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Invited Review

Behavioral Teratology of Mercury and Its Compounds

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Satoh, H. *Behavioral Teratology of Mercury and Its Compounds.* Tohoku J. Exp. Med., 2003, **201** (1), 1–9 —— Mercury and its compounds have a wide spectrum of toxicities depending upon the chemical forms and modes of exposure. Among the various chemical forms, mercury vapor and methylmercury are well known and established as neurotoxic agents. Since the disasters in Minamata and Iraq, in which fetuses were more susceptible than adults to methylmercury exposure, much attention has been focused on prenatal exposure to mercury and its consequence. Recently postnatal effects of in utero exposure to methylmercury through fish (and marine mammals) consumption by mothers have been concerned and several epidemiological studies have been conducted. Therefore, one of the most seriously concerned issues is the postnatal effects of in utero exposure to methylmercury. Because of these observations in humans, animal experiments have been conducted employing prenatal exposure to low levels of mercury. This paper reviews the animal (rodents) experiments concerning "behavioral teratology" of mercury for better understanding of effects of prenatal exposure to mercury and its compounds in addition to commentary on history and framework of behavioral teratology. ——— mercury; methylmercury; prenatal exposure; postnatal effects; behavioral teratology

Mercury and its compounds have a wide spectrum of toxicities depending upon the chemical forms and mode of exposure (Clarkson 2002). Among its various chemical forms, mercury vapor and alkylmercury compounds, especially methylmercury, are well known as neurotoxic agents. In human subjects repeated exposure to mercury vapor at low concentration caused mercurial erethism, which is characterized by behavioral and personality changes (Hunter 1969). Methylmercury exposure has been repeatedly shown to cause neurotoxicity;

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the typical signs and symptoms are described as Hunter-Russell syndrome (Hunter 1969).

Since the disasters in Minamata (Harada 1978) and Iraq (Bakir et al. 1973), in which fetuses were more susceptible than adults to methylmercury exposure, much attention has been focused on prenatal exposure to mercury and its consequence. Recently postnatal effects of in utero exposure to methylmercury through fish (and marine mammals) consumption by mothers have been concerned (Davidson et al. 1995; Myers et al. 1995b; Grandjean et al. 1997). Several epidemiological studies have been conducted (Kjellstrom et al. 1986; Kjellstrom et al. 1989; Myers et al. 1995a; Grandjean et al. 1997). The source of mercury is naturally occurring and there are populations who depend on fish as main protein source. Therefore, one of the most seriously concerned issues is the postnatal effects of in utero exposure to low levels of methylmercury.

Based on these observations in humans, animal experiments have been conducted employing prenatal exposure to methylmercury at low concentrations. In this paper, the animal (rodents) experiments concerning "behavioral teratology" of mercury are reviewed for better understanding of effects of prenatal exposure to mercury and its compounds.

What is behavioral teratology ?

"Behavioral teratology" is a field of science where postnatal effects of prenatal exposure to any foreign stimulant are investigated. It is considered that the concept of behavioral teratology was first established by Werboff in 1960s (Werboff and Gottleib 1963). He showed behavioral effects on the offspring of the maternal rats that had taken tranquillizers during pregnancy (Werboff 1966). He reviewed earlier and his studies concerning the behavior of the offspring born to mother animals given psychotropic drugs during pregnancy and claimed, "the behavior, functional adaptation of the offspring to its environment, is susceptible to teratogenic effects of drugs" (Werboff and Gottleib 1963). This behavioral teratology has later expanded the harmful agents by including environmental pollutants.

The dawn of behavioral teratology in mercury toxicology

Spyker and colleagues are the pioneers to study the postnatal effects of in utero methylmercury exposure. They revealed impaired swimming ability in offspring mice exposed to methylmercury in utero (Spyker et al. 1972). The control mice were able to swim easily but the treated mice showed "freezing; floating in a vertical position with only head above water" and swimming with legs askew. They also found changes in behaviors in the open field test. These results indicated the important conclusion that motor dysfunction and emotional change are detectabe postnatally. It was noteworthy that the offspring mice did not show any physical retardation or overt neurological signs and were considered to be normal until being examined by the above tests.

