diamanti-Kandarakis, E., Bourguignon, J.P., Giudice, L.C., Hauser, R., Prins, G.S., Soto, A.M., Zoeller, R.T. and Gore, A.C. (2009): Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr. Rev., **30**, 293-342.

George, Xu, Umezawa, M. and Takeda, K. (2009): Early Development Origins of Adult Disease Caused by Malnutrition and Environmental Chemical Substances. J. Health Sci., **55**. 11-19.

Gnoth, C., Bremme, M., Klemm, R., Frank-Herrmann, P., Godehardt, E. and Freundl, G. (1999): Research and quality control in natural family planning with relational database systems. Adv. Contracept., **15**, 375-380.

Handa, R.J., Nunley, K.M., Lorens, S.A., Louie, J.P., McGivern, R.F. and Bollnow, M.R. (1994): Androgen regulation of adrenocorticotropin and corticosterone secretion in the male rat following novelty and foot shock stressors. Physiol. Behav., **55**, 117-124.

Heffner, T.G., Hartman, J.A. and Seiden, L.S. (1980): A rapid method for the regional dissection of the rat brain. Pharmacol. Biochem. Behav., **13**, 453-456.

Heinrich, U., Fuhst, R., Rittinghausen, S., Creutzenberg, O., Bellmann, B., Koch, W. and Levsen, K. (1995): Chronic inhalation exposure of wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide. Inhalation Toxicol., **7**, 533-556.

Hougaard, K.S., Jensen, K.A., Nordly, P., Taxvig, C., Vogel, U., Saber, A.T. and Wallin, H. (2008): Effects of prenatal exposure to diesel exhaust particles on postnatal development, behavior, genotoxicity and inflammation in mice. Part. Fibre Toxicol., **5**, 3.

Ichinose, T., Yajima, Y., Nagashima, M., Takenoshita, S., Nagamachi, Y. and Sagai, M. (1997): Lung carcinogenesis and formation of 8-hydroxy-deoxyguanosine in mice by diesel exhaust particles. Carcinogenesis, **18**, 185-192.

Itoi, K., Suda, T., Tozawa, F., Dobashi, I., Ohmori, N., Sakai, Y., Abe, K. and Demura, H. (1994): Microinjection of norepinephrine into the paraventricular nucleus of the hypothalamus stimulates corticotropin-releasing factor gene expression in conscious rats. Endocrinology, **135**, 2177-2182.

Kilburn, K.H. (2000): Effects of diesel exhaust on neurobehavioral and pulmonary functions. Arch. Environ. Health, **55**, 11-17.

Landrigan, P.J., Sonawane, B., Butler, R.N., Trasande, L., Callan, R. and Droller, D. (2005): Early environmental origins of neurodegenerative disease in later life. Environ. Health Perspect., **113**, 1230-1233.

Matsui, Y., Sakai, N., Tsuda, A., Terada, Y., Takaoka, M., Fujimaki, H. and Uchiyama, I. (2009): Tracking the pathway of diesel exhaust particles from the nose to the brain by X-ray florescence analysis. Spectrochimica. Acta. Part. B., **64**, 796-801.

Matsuoka, Y., Furuyashiki, T., Yamada, K., Nagai, T., Bito, H., Tanaka, Y., Kitaoka, S., Ushikubi, F., Nabeshima, T. and Narumiya, S. (2005): Prostaglandin E receptor EP1 controls impulsive behavior under stress. Proc. Natl. Acad. Sci. USA, **102**, 16066-16071.

McEwen, B.S. and Alves, S.E. (1999): Estrogen actions in the central nervous system. Endocr. Rev., **20**, 279-307.

Mitoma, H. and Konishi, S. (1999): Monoaminergic long-term facilitation of GABA-mediated inhibitory transmission at cerebellar synapses. Neuroscience, **88**, 871-883.

Nel, A., Xia, T., Mädler, L. and Li, N. (2006): Toxic potential of materials at the nanolevel. Science, **311**, 622-627.

Oberdörster, G., Oberdörster, E. and Oberdörster, J. (2005): Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ. Health. Perspect., **113**, 823-839.

