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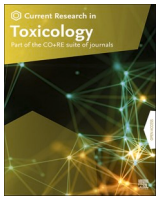

Thallium - poisoner's poison: An overview and review of current knowledge on the toxicological effects and mechanisms

Junko Fujihara [a,*], Naoki Nishimoto [b]

[a] Department of Legal Medicine, Shimane University Faculty of Medicine, 89-1 Enya, Izumo, Shimane 693-8501, Japan
[b] Shimane Institute for Industrial Technology, 1 Hokuryo, Matsue, Shimane 690-0816, Japan

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ABSTRACT

Thallium (Tl) is one of the most toxic metals and its historic use in homicides has led it to be known as "the poisoner's poison." This review summarizes the methods for identifying Tl and determining its concentrations in biological samples in recently reported poisoning cases, as well as the toxicokinetics, toxicological effects, toxicity mechanisms, and detoxication methods of Tl. Recent findings regarding Tl neurotoxicological pathways and toxicological effects of Tl during pregnancy are also presented. Confirmation of elevated Tl concentrations in blood, urine, or hair is indispensable for diagnosing Tl poisoning. The kidneys show the highest Tl concentration within 24 h after ingestion, while the brain shows the highest concentration thereafter. Tl has a very slow excretion rate due to its large distribution volume. Following acute exposure, gastrointestinal symptoms are observed at an early stage, and neurological dysfunction is observed later: Tl causes the most severe damage in the central nervous system. Alopecia and Mees' lines in the nails are observed within 1 month after Tl poisoning. The toxicological mechanism of Tl is considered to be interference of vital potassium-dependent processes with Tl^+ because its ionic radius is similar to that of K^+, as well as inhibition of enzyme reactions by the binding of Tl to -SH groups, which disturbs vital metabolic processes. Tl toxicity is also related to reactive oxygen species generation and mitochondrial dysfunction. Prussian blue is the most effective antidote, and metallothionein alone or in combination with Prussian blue was recently reported to have cytoprotective effects after Tl exposure. Because Tl poisoning cases are still reported, early determination of Tl in biological samples and treatment with an antidote are essential.

1. Introduction

Thallium (Tl) is a nonessential element that is homologous for aluminum, gallium, and indium in group IIIA of the periodic table. Tl, which discovered in 1861, is one of the most toxic metals (Goyer and Clarkson, 2001), with higher toxicity than Hg, Cd, Pb, Cu, and Zn (Cvjetko et al., 2010). Tl is listed by the US Environmental Protection agency as one of the major pollutants, along with Hg, Cd, and Pb (ATSDR, 2015). The lethal Tl dose is 10–15 mg/kg in humans and death can even occur at a lower dose of 8 mg/kg (Al Hammouri et al., 2011; Riyaz et al., 2013). Compared with adults, children are more sensitive to Tl exposure: one-tenth of the adult lethal dose can cause death in children (Duan et al., 2020).

Tl exists in two oxidation states: Tl^+ and Tl^{3+}. Both forms are toxic to living organisms (Rickwood et al., 2015), although the toxicity of Tl^{3+} is about 50,000 times higher than that of Tl^+ on the basis of the free ion concentration of each Tl redox state (Ralph and Twiss, 2002). However, the bioavailable concentration of Tl^{3+} is much lower than that of Tl^+. In contrast to other metals (Al^{3+}, Ga^{3+}, and In^{3+}) in group IIIA, Tl^+ is more stable than Tl^{3+} (Rodríguez-Mercado and Altamirano-Lozano, 2013). The properties of Tl^+ and potassium ion (K^+) are similar due to their comparable ionic radii, and Tl^+ generally forms the most stable Tl salts (John Peter and Viraraghavan, 2005). Tl^{3+} is similar to aluminum, which has strong oxidizing properties and rarely exists in nature (Zhuang and Song, 2021). Tl salts with high solubility are uncolored, inodorous, and tasteless compounds. At low doses, symptoms are slow to manifest and can easily be misdiagnosed as other ailments. The English writer Agatha Christie made Tl poisoning a central part of her 1961 novel *The Pale Horse*. Due to their properties, high toxicity, and high recognition as a poison, Tl-based salts have been used as "the poisoner's poison" to the present (Lennartson, 2015). This review summarizes the analytical methods for Tl determination in biological samples, Tl

* Corresponding author.
E-mail address: jfujihar@med.shimane-u.ac.jp (J. Fujihara).