Spyker and colleagues (Weiss and Spyker 1974; Spyker 1975a, b) defined "behavioral teratology" as the overlapping area between behavioral toxicology and teratology, the biological study of malformations. This means that the cause of abnormality occurs during pregnancy and the effects become overt after birth over the lifetime of an individual. This was clearly shown by the "Six D's" in behavioral teratology (Spyker 1975a):

Abnormal Development
Behavioral Deviation
Neurological Disorder
Immunological Deficiency
Generalized Debilitation
Premature Death

In spite of prenatal exposure to an environmental stimulant offspring may be born as "normal" at birth. During lactational period, abnormal development may be observed; examples will be shown later. When the offspring become more mature, various kinds of behavioral examinations are possible and behavioral deviation and neurological disorder may be found. With aging, immunological deficiency and generalized debilitation may be observed and finally the individual may die earlier than expected indicates as premature death. Every item contains "D," thus they are called six D's.

As the framework of a behavioral teratology study, observations such as above were proposed by Spyker. Behavioral teratology tries to find effects of prenatal exposure not only at the early stage of life but also over the lifetime after development and aging.

Current framework of behavioral teratology study: Eight D's

However, six D's do not include very important item for the life, reproduction. Later Tanimura (Tanimura 1980) proposed another D, *Reproductive Debility*. As the issues concerning endocrine disrupting chemicals are being argued, reproductive debility must be seriously concerned. He also emphasized *Birth Defects* that are found at birth because of his expertise, anatomy. Thus, current framework of behavioral teratology study can be shown as Eight D's (Fig. 1), although all the D's in the framework are not examined by the actual studies.

Subtle consequences: Important observation items in the investigation

As emphasized by Spyker and colleagues, subtle consequences are the important findings of behavioral teratology (Spyker et al. 1972; Zbinden 1981). Subtle consequences may mean, 1. so slight as to be difficult to detect or 2. not immediately obvious. Therefore, birth defect that is obvious at once may not be considered by actual studies on behavioral teratology. Abnormal development, behavioral deviation and neurological disorder are items usually examined in behavioral teratology studies.

Immunological deficiency, generalized debilitation or premature death is not usually considered, probably because immunological deficiency may not be directly detected by the behavioral methods. As for generalized

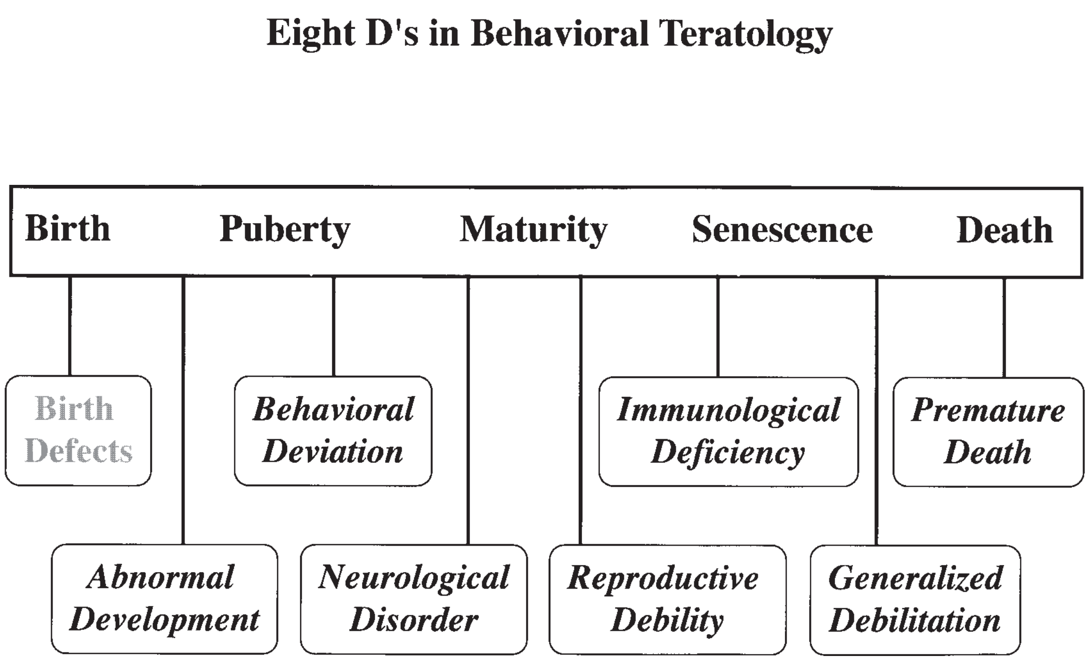

Fig. 1.

debilitation and premature death, previous experiments did not continue such long. Scientists are forced into publishing their studies quickly; they are unable to wait until experimental animals age enough to evaluate debilitation or to observe their death. Generalized debilitation and premature death are two important items, because an individual develops its abilities depending upon its age and accelerated aging may deteriorate the abilities. If deteriorating earlier than normal aging, the individual may not feel totally happy. Therefore, evaluating the possible effect by animal is important.

Findings in behavioral teratology studies

A considerable number of investigations on the effects of in utero methylmercury exposure using animal experimental models have been reported so far (see reviews by Shimai and Satoh 1985; Watanabe and Satoh 1996). The following were observed and reported; development of reflexive behavior during lactational period, swimming ability before and after weaning, passive and active avoidance learning, maze and water escape learning, operant learning, sensory function, spontaneous activity, open field test, susceptibility to convulsion and seizure, and ultrasonic vocalization. Most of the reports revealed retardation, impairment or change, although some failed.

The observed effects above are classified as follows according to the functional category (Table 1, Shimai and Satoh 1985; Watanabe and Satoh 1996). Sensory functions are difficult to examine in animal experiments (Evans et al. 1975; Rice and Gilbert 1995). Most of the experiments examining this functional category were done with primates on visual functions. Although Elsner (1991) trained rats to press a lever with predetermined forces and found impaired performance in methylmercury exposed rats. They had been given methylmercury during the period between 2 weeks before conception and lactation at the concentrations of 1.5 or 5.0 mg Hg/liter in drinking water. It is also interesting that they were examined at 300 days old.

Each function is important for an individual animal to survive. Further, most of these functions develop with age and deteriorate later in the lifetime. It is important that these functions develop under controlled conditions and in the right order of time. If a function does not develop at appropriate time, the individual may have difficult time to survive. Therefore, in behavioral teratology abnormality in ontogeny or ontogenesis must be considered as well as deficit of functions.

Examples of investigations

1. Development of righting reflex and walking activity

As mentioned above, behavioral teratology study has tendency to examine the offspring animal in early development stage. Satoh and colleagues (Satoh et al. 1985) examined the effects on development of righting reflex and walking activity by prenatal exposure. Preg-

TABLE 1. *Functional categories of behavioral teratology*

Functions	Behavior and response
Motor development and functions	Reflexive behavior; Swimming ability
Cognitive functions	Maze, Avoidance, or Operant learning
Motivation and arousal behavior	Spontaneous or Open field activity; Susceptibility to convulsion and seizure
Social functions	Ultra sonic vocalization
Sensory functions	

nant mice were injected with methylmercury at the dose of 6.0 mg Hg/kg on gestational day 9. They were allowed to litter and offspring mice were examined postnatal days 1, 3 and 8 for development of righting reflex and walking activity. The average righting reflex scores of methylmercury treated offspring were lower than the control on postnatal days 1 and 3. On postnatal day 8, however, no difference was found between the two groups. The methylmercury treated offspring showed similar ontogenic pattern (score increases with age of days) to the control, though the scores postnatal days on 1 and 3 were lower. Therefore methylmercury treatment makes the progress slightly being retarded. Similar findings were observed for the score of walking activity.

2. Avoidance learning

With young adult offspring, two-way avoidance can be conducted: An animal has to move from a compartment of a shuttle box to another compartment to avoid electric shock. The animal is warned by sound before electric shock is applied. The learning ability is evaluated how many trials are necessary to avoid electric shock (moving to the safe compartment before electric shock by hearing the sound). On gestational day 8 or 15, methylmercury (4.0 or 6.4 mg Hg/kg) was given to maternal rats by gastric intubations (Eccles and Annau 1982). When the offspring were 63 days old, acquisition was evaluated in a shuttle box. The offspring born to the treated mother needed more trials to learn avoidance. The difference was more distinct among the groups whose mother were given methylmercury on gestational day 15 than those given on gestational day 8. The control offspring needed 50 trials to acquire avoidance and the offspring born to the methylmercury treated mothers needed more than 200 trials. There is no difference between the two doses. Among the offspring given methylmercury on gestational day 8, the effect was not distinguished from the control.

The offspring were also examined later for reacquisition. After acquisition was established the same procedure is repeated without electric shock and thus offspring soon learn that electric shock does not come and they do not move and stay in the same compartment. This is the extinction training. Then again electric shock is applied and reacquisition is evaluated. Learning deficit was clearly shown among the offspring groups with prenatal methylmercury exposure in a dose-dependent manner. The control needed approximately 40 trials for reacquisition, while offspring treated with methylmercury on gestational day 15 with 4.0 or 6.4 mg Hg/kg of methylmercury needed 100 or 150 trials, respectively.

3. Maze learning test with methylmercury exposure originated from marlin or tuna meat

In these experiments described above mostly methylmercury compounds were given. In one experiment (Olson and Boush 1975), however, they gave marlin meat containing methylmercury to maternal rats and found deficit of the offspring in a maze test. Maternal rats were given one of the three diets from gestational day 0 throughout the experiment. Thus, first the maternal rats were exposed and later after weaning offspring rats were exposed. The diets were 1) rat chow for the control, 2) marlin meat+rat chow to adjust methylmercury concentration at 2 mg Hg/kg diet and 3) tuna meat+rat chow+methylmercury hydroxide to adjust methylmercury concentration at 2 mg Hg/kg diet. Offspring rats of 60 day old were examined in symmetrical mazes. It is interesting that offspring given marlin meat diet showed more errors than did the control, while offspring rats given tuna meat did not show more errors. Does methylmercury from different sources affect differently, or tuna meat possibly contained protective agent? No difference between selenium concentrations in both fish meats was reported.

4. Differential reinforcement of high rate; the lowest dose that produced prenatal methylmercury effects experimentally

The doses of methylmercury were various among experiments. They range roughly from the tenth of mg to ten mg Hg/kg body weights of maternal animals. Dosing regimens were single or repeated injections or gastric intubations. Only a few experiments employed dosing through diet (or drinking water).

The lowest dose that produced postnatal effects of prenatal methylmercury exposure in the animal experiment was, however, much smaller (Musch et al. 1978; Bornhausen et al. 1980). The offspring showed deficit in operant learning. In their experiment using the lowest dose (Bornhausen et al. 1980) maternal rats were given methylmercury chloride during gestational day 6–9 by gastric intubations. The doses were 0.004, 0.008 or 0.04 mg Hg/kg per day. At 4 month old, offspring rats were examined by an operant test called differential reinforcement of high rate (DRH). In this test schedule a rat is required to press a small lever at a predetermined number of times within a predetermined time interval to obtain a small pellet of food. Thus, DRH2/1 means two lever presses within one second. No difference was found among the four different dose groups (0, 0.004, 0.008 or 0.04 mg Hg/kg) for the success rate of the DRH2/1 test. But as for the DRH4/2 and 8/4, which require more lever presses, performance decreased in a dose-dependent manner. It is noteworthy that the total dose given to a mother rat is 0.16 mg Hg/kg at the highest dose group. This experiment has shown the lowest amount of methylmercury to produce behavioral changes ever.

5. Postnatal effects of mercury vapor exposure during gestation

Experiments investigating postnatal effects of in utero exposure to mercury vapor are scarce. One (Danielsson et al. 1993) of the few studies is as follows: Maternal rats were exposed to mercury vapor at 1.8 mg Hg^0 for 1 hour or 4 hours during gestational day 11–14 and 17–20. Spatial learning of offspring rats was tested in a radial arm maze. This test is to time the latency to obtain all the food pellets in distal ends of the radial arms. Reentry to the arm of which pellet was already taken was counted as an error. Offspring rats with in utero mercury vapor exposure needed longer time to get the pellets and made more errors. This result indicates neurobehavioral effects of prenatal exposure to mercury vapor in utero.

6. Interaction of methylmercury and mercury vapor co-exposure

It is likely that people in real life are exposed to various kinds of pollutants. As for mercury, people may be exposed to methylmercury by fish consumption and to mercury vapor with dental amalgam. Therefore, an experiment where animals were exposed to both mercury vapor and methylmercury was done (Fredriksson et al. 1996). The test procedure is similar to the previous one. Maternal rats were exposed to mercury vapor at 1.8 mg Hg^0 for 1.5 hour/day during gestational day 14–19. They were also given methylmercury chloride at a daily dose of 2 mg Hg/kg during gestational day 6–9. Co-exposure to mercury vapor and methylmercury caused longer time and more errors in the radial maze test comparing with single exposure to either methylmercury or mercury vapor.

7. Postnatal effects of maternal stress and methylmercury exposure during pregnancy

Whether postnatal development and behavior are affected by interaction with maternal stress was also examined (Colomina et al. 1997). Pregnant mice were exposed to methylmercury (1.6 mg Hg/kg/day) during gestational day 15–18. Stress was given as immobilization in a cylinder, 2 hours/day. However, no significant interaction on developmental landmarks or neurobehavioral development of offspring mice

TABLE 2. *Factors that may influence the effects of prenatal mercury exposure*

Species, strain and sex of experimental animals
Time of exposure during pregnancy
Heat exposure during pregnancy
Maternal behavior, Maternal care and Fostering
Nutrition, e.g. Selenium and Poly unsaturated fatty acids
Environment after birth, e.g. Enriched environment
Behavioral examinations employed
Age at examination
Miscellaneous

during lactational period was observed.

Factors that may influence the postnatal behavioral effects of prenatal mercury exposure

Retardation of development of reflexes was partly counteracted by co-administration of selenium (Satoh et al. 1985). Moreover, offspring mice born to the dams fed with selenium deficiency diet and given methylmercury injections during gestation were more severely affected than the offspring of groups of selenium deficiency alone or methylmercury administration alone (Satoh et al. 1997). Maternal heat exposure before methylmercury administration during gestation did not enhance the postnatal effects of methylmercury, though heat exposure showed interactions (Yin et al. 1997). Since in the studies of behavioral teratology, the main goal is to elucidate postnatal effects of in utero exposure that does not cause overt maternal, fetal or neonatal toxicities, the doses become necessarily low. This also means the effect is more easily influenced by other factors and agents in the environment. Therefore, recognition of these factors and agents are important to evaluate experimental results. In Table 2 factors to be considered are listed.

Most behavioral evaluations were done during lactational periods or at several tens days of age. Few examined the effects at the elderly, though aging is an important factor to evaluate full spectrum of methylmercury toxicity.

Conclusions

This review shows that behavioral teratology reveals subtle consequences of in utero exposure to mercury vapor and methylmercury; namely, behavioral teratology is sensitive to detect postnatal effects of prenatal exposure to mercury. However, some experiments, which were not described here, failed to detect the effects. In these experiments the doses used were similar to those above mentioned. Therefore, behavioral teratology is not always sensitive. For example, the behavioral effects may be masked by the age of examination.

Another problem of behavioral teratology is the underlying mechanism(s) of behavioral changes have not been fully investigated. What is the mechanism of behavioral changes? It may be alteration(s) in 1) developmental and ontogenetic, 2) physiological and psychological, 3) neurochemical and pharmacological function(s), or 4) histopathological changes. Further studies including investigation into mechanisms are necessary with the considerations on possible "interactions" such as selenium status and other environmental exposure and with the efforts expanding of investigation period over the lifetime of animals as indicated by the framework, namely, "Eight D's."

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