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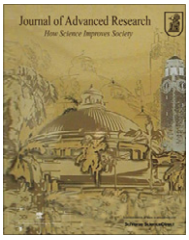

MINI REVIEW

Neurotoxicity of 1-bromopropane: Evidence from animal experiments and human studies

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Abstract 1-Bromopropane was introduced as an alternative to ozone layer-depleting solvents such as chlorofluorocarbons and 1,1,1-trichloroethane. However, a dozen human cases have been reported with symptoms and signs of toxicity to 1-bromopropane including numbness, diminished vibration sense in the lower extremities as well as ataxic gait. An epidemiological study also demonstrated dose-dependent prolongation of distal latency and decrease in vibration sense in the lower extremities. The initial animal experiments helped to identify and analyze the initial human case of 1-bromopropane toxicity. However, animal data that can explain the central nervous system disorders in humans are limited. Nonetheless, animal data should be carefully interpreted especially in a high-order function of the central nervous system or neurological signs such as ataxia that is influenced by fundamental anatomical/physiological differences between humans and animals. Enzymatic activity in the liver may explain partly the difference in the susceptibility between humans and animals, but further studies are needed to clarify the biological factors that can explain the difference and commonality among the species.

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Introduction

1-Bromopropane is a chemical that was initially used as an intermediate for chemical synthesis. However, it has been labeled as a solvent since the end of 1990's and used for cleaning metals including electronic parts [1] based on its less harmful ozone layer-depletion property. However, workers exposed to 1-bromopropane-containing solvents were reported to complain of numbness, weakness, vibration sense loss in the lower extremities, in addition to ataxic gait [2–5]. This was later followed by an epidemiological field

study, which showed dose-dependent neurologic deficits in workers exposed to 1-bromopropane [6]. In this regard, animal studies have played a critical role in our understanding the causality of 1-bromopropane-related neurologic deficits in humans [5]. This review outlines the neurotoxicity of 1-bromopropane in humans, and compares these with those noted in the experimental animal, as well as discusses the possible mechanisms of toxic effects of 1-bromopropane.

Neurotoxicity of 1-bromopropane in humans (Tables 1 and 2)

The first case of 1-bromopropane intoxication was reported in New Jersey, USA [5]. A worker engaged in degreasing of metals using solvent containing mainly 1-bromopropane, complained of weakness of the lower extremities and right hand, numbness, dysphagia and difficulty in micturition. Nerve conduction velocity test showed prolongation of distal latency and reduction of sensory nerve conduction velocity in the lower extremities, but the amplitudes of the corresponding motor and sensory-evoked potentials were within the normal ranges except for mild reduction (3.1 μV) in the left sural nerve. Gadolinium-enhanced magnetic resonance image (MRI) of the brain showed patchy areas of increased T2 signal in the periventricular white matter. MRI of the spinal cord showed enhancement in the neuronal region in the proximity of the root ganglia at several thoracic and lumbar levels. Somatosensory evoked potential test also suggested a lesion at the dorsal column of the spinal cord or lemniscal level. While that paper described a single case report, the author hypothesized that the neurologic deficits were due to exposure to 1-bomopropane citing previous animal experiments on 1-bromopropane neurotoxicity [7–9]. The second report of human cases of 1-bromopropane toxicity described three female workers who were engaged in the manufacture of furniture in North Carolina, USA [2]. After 10-month exposure to 1-bromopropane, one worker developed irritation of the mucosal membranes of the sinuses and throat as well as urinary incontinence. Further exposure to 1-bromopropane resulted in gait disturbances during standing and walking. The worker also complained of numbness, dysesthesia in the lower limbs, numbness in the perineum, abnormal sweating, diarrhea, headache and memory disturbance. The other two workers in the same factory complained of similar symptoms and signs. These cases suggested not only sensory abnormalities in the lower extremities as reported previously [5], but also numbness in the perineum, headache, diarrhea, urinary incontinence and abnormal sweating.