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concentrations in biological samples from recent criminal cases of Tl poisoning, and the toxicokinetics, toxicological effects, toxicological mechanisms, and recent detoxication methods of Tl. The neurotoxicity of Tl exposure and the toxicological effects of Tl during pregnancy have not been fully elucidated, although current studies are investigating these topics. This review also covers the findings of a recent study on Tl neuro-toxicological pathways and the toxicological effects of Tl during pregnancy.

2. Tl in the environment

Tl is widely distributed in the environment at very low concentrations (Fig. 1a). It is naturally found as sulfide minerals (e.g., lorandite and crookesite). The average Tl concentrations in the Earth's crust are between 0.3 and 0.5 mg/kg and it is present mainly in the sulfide ores of Zn, Cu, Pb, Cd, and Fe (Galván-Arzate and Santamaría, 1998; John Peter and Viraraghavan, 2005). Tl concentrations in uncontaminated sediment range from 0.22 to 0.55 mg/kg (Liu et al., 2019), while those in soil range from 0.1 to 1 mg/kg (Rodríguez-Mercado and Altamirano-Lozano, 2013). Tl is released into the environment as Tl_2O by air emissions from coal burning and by Zn, Cu, Pb, and Cd smelters. Tl concentrations are less than 1 ng/m^3 in unpolluted air, approximately 10–20 ng/L in sea water and less than 1 μg/L in fresh water. Elevated Tl concentrations (1–88 μg/L) have been reported in river waters near metal mining areas (Zitko et al., 1975). The maximum permissible Tl contaminant level in drinking water is suggested to be 2 μg/L (USEPA, 2022). Tl concentrations in food are less than 100 μg/kg dry weight, and higher concentrations have been found in seafood (IPCS, 1996). A recent study reported that Tl^+, $TlSO^{4-}$, TlCl, and $TlNO_3$ are the main forms of Tl in ground water (Liu et al., 2021). In most natural environments, Tl^+ ions are the predominant species because they are thermodynamically stable (Lan and Lin, 2005).

3. Production and use of Tl

Tl is obtained from Fe, Cd, and Zn refining as a by-product (Galván-Arzate and Santamaría, 1998) and is separated by electrolysis (Blain and Kazantzis, 2015). The most common commercial forms of Tl are Tl acetate (CH_3COOTl), Tl carbonate (Tl_2CO_3), and Tl sulfate (Tl_2SO_4), which have oxidation states of I, while compounds with an oxidation state of III include Tl trichloride ($TlCl_3$) and Tl sesquioxide (Tl_2O_3) (Rodríguez-Mercado and Altamirano-Lozano, 2013). With the exception of Tl sesquioxide, Tl compounds are stable in aqueous solutions and soluble in water (Rodríguez-Mercado and Altamirano-Lozano, 2013).

The uses of Tl are shown in Fig. 1b. Tl_2SO_4 and CH_3COOTl have been used as rodenticides and insecticides. They were banned in 1965 in the United States due to concerns about environmental pollution and high toxicity (Riyaz et al., 2013). However, they are still used in many developing countries (Sánchez-Chapul et al., 2023). ^{201}Tl-thallous chloride has been used in myocardial imaging to evaluate ischemic heart disease; this radioactive Tl emits X-rays and gamma-rays and is intravenously administered (Genchi et al., 2021). Tl^+ shows good nuclear magnetic resonance properties and can be used as a probe to emulate the biological functions of K^+ and Na^+ (Blain and Kazantzis, 2015). Tl is used to produce imitation jewelry and artificial diamonds, to create the green color in fireworks, and as a catalyst of organic compound synthesis (Rodríguez-Mercado and Altamirano-Lozano, 2013). Contemporary demand for Tl is increasing in advanced industrial technologies. Tl is

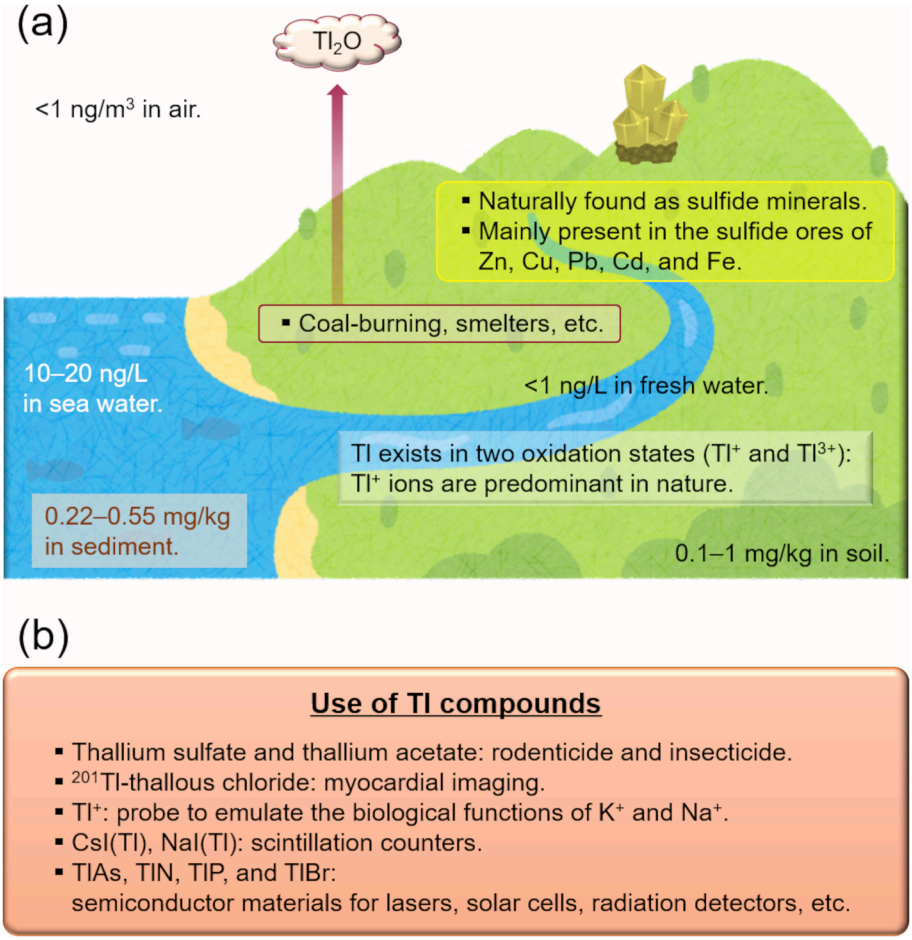

Fig. 1. Thallium in the environment and its usage.

utilized in camera lenses, scintillation counters (CsI(Tl)), and low-temperature thermometers in alloys with mercury (Genchi et al., 2021). In addition, Tl-containing semiconductor materials have been expected to apply for various electronic devices. The theoretical band gap energies of TlAs, TlN, and TlP that have zinc blende structure are ~0 eV (Ferreira da Silva et al., 2005; Gulebaglan et al., 2013). Accordingly, Tl-containing III–V compound semiconductors are attractive materials for optoelectronic devices operating at infrared region. For instance, TlGaAs could be used to fabricate higher-quality and more efficient devices (e.g., laser diodes, solar cells) (Nishimoto et al., 2003; Zayan and Vandervelde, 2019; Nikoo et al., 2022). TlBr with cesium chloride structure has high density (7.56 g/cm^3) and a comparatively wide band gap energy (2.68 eV) (Dönmez et al., 2010). Due to these properties, the gamma-ray absorption efficiency is high. Hence, TlBr is suitable material for radiation detector (Churilov et al., 2009; Park and Lee, 2023).

4. Methods for determining Tl in biological samples

Atomic absorption spectrometry (AAS) is most frequently used method for determining Tl in biological samples and includes flame AAS (Richelmi et al., 1980; Chandler et al., 1990), flameless AAS, graphite furnace AAS (Tanaka et al., 1978; Ríos et al., 1989), and electrothermal AAS (Yang and Smeyers-Verbeke, 1991). The detection range of flame AAS is in the order of ppb to ppm, whereas that of flameless AAS is in ppb. Atomic fluorescence spectrometry is rarely used for Tl analysis in biological samples (Mori et al., 1994). Inductively coupled plasma-mass spectrometry (ICP-MS) has recently become the most commonly used method for Tl determination in biological specimens due to its high sensitivity (dynamic range: ppq to ppb) (Das et al., 2006; Li et al., 2015; Di Candia et al., 2020; Pragst and Hartwig, 2022). In addition, laser ablation-inductively coupled plasma-sector field-mass spectrometry (LA-ICP-SF-MS) was used to determine the Tl concentration in the bone of someone who was killed by Tl poisoning 38 years ago (Hann et al., 2005). Inductively coupled plasma-optical emission spectrometry (ICP-OES) is also used for detecting Tl in biological samples, with a dynamic range from ppb to ppm (Lech and Lachowicz, 2009; Gupta et al., 2023). Microwave plasma-atomic emission spectrometry, which is a recently introduced technique for multi-element analysis with a low running cost (Fujihara and Nishimoto, 2020; Fujihara and Nishimoto, 2023), is also expected to be applied to Tl analysis in biological samples.