Ono, N., Oshio, S., Niwata, Y., Yoshida, S., Tsukue, N., Sugawara, I., Takano, H. and Takeda, K. (2008): Detrimental effects of pre-

natal exposure to filtered diesel exhaust on mouse spermatogenesis. Arch. Toxicol., **82**, 851-859.

Paxinos, G. and Franlin, K.B.J. (2001): The mouse brain in stereotaxic coordinates. Academic Press, 2.

Pope, C.A. 3rd. (2004): Air pollution and health-good news and bad. N. Engl. J. Med., **351**, 1132-1134.

Santodonato, J. (1997): Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: relationship to carcinogenicity. Chemosphere, **34**, 835- 848.

Shimizu, H., Ohgoh, M., Momose, Y., Nishizawa, Y. and Ogura, H. (2002): Massive cell death of cerebellar granule neurons accompanied with caspase-3-like protease activation and subsequent motor discoordination after intracerebroventricular injection of vincristine in mice. Neuroscience, **115**, 55-65.

Sugamata, M., Ihara, T., Takano, H., Oshio, S. and Takeda, K. (2006a): Maternal diesel exhaust exposure damages newborn murine brains. J. Health Sci., **52**, 82-84.

Sugamata, M., Ihara, T., Sugamata, M. and Takeda, K. (2006b): Maternal exposure to diesel exhaust leads to pathological similarity to autism in newborns. J. Health Sci., **52**, 486-488.

Suzuki, T., Oshio, S., Iwata, M., Saburi, H., Odagiri, T., Udagawa, T., Sugawara, I., Umezawa, M. and Takeda, K. (2010): In utero exposure to a low concentration of diesel exhaust affects spontaneous locomotor activity and monoaminergic system in male mice. Part. Fibre Toxicol., **7**, 7.

Szafarczyk, A., Malaval, F., Laurent, A., Gibaud, R. and Assenmacher, I. (1987): Further evidence for a central stimulatory action of catecholamines on adrenocorticotropin release in the rat. Endocrinology, **121**, 883-892.

Szafarczyk, A., Guillaume, V., Conte-Devolx, B., Alonso, G., Malaval, F., Pares-Herbuté, N., Oliver, C. and Assenmacher, I. (1988): Central catecholaminergic system stimulates secretion of CRH at different sites. Am. J. Physiol., **255**, E463-468.

Takeda, K., Tsukue, N. and Yoshida, S. (2004): Endocrine-disrupting activity of chemicals in diesel exhaust and diesel exhaust particles. Environ. Sci., **11**, 33-45.

Tsukue, N., Watanabe, M., Kumamoto, T., Takano, H. and Takeda, K. (2009): Perinatal exposure to diesel exhaust affects gene expression in mouse cerebrum. Arch. Toxicol., **83**, 985-1000.

Umezawa, M. and Takeda, K. (2011): Automobile exhaust: Detrimental effects on pulmonary and extrapulmonary tissues and offspring. "Encyclopedia of Environmental Health", **1**, 247-252.

Van den Hove, D.L., Jakob, S.B., Schraut, K.G., Kenis, G., Schmitt, A.G., Kneitz, S., Scholz, C.J., Wieschollek, V., Ortega, G., Prickaerts, J., Steinbusch, H. and Lesch, K.P. (2011): Differential effects of prenatal stress in 5-Htt deficient mice: towards molecular mechanisms of gene × environment interactions. PLoS One., **6**, e22715.

Yokota, S., Mizuo, K., Moriya, N., Oshio, S., Sugawara, I. and Takeda, K. (2009): Effect of prenatal exposure to diesel exhaust on dopaminergic system in mice. Neurosci. Lett., **449**, 38-41.

Yoshida, S., Ono, N., Tsukue, N., Oshio, S., Umeda, T., Takano, H. and Takeda, K. (2006): In utero exposure to diesel exhaust increased accessory reproductive gland weight and serum testosterone concentration in male mice. Environ. Sci., **13**, 139-147.

Watson, M. and McElligott, J.G. (1984): Cerebellar norepinephrine depletion and impaired acquisition of specific locomotor tasks in rats. Brain Res., **296**, 129-138.