Other similar cases were also reported in Utah [3] and in North Carolina, USA [4]. These cases are summarized in Table 2. Numbness and decrease in vibration sense in the lower extremities were common in these cases. Dizziness, nausea and headache were also often reported. In Utah cases, hyperreflexia, which indicates disorders of the central nervous system, was described in five patients out of six. On the other hand, the first New Jersey case showed trace to absent ankle jerk reflex, neutral plantar reflex, and +3 for knee ankle reflex. The discrepancy between the reduced ankle jerk reflex in the New Jersey case and hyperreflexia in the Utah cases may be explained by the degree of damage to the peripheral nerve, which could reduce the reflex, but this possibility should be examined in further studies.

With regard to the electrophysiological studies, the Utah cases did not show abnormality in conduction velocity of the peripheral nerves, except for the motor distal latency of the peroneal and ulnar nerves being at the upper limit of the normal range (6.1 ms and 3.5 ms, respectively) [3]. In comparison, a recent epidemiological study showed that exposure to 1-bromopropane caused prolongation of tibial distal latency and reduction of sural sensory nerve conduction velocity without significant changes in the amplitude of the corresponding potentials and dose-dependent diminished vibration sense in the lower extremities [6]. The findings of this epidemiological study [6] is in agreement with the first New Jersey case [5], regarding the results of the electrophysiological studies of lower extremities. Whether nerve conduction velocity is affected or not depends on the exposure level and period. A slow conduction velocity and long distal latency without a marked decrease in the amplitude of the corresponding potentials suggest demyelinating polyneuropathy, rather than axonal polyneuropathy [10]. This interpretation is supported also by rat experiments that showed myelin degeneration in the muscle branch of the posterior tibial nerve, tibial nerve and/or peroneal nerve after exposure to 1-bromopropane for 12 weeks at 800 ppm [11] or for 5–7 weeks at 1000 ppm [7].

Regarding the neurobehavioral effects, the two severely intoxicated cases out of the three North Carolina cases [2] were depressed, but sometimes irritated and tended to get angry. The Utah cases [3] also complained of depressive mood. One epidemiological study showed lower scores for tension, depression, anxiety, fatigue and confusion in profile of mood status (POMS) in the exposed group than in the age-matched control [12], but a recent epidemiological study did not show dose-dependency in any of the POMS scores [6]. There are no epidemiological studies that can explain the mood status in the above human cases. Three of the North Carolina cases [2] and one of the Utah cases [3] complained of reduced short-term memory and the latter was confirmed by a cognitive test. Epidemiological studies also showed lower cognitive function [6,12].

In summary, human cases intoxicated with 1-bromopropane mainly develop numbness and diminished vibration sense in the lower extremities. One case and one epidemiological study showed prolongation of the distal latency without marked reduction of the amplitude of the corresponding potential, suggesting myelin damage in the peripheral nerves. Reflexes in the lower extremities were reported to be enhanced as well as diminished, suggesting that 1-bromopropane is toxic to the central nervous system and peripheral nerves.

Neurotoxicity of 1-bromopropane in animals (Table 3)

Using the mouse as the laboratory animal, a few studies investigated the kinetics [13], reproductive toxicity [14,15] and liver toxicity [15,16] of 1-bromopropane. However, no studies have provided data on neurotoxicity of 1-bromopropane in mice. Thus, the following discussion on animal experiments on 1-bromopropane-associated neurotoxicity is limited to rat experiments.

Exposure of rats to 1-bromopropane induced prolongation of motor distal latency and reduction of motor nerve conduction velocity in the tail nerve [7–9,11,17]. These results paralleled those of the human case that showed prolongation of

Table 1 Summary of human and epidemiological studies on 1-bromopropane neurotoxicity.

Place and workers	Work and exposure period	Summary of clinical signs and symptoms	Reference
Human cases. New Jersey, US. Male (19-year-old)	Metal stripper, degreasing, 2 months	Numbness and diminished vibration sense, Elongated in distal latency of lower extremities and decreased in sensory nerve conduction velocity, MRI change in periventricular white matter and in the region of neural foramen, in the proximity of the nerve root ganglia at thoracic and lumbar levels, A lesion at the dorsal column or lemniscal level in somatosensory-evoked potential studies	[5]
North Carolina, US. 3 Females (30, 35, 50-year-old)	Manufacturer of furniture, glue spray. Time weighted average of 1BP: 133 ppm (range 60–261 ppm) after improvement of ventilation	Numbness, paresthesia/dysesthesia, diminished vibration sense in lower extremities and perineum, diarrhea, dizziness, headache, depression or anger, dizziness, sleep disturbance	[2]
Utah, US. 4 Females (26, 28, 29 and 43-year-old). 2 Males (16 and 46-year-old)	Manufacturer of furniture, glue spray. The mean ambient air concentration of 1BP: 130 ppm (range 91–176 ppm). Time weighted average of 1BP: 108 ppm (range 92–127 ppm)	Numbness, paresthesia and diminished vibration sense, hyperreflexia, poor tandem gait, poor balance nausea, dizziness, nausea, headache	[3]
North Carolina, US. 3 Females (22, 28 and 42-year-old). 1 Male (29-year-old)	Manufacturer of furniture, glue spray. The geometric mean of 1BP for spray: 107 ppm (range 58–254 ppm) after improvement of ventilation. Confounding factor: high urinary arsenic levels	Numbness in lower extremities, depression, sleep disturbance, headache, nausea, anorexia, hyperreflexia, ataxic gait, poor tandem gait, ocular symptoms	[4]
New Jersey, Pennsylvania, US. Male 50-year-old. Male 43-year-old	Degreasing (short term air sampling, 178 ppm). Dry cleaning	paresthesia, dysarthria, ataxia, confusion, dizziness, headache, malaise, dizziness, nausea, slight tremor in upper extremity	[37]
Epidemiology. Jiangsu, China. 24 Females, 13 males	Production of 1BP. ND–170 ppm	Symptoms suggesting mucous irritation and adverse effects on the central nervous system. No severe chronic symptoms suggestive of neurological damage	[38]
Epidemiology. Jiangsu, China. 23 Females, 23 non-exposed age-matched females	Production of 1BP. Geometric mean: 2.92 ppm (range 0.34–49.19 ppm)	Elongation of tibial distal latency, decrease in sural sensory nerve conduction velocity, decrease in vibration sense in toes. Lower scores in Digit span, Benton, Pursuit aiming test, Tension, Depression, Anxiety, Fatigue and Confusion of Profile of Mood Status (POMS)	[12]
Epidemiology. Jiangsu and Shandong, China. 60 Females, 26 Males. 60 Non-exposed age-matched females. 26 Non-exposed age-matched males	Production of 1BP. 0.07–106.4 ppm (males). 0.06–114.8 ppm (females)	Dose-dependent prolongation of tibial distal latency, decreased vibration sense in toes, increase in LDH, TSH and FSH in female workers	[39]

Table 2 Comparisons of human cases intoxicated with 1-bromopropane.

Location	NJ	NC			UT						NC				NJ	PA
Work	Degreasing	Gluing			Gluing						Gluing				Degreasing	Dry cleaning
Age (years)	19	35	30	50	29	43	28	26	46	16	42	22	29	28	50	43
Gender	M	F	F	F	F	F	F	F	M	M	F	F	M	F	M	M
Exposure period	2m	12m	5m	9m	3m	3m	3m	3m	3m	3m	2w	2w	3w	3w	3y	2d
Numbness/ diminished sensation in LEs	+	+	+	+	+	+	+	+	+	–	+	+	+	+		
Paresthesia/ dysesthesia in LEs		+	+	+	+	+	+	+	+	Nr	+	+	+		+	+
Diminished vibration sense in LEs	+	+	+	+	+	+	Nr	+	+	Nr		+	+			
Dysphagia	+	+	+													
Diarrhea		+	+	+							+					
Dysuria or incontinence	+	+	+													
Depressive mood		+	+									+	+			
Dizziness/nausea		+	+	+	+	Nr	Nr	+	+	Nr		+	+		+	+
Memory disturbance		+	+	+	+											
Headache		+	+	+	+	–	Nr	+	+	Nr	+	+		+		+
Sleep disturbance		+	+	+							+	+	+			
Hyperreflexia in LEs	+/–				+	+	+	+	+	–		+	+			
Ataxic/unsteady gait		+	+								+	+	+	+	+	
Poor tandem gait			–		+	+	+	+	–	+	+	+				

LE: lower extremities, NJ: New Jersey, NC: North Carolina, UT: Utah, PA: Philadelphia, Nr: Not reported.

the distal latency in the lower extremities [5]. In other studies [7,11], exposure of rats to 1-bromopropane also resulted in myelin sheath degeneration in the common peroneal and tibial nerves, which also corresponded with the prolongation of the distal latency without reduction of amplitude of the corresponding potentials in the human case [5]. Initial rat studies [7,11] were conducted even before the first report of the first human case, and thus helped understand and assess the seriousness of the neurotoxicity identified in the first human case [5]. On the other hand, the neurotoxic effects of 1-bromopropane in human cases were expected to be evident at the dorsal column or lemniscal level based on somatosensory evoked potentials [5]. Swelling of the preterminal axons in the gracile nucleus of the medulla oblongata [7,11] might correspond with the above expected lesions of the dorsal column. MRI of the brain and spinal cord in the first human case [5] showed abnormal areas in the periventricular white matter and multiple thoracic levels in the areas of the neural foramina, in the proximity of the nerve root ganglia, but to the best of our knowledge, there are no histopathological studies in animals that provide direct support to the human MRI changes.

The initial rat studies on dose-dependency [9,11] showed a decrease in cerebral weight at 800 ppm, 8 h/day, 7 days/week for 12 weeks. This decrease in cerebral weight should be noted as a possible indicator of toxicity to the central nervous system, given that toluene, which is known to cause atrophy in the human brain, did not decrease any brain regions of cerebrum, cerebellum or brainstem in rats at 1000 ppm, 8 h/day, 6 days/week for 16 weeks [18]. On the other hand, there is no report yet of brain atrophy in human cases intoxicated with 1-bromopropane.

The initial rat studies showed pyknotic shrinkage in the cerebellum after exposure to 1-bromopropane for 5–7 weeks and degeneration of Purkinje cells in the vermis of the cerebellum after exposure at 1500 ppm for 4 weeks. Since the morphological changes in Purkinje cells were not evident following exposure to $\leqslant$800 ppm for 12 weeks, the cerebellar toxicity seems to be limited to exposure greater than 1000 ppm. While other groups [19,20] described ataxic gait in rats, it is difficult to compare this with the ataxic gait in humans since the 4-footed walking rat is different from the bipedal walking human in terms of expression of ataxia. Regarding ataxia in humans, the authors of a case report on the four patients from North Carolina discussed the involvement of sensory deficits in ataxia [4], but they also pointed out that the severity of ataxia seemed out of proportion to the sensory deficit. Among the four cases reported, one individual showed positive Romberg sign, while another showed moderate past-pointing in finger to nose testing [4]. On the other hand, none of the three cases described by our group showed any positive signs in Romberg test or finger to nose, heel–shin, line-drawing or pronation-supination test. Further studies are needed to localize the responsible lesion in the brain that accounts for the ataxic gait in humans caused by 1-bromopropane neurotoxicity.

Serial studies [19–23] using brain slices from rats exposed to 1-bromopropane showed decreased paired-pulse inhibition of the population spikes in the granular cells of the dentate gyrus (DG) and hippocampus CA1, but this disinhibition was reversible and not accompanied by morphological changes, in contrast to kainic acid-induced neurotoxicity [21]. Further studies are needed to interpret the disinhibitory effects of 1-bromopropane on DG and CA1 in relation to the neurological abnormalities in humans with 1-bromopropane neurotoxicity.

Honma et al. [24] investigated the neurobehavioral effects of 1-bromopropane in rats exposed to the vapor of the solvent

at 10, 50, 200 and 1000 ppm for three weeks. Spontaneous locomotor activity increased following exposure to 50 and 200 ppm, but reversed to the baseline level within 6 days after cessation of exposure. In the open field test, ambulation and rearing increased at 200 ppm but defecation/urination decreased at 1000 ppm. In the water maze performance test, the latency increased at days 14 and 21 at 1000 ppm, but reversed to the baseline level. This decrease in Water maze test might explain the memory disturbance in human cases, but the authors interpreted this change to be due to impaired muscle system as shown by decrease in traction time at 200 and 1000 ppm, which did not reverse at day 7 after the end of the exposure. The authors discussed the decrease in traction time, which was more persistent than other neurobehavioral indices, and suggested it was due to peripheral nerve toxicity of 1-bromopropane. This change in the traction time might correspond with the decrease in forelimb muscle strength, which was found in our initial animal study [11]. Thus, animal studies showed clear evidence of 1-bromopropane toxicity on the peripheral nerves. On the other hand, these studies indicate that the neurotoxic effects of 1-bromopropane on the central nervous system are limited to axonal swelling of preterminal axons in the gracile nucleus at 800 and 1000 ppm, reversible paired pulse inhibition in DG at 400–700 ppm and CA1 at 700 ppm, increase in spontaneous locomotor activity at 50 and 200 ppm, increase in ambulation and rearing in the open field test at 200 ppm, increase in latency of water maze performance at 1000 ppm, and degeneration of Purkinje cells in the cerebellum at very high concentration of 1000–1500 ppm (Table 3). The results of the animal studies provide experimental support to the toxicity of 1-bromopropane on peripheral nerves in humans. On the other hand, animal experiments on the toxicity of 1-bromopropane on the central nervous system are limited and further studies are needed to obtain data supporting the data on humans, such as the change in brain or spinal cord MRI or somatosensory evoked potential studies as well as explaining the symptoms related to the central nervous system, such as memory disturbance and depressive mood in humans.

History of investigation of neurotoxicity of 1-bromopropane in animals and human

The first experiment that hinted to possible neurotoxicity of 1-bromopropane was originally designed to investigate possible neurotoxicity of its isomer 2-bromopropane where 1-bromopropane was used as a possible negative control [7,17]. However, the results were different from the expectation that 2-bromopropane is more reactive than 1-bromopropane in living systems, which was an assumption based on the result of mutagenicity tests [25,26]. The initial experiments provided the basis to suspect 1-bromopropane toxicity in the initial group of human cases [2–5]. The first human case was differentiated from multiple sclerosis and described and analyzed by referring to the first animal experiments [5], although, retrospectively speaking, these animal studies had several limitations. For example, the methods of investigating peripheral nerve deficits in 1-bromopropane toxicity had been developed for analysis of hexane neuropathy [27], which is known to induce mainly peripheral polyneuropathy in humans, although the distribution of sensory deficits in humans and histopathological features of paranodal swelling in the peripheral nerves of rats induced by hexane are quite different from those induced by 1-bromopropane [2]. The human cases of 1-bromopropane intoxication identified after the initial animal experiments showed more obvious clinical symptoms/signs related to the central nervous system than the hexane intoxication cases [3]. In this regard, the initial animal experiments without awareness of the human cases were more oriented to the analysis of peripheral nerves than the central nervous system.

Furthermore, after finding the human cases intoxicated with 1-bromopropane, neuro- or glia-specific markers that had been developed to investigate toluene toxicity [18,28] were used to examine the effects of 1-bromopropane on the central nervous system [29,30]. However, interpretation of the behavior of such markers of neuron-specific proteins or glia-specific proteins is still uncertain, because how these proteins are involved in the toxicity of 1-bromopropane on the central nervous system remains obscure. Thus, we have to find new biomarkers to understand the mechanism of 1-bromopropane neurotoxicity.

Exploration of new biomarkers of central nervous system toxicity

A previous inhalation study on the effects of 1-bromopropane on two rat generations showed changes in maternal behavior after exposure [31]. Neurobehavioral effect of 1-bromopropane was also suggested by the irritation noted in workers exposed to 1-bomopropane. A four-week rat inhalation study screened the most affected areas of the brain by quantitative real-time polymerase chain reaction (PCR) method for mRNA expression levels of various neurotransmitter receptors [32]. The study showed reductions in the mRNA expression levels of dopamine R2 receptor in the hippocampus and 5-hydroxytryptamine receptor (5HTr)1a and 5HTr3a in the pons-medulla oblongata at the lowest level of exposure (400 ppm), suggesting they are the most sensitive markers to 1-bromopropane exposure, although analysis of the corresponding protein levels did not confirm these changes. However, at least practically, the study provides the rationale to focus on the hippocampus in future DNA microarray and proteomics analysis studies to identify biomarkers of central nervous system toxicity of 1-bromopropane. Suda et al [33] measured the neurotransmitter levels in different areas of the brain in rats exposed for three weeks to 1-bromopropane at 10, 50, 200 and 1000 ppm. However, their study did not show dose-dependent changes in dopamine in any of the investigated brain areas, although dopamine decreased significantly only at 50 ppm.

Other studies approached the neurotoxicity of 1-bromopropane by analyzing its electrophysiological disinhibitory effects in DG and CA1 of the hippocampus [19,20]. However, it is not clear whether these electrophysiological effects are related to the above analysis of mRNA expression of neurotransmitter receptors. The reported electrophysiological changes were not accompanied by morphological changes [21]. Based on several studies, changes in the morphological structure of the central nervous system are the most robust compared to electrophysiological or biochemical indices. Thus, development of biomarkers for studying the central nervous system is important for the assessment of the risk of inhalational chemicals on the central nervous system.

Table 3 Summary of results of animal studies on neurotoxicity of 1-bromopropane.

Exposure level	Observed changes	Reference
Rats, 1000 ppm, 8 h/day, 7 days/week, 5–7 weeks	Increase in distal latency (DL), decrease in motor nerve conduction velocity (MCV) of tail nerve, axonal swelling in the gracile nucleus of medulla oblongata, degeneration of myelin in the common peroneal nerve, pyknotic shrinkage of Purkinje cells in the cerebellum	[7]
Rats, 200, 400, 800 ppm, 7 days/week, 12 weeks	Dose-dependent decrease in muscle strength of fore- and hind-limbs, increase in DL, decrease in MCV of the tail nerve, swelling of pre-terminal axons in the gracile nucleus of medulla oblongata, degeneration of myelin in muscle branch of posterior tibial nerve and tibial nerve, irregular banding in soleus muscle, decrease in cerebral weight	[9,11]
Rats, 1500 ppm, 6 h/day, 5 days/week, 4 weeks	Degeneration of Purkinje cells in the vermis and hemisphere of the cerebellum, ataxic gait	[40]
Rats, 200, 400, 800 ppm, 7 days	Dose-dependent decrease in cerebral and cerebellarγ-enolase with a significant change at 400 and 800 ppm, swelling of pre-terminal axons in the gracile nucleus of medulla oblongata, degeneration of myelin in muscle branch of posterior tibial nerve at 800 ppm	[29]
Rats, 200, 400, 800 ppm, 7 days/week, 12 weeks	Dose-dependent decrease in cerebral γ-enolase with a significant change at 400 and 800 ppm	[30]
Rats, 10, 50, 200, 1000 ppm, 8 h/day, 3 weeks	Increase in spontaneous locomotor activity at 50 and 200 ppm (reversible). Increase in ambulation and rearing at 200 ppm. Decrease in defecation and urination at 1000 ppm. Increase in latency for water maze performance at days 14 and 21 at 1000 ppm (reversible). Decrease in traction time at 200 and 1000 ppm (not reversed 7 days after the end of exposure).	[24]
Rats, 1500 ppm, 6 h/day, 5 days/week, 1, 3, 4 weeks	Increase in paired pulse ratios (PPRs) of population spike (PS) in granule cell layers of dentate gyrus (DG) in brain slice obtained from the rats	[20]
Rats, 1500 ppm, 6 h/d, 5d/w, 1, 3, 4 weeks	Field excitatory postsynaptic potentials (fEPSPs)/spike (E/S) potentiation, lower subthreshold of population spikes (PSs) in DG at week 3 and 4. Decrease in paired-pulse inhibition in CA1 and DG	[19]
Rats, 800 ppm, 6 h/d, 5d/w, 8 weeks	Increase in PPRs of PS in DG and CA1, increase in phosphorylated mitogen-activated protein kinase (MAPK) and total amount of Ca^{+2}/calmodulin-dependent kinase (CaMKII) α and β, decrease in CaMKIIβ.	[22]
Rats, 700 ppm, 6 h/day, 5 days/week, 12 weeks	Increase in PPRs of PS in DG and CA1 (reversible)	[21]
Rats, 200 and 400 ppm, 6 h/day, 5 days/week, 12weeks. Rats, 400 ppm, 6 h/day, 5 days/week, 1, 4, 8, 12 weeks	Increase in PPRs of PS in DG at 400 ppm after 8- and 12-week exposure	[23]
Rats, 400 ppm, 6 h/day, 5 days/week, 12 weeks	Increase in PPRs of PS in DG at 400 ppm, decrease in mRNA expression of $GABA_A$ β3 and δ receptors	[41]
Rats, 400 ppm, 6 h/day, 5 days/week, 12 weeks	Decrease in mRNA expression of Bcl-xL in neocortex, HIP and cerebellum	[42]
Rats, 50, 200, 1000 ppm, 8 h/day, 7 days/week, 3 weeks	Two hours after the end of the last exposure: DA↓(STR: 50 ppm), DOPAC↓(HIP*), 5HIAA↓(FC: 50, 1000 ppm, STR: 200 and 1000 ppm), GABA↓(HIP*), aspartate↑(HIP*, midbrain*, cerebellum*), glutamine↑(HIP*, midbrain*, cerebellum*). 19 hrs after the end of the last exposure: HVA↓(STR*), HVA/DA↓(STR*), NE↓(HT*), MHPG↓(OC*), MHPG/NE↓(OC*), 5HT↑(OC*), 5HIAA↑(medulla oblongata*), aspartate↑(OC*, HIP*, STR*, HT*, cerebellum*), glutamate↓(midbrain: 50,200 ppm), glutamine↑(FC*, OC*, HIP*, STR*, midbrain*, HT*, cerebellum*), GABA↓(FC*, OC*, HIP*), taurine↓(OC*, HIP: 200 and 1000 ppm, STR*, midbrain: 50, 200 and 1000 ppm, HT*, medulla-oblongata*, cerebellum*), methionine↓(HT*), cystathionine↑(OC*, midbrain*, cerebellum*), cystathionine↓(OC: 200 ppm, HT: 50 ppm), serine↑(FC*, OC*, HT*, cerebellum*), serine↓(midbrain: 50 and 200 ppm), threonine↑(FC*, OC*, HIP*, STR*, HT*, cerebellum*), threonine↓(midbrain: 50 and 200 ppm), β-alanine↑(FC*, OC*, HIP*, STR*, midbrain*, HT*, medulla oblongata*, cerebellum*)	[33]
Rats, 400, 800, 1000 ppm, 8 h/day, 7 days/week, 4 weeks	mRNA level of neurotransmitter receptors: 5HTr1a↓(pons-medulla: 400, 800 and 1000 ppm, cortex: 800 and 1000 ppm), 5HTr2a↓(HIP*, cortex: 800 ppm), 5HTr2c↑(cortex*), 5HTr3a↓(midbrain*, pons-medulla: 400, 800 and 1000 ppm), 5HTr3a↑ (amygdala: 400 and 1000 ppm), D1R↓(cerebellum: 800 ppm, cortex: 800 ppm), D2R↓(HIP: 400, 800 and 1000 ppm), GABAa1↓(HIP: 800 ppm, 1000 ppm, cortex: 800 ppm), GABAa2↑(amygdala*)	[32]

DA: dopamine, DOPAC: 5HIAA: 5-hydroxyindoleacetic acid, GABA: gamma-amino butyric acid, HVA: homovanillic acid, NE: norepinephrine, MHPG: 4-hydroxy-3-methoxyphenyl-glycol, 5HT: 5-hydroxytryptamine (serotonin), STR: striatum, HIP: hippocampus, HT: hypothalamus, FC: frontal cortex, OC: occipital cortex, *Significant change only at the highest level of 1000 ppm.

Mechanism of 1-bromopropane neurotoxicity

The decrease in cerebral weight and neuro-specific gamma-enolase suggests that 1-bromopropane induces severe toxicity of the central nervous system, though the direct action sites of 1-bromopropane and its cellular mechanisms remain elusive. Here, we focus on recent studies on the molecular mechanism of 1-bromopropane toxicity.

1-bromopropane is conjugated with glutathione and depletes glutathione in the liver and brain, although a compensatory increase in glutathione was also observed in the spinal cord and brain stem in rats [29,30]. Part of 1-bromopropane is oxidized by cytochrome P450IIE1(CYPIIE1). Comparison of CYPIIE1 null mice and wild type mice showed that CYPIIE1 enhanced the toxicity of 1-bromopropane on sperm motility [14]. Another comparative study of three inbred mice, C57BL/6 J, DBA/2 J and BALB/CA also showed higher levels of CYPIIE1 and lower levels of glutathione S-transferase (GST) and that glutathione contributes to the hepatotoxicity of 1-bromopropane [15]. The same comparative study in mice also showed higher susceptibility of the liver in mice relative to rats [15], which may be explained by the greater capacity for metabolism of 1-bromopropane via oxidation in the B6C3F1 mouse than in F344 rat [14]. The difference in susceptibility of the liver may be due to the higher levels of CYP2E1 in the liver of male B6C3F1 mice than male Wistar rats [34]. However, human cases and epidemiological studies did not show any evidence of hepatotoxicity, so it is possible that human resembles the rat more than the mouse, with regard to hepatotoxicity [15]. The extremely high susceptibility of the liver in mice discourages us from increasing the exposure level of 1-bromopropane [15], resulting in difficulty in producing observable neurotoxic effects in mice.

1-Bromopropane also produces S-propyl cyteine adduct in neurofilaments as well as globin in rats and humans, suggesting alkylating effect of 1-bromoporopane on the sulfhydryl base of the cysteine in proteins [35]. These effects explain the result of low levels of protein bound sulfhydryl base in the brain of intoxicated rats [29,30]. A study using the nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2)-null mice demonstrated the involvement of oxidative stress in the hepatotoxic effect of 1-bromopropane, but whether the same mechanism explains its neurotoxicity remains elusive [16]. Further studies are needed to clarify the role of alkylation of sulfhydryl base in the toxic effect of 1-bromopopane.

Conclusions

The toxicity of 1-bromopropane was first described in animals [7,11,36] followed by description in human. Animal experiments helped the identification and analysis of the initial human case of 1-bromopropane toxicity [5]. On the other hand, animal data that can explain the clinical symptoms and signs of neurotoxicity in human cases are limited. Animal data should be carefully interpreted especially in a high-order function of the central nervous system or neurological signs such as ataxia, due to fundamental anatomical and physiological differences between humans and animals. Liver enzymatic activity may explain at least in part the differences in the susceptibility between humans and animals, but further studies are needed to fully clarify the biological factors that explain the difference and commonality among species.

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