To determine Tl in biological samples (body fluids and tissues) by using the above methods, pretreatment is required. In the case of urine and serum analysis, pretreatment can be achieved by HNO_3 dilution. In Tl analysis using GF-AAS, Duan et al. (2020) performed a 10-time dilution of urine with a diluent containing 0.03 % HNO_3, 0.02 % Triton, and 0.66 g/L palladium chloride. In other studies, urine samples were diluted 1/10 (v/v) in a solution containing 1 % HNO_3, and blood and serum were diluted by an alkaline solution containing 0.02 % Triton X-100 and 3 % ammonia solution before ICP-MS analysis (Heitland and Köster, 2021; Pragst and Hartwig, 2022). For tissue analysis, acid digestion by concentrated HNO_3 (65 %) with or without H_2O_2 (30 %) is performed by heating, using a microwave, heat block, and so on (Tanaka et al., 1978; Hann et al., 2005; Das et al., 2006; Di Candia et al., 2020). For example, Lech and Lachowicz (2009) performed acid digestion with a microwave by adding 4 mL of HNO_3 and 1 mL of H_2O_2 to blood (1 mL), urine (2–8 mL), and tissue (1–2 g) and then heating at 250 W (1 min), 0 W (2 min), and 250, 400, and 600 W (5 min each). Following digestion, the samples were diluted to 10 or 25 mL. Hair samples should be washed with detergent such as Triton X-100 before acid digestion to remove exogenous contaminants.

In contrast to the above destructive methods, nondestructive methods are also available to determine Tl levels in biological specimens. Goldman et al. (1966) performed Tl determination using X-ray emission spectroscopy in urine and feces at ppm levels. Neutron activation analysis (NAA) is another nondestructive analytical technique for trace element determination with an ultralow detection limit and simple preparation of samples (Das et al., 2023). Minoia et al. (1990) used NAA to perform Tl determination in urine and blood from healthy Italians. Similarly, Henke (1991) performed Tl analysis in bovine liver and bone with NAA.

5. Tl concentrations in biological samples

Equipment for Tl analysis is present in a minority of reference laboratories and evidence for Tl exposure is not rapidly available to clinicians (Ghannoum et al., 2012). However, confirmation of an elevated Tl concentration in blood, urine, or hair is necessary for the definitive diagnosis of Tl poisoning. Tl concentrations in biological specimens in Tl poisoning cases are summarized in Table 1.

A 24-h urine sample is considered necessary to identify Tl poisoning. Tl cannot be detected in most persons, and levels up to 20 μg/specimen are considered to be normal for occupational and environmental exposure (Rusyniak et al., 2010). The normal urine Tl concentration is less than 5 μg/L. The typical clinical symptoms are observed when the urinary Tl concentration exceeds 500 μg/L (Huang et al., 2014), and a concentration greater than 200 μg/L can be used as a basis for diagnosing acute Tl poisoning (Moore et al., 1993). Renal excretion reflects the total Tl load (Moore et al., 1993). However, urinary Tl concentrations do not correlate with blood concentrations or symptoms (Ghannoum et al., 2012). Serum Tl levels are much lower than in other tissues and poorly representative of the toxicokinetic profile of target organs (Richelmi et al., 1980). The normal total blood Tl concentration is less than 2 μg/L and levels greater than 100 μg/L are toxic (Moore et al., 1993).

Hair is an important specimen for understanding the historical internal exposure to heavy metals: the keratin in hair, due to its high cysteine content, has high affinity for Tl, similar to other heavy metals. Tl levels in hair less than 15 ng/g are considered normal (Mulkey and Oehme, 1993). Hirata et al. (1998) reported elevated Tl concentrations (0.02–0.58 ng/mg) in the hair of workers at a glass factory, based on ICP-MS results. Ash and He (2018) evaluated the Tl concentration in the hair of a "cold case" victim of Tl poisoning that occurred 24 years ago using LA-ICP-MS and revealed that the victim had been repeatedly exposed to Tl for 4 months.

6. Toxicokinetics of Tl

6.1. Absorption

The toxicokinetics of Tl follow a three-compartment model. The first compartment with rapid exchange comprises the intravascular system and highly perfused organs (within 4 h of exposure). The second compartment with slow exchange includes the central nervous system, which lasts 4–48 h (Riyaz et al., 2013). The third compartment comprises the large and small intestines, which are responsible for wide enteroenteric circulation and the long half-life of Tl (De Groot and van Heijst, 1988). The toxicokinetics of Tl are summarized in Fig. 2a.

Both Tl^+ and Tl^{3+} can exist under biological conditions (Harris and Messori, 2002). Tl^+ salts, which are water-soluble, can enter the body through the K^+ uptake mechanism (Mulkey and Oehme, 1993; Galván-Arzate and Santamaría, 1998). Tl is absorbed through almost all routes: the skin, inhalation, and the gastrointestinal tract (Goyer and Clarkson, 2001; Rodríguez-Mercado and Altamirano-Lozano, 2013). Respiration is the main absorption route (in the form of fumes) in the industrial environment, and significant amounts of Tl can also be absorbed via the skin (Rodríguez-Mercado and Altamirano-Lozano, 2013). When ingested, Tl is rapidly and completely absorbed through the gastrointestinal tract (Achenbach et al., 1980; Rodríguez-Mercado and Altamirano-Lozano, 2013). The oral bioavailability of hydrophilic Tl salts reaches 90 %–100 % (De Groot and van Heijst, 1988; Mulkey and Oehme, 1993).

Table 1
Summary of thallium poisoning cases and thallium concentrations in biological samples.

Survival time after Tl ingestion	Case	Time after ingestion	Tl concentrations at hospital	Postmortem Tl Concentrations	Detection method	Reference
Survivor	A 28-year-old woman ingested about 1 g of thallium sulphate and was discharged 28 days after admission	4 days 7 days	Urine: 3 mg/L Gastric content: 10.8 mg/L Saliva: 9 mg/L	–	AAS	Richelmi et al., 1980
	A 43-year-old man developed acute abdominal colic and diarrhea a few hours after drinking a beverage contaminated with thallium sulphate	21 months	Blood: 336.5 μg/L Urine: 252.3 μg/L	–	AAS	Liu and Liao, 2021
	Five adult patients who attended a banquet ate a Tl-contaminated meal (33–49 years old)	9–12 days	Blood: 40–280 μg/L Urine: 250–7200 μg/L	–	AAS	Wang et al., 2021
	A 40-year-old man ate a thallium nitrate-contaminated supper	3 days	Blood: 3764 ng/mL	–	ICP-MS	Huang et al., 2014
	A 44-year-old man ate a meal contaminated with thallium sulphate	49 days	Blood: 175 μg/L	–	ICP-MS	Pragst and Hartwig, 2022
	A 23-year-old woman drank tea contaminated with thallium sulphate	10 days	Blood: 223 μg/L Urine: 351 μg/L	–	Unknown	Yumoto et al., 2017
	A 28-year-old woman lapsed into a coma due to severe thallium poisoning (source unknown) and was discharged 137 days after admission	35 days	Blood: 950 ng/mL Urine: 7600 ng/mL	–	Unknown	Lin et al., 2019
	A 24-year-old woman ingested food deliberately mixed with Tl	22 days	Blood: 180 ng/μL Urine: 930 ng/μL	–	Unknown	Zhao et al., 2008
	A 31-year-old man ingested food deliberately mixed with Tl	23 days	Blood: 90.9 ng/μL Urine: 1825 ng/μL	–	Unknown	
	A 37-year-old man drank water deliberately mixed with Tl	21 days	Blood: 288.4 ng/μL Urine: 2359 ng/μL	–	Unknown	
	Eleven members of two families (2–42 years old) ingested Tl	5–7 days	Blood: 323.5 μg/L Urine: 1959 μg/L	–	Unknown	Al Hammouri et al., 2011
	Nine patients (3 adults and 6 children) (2–73 years old) from a family ingested Tl-contaminated rice	9–15 days	Serum: 506.3–985.2 μg/L Urine: 4345–9998 μg/L	–	Unknown	Zhang et al., 2014
	A 35-year-old woman exposed to rodenticide at her workplace at 13 weeks of pregnancy experienced a spontaneous abortion at 18 weeks	Unknown	Urine (24 h): 3400 μg/L	–	Unknown	Hoffman, 2000
30 days	A 22-year-old man ingested 50 mL of 2 % thallium sulphate and died 30 days later	30 days	–	Brain: 0.02 μg/g Liver: 0.015 μg/g Kidney: 0.01 μg/g	GF-AAS	Tanaka et al., 1978
23 days	A 49-year-old woman ingested thallium sulphate mixed with table salt	About a week	Urine: 8.8 μg/mL	Hair: 10.20 μg/mL Blood: 0.019 μg/mL Urine: 3.15 μg/mL Brain: 2.03 μg/mL Liver: 0.98 μg/mL Kidney: 0.98 μg/mL Heart: 0.57 μg/mL Lung: 0.46 μg/mL Stomach: 0.38 μg/mL	ICP-MS	Li et al., 2015
3 days	A 50-year-old man ingested thallium sulphate mixed with table salt	About 2 weeks	Urine: 4.3 μg/mL	Hair: 13.75 μg/mL Blood 0.15 μg/mL Urine: 3.60 μg/mL Brain: 2.58 μg/mL Liver: 5.08 μg/mL Kidney: 2.21 μg/mL Heart: 1.83 μg/mL Lung: 0.88 μg/mL Stomach: 4.02 μg/mL	ICP-MS	
2 days	Thallium sulfate poisoning of 8 members of a family (3 of whom died) Father	Unknown	Blood: 3.4 μg/mL Urine: 22.7 mg/L	Blood: 2.75 μg/mL Urine: 1.49 mg/L Hair: 10.11 ng/mg	ICP-MS	Di Candia et al., 2020

(continued on next page)

Table 1 (*continued*)

Survival time after Tl ingestion	Case		Time after ingestion	Tl concentrations at hospital	Postmortem Tl Concentrations	Detection method	Reference
2 days		Mother	Unknown	Blood: 10 μg/mL Urine: 42.0 mg/L	Blood: 1.15 μg/mL Gastric content: 1.11 mg/L Hair: 10.38 ng/mg	ICP-MS	
14 days		Daughter	Unknown	Blood: 5.7 μg/mL Urine: 16.3 mg/L	Blood: 6.01 μg/mL Gastric content: 3.43 mg/L Hair: 5.72 ng/mg	ICP-MS	
–	A man poisoned with rodenticide by his daughter-in-law and buried for 29 years		Unknown	–	Bone: 1.07–2.63 μg/g	LA-ICP-MS	Hann et al., 2005
4 days	A 36-year-old man ingested an unknown amount of thallium sulphate from rodenticide and died after 4 days		1 days	Blood: >1000 μg/L Urine: >2000 μg/L	Blood: 5349 μg/L	Unknown	Riyaz et al., 2013

AAS, atomic absorption spectrometry
ICP-MS, inductively coupled plasma-mass spectrometry
GF-AAS, graphite furnace-atomic absorption spectrometry
LA-ICP-MS, laser ablation-inductively coupled plasma-mass spectrometry

6.2. Tissue distribution

Following its rapid absorption, Tl^+ is widely distributed to organs and tissues (Ríos et al., 1989; Mulkey and Oehme, 1993) through the systemic circulation after binding to serum transferrin (Harris and Messori, 2002). A large apparent volume of distribution of Tl (3–10 L/kg) has been reported (De Groot and van Heijst, 1988). The highest concentration of Tl is found in the kidney after acute poisoning (Goyer and Clarkson, 2001). Ríos et al. (1989) reported that the Tl concentration in the kidney was about three times higher than that in other tissues and that the whole brain had the lowest concentration following 24 h of intraperitoneal administration of Tl_2SO_4 in rats. They reported differential Tl distribution within the brain: the hypothalamus showed the highest concentration, while the cortex showed the lowest concentration. Achenbach et al. (1980) reported the organ-specific uptake of Tl by the heart, liver, kidney, and stomach during the first 2–3 h, and the Tl concentration in the brain was relatively low and constant during the first 12 h; all organs showed increased Tl concentrations after 24 h following oral administration to mice. Galván-Arzate et al. (2005) showed higher Tl concentrations in the brain following subchronic intraperitoneal administration (30 days) of a sublethal dose (0.8 and 1.6 mg/kg) of CH_3COOTl to adult rats. In a human case (Table 1), the Tl concentration was highest in the brain (0.02 μg/g), followed by the liver (0.015 μg/g) and kidney (0.01 μg/g) in a man who died 30 days after the ingestion of 50 mL of 2 % Tl_2SO_4 (Tanaka et al., 1978) (Table 1). Li et al. (2015) also reported that the brain showed the highest Tl concentration among tissues in a man and woman who died about a week after Tl_2SO_4 ingestion (Table 1). Tl can easily cross the blood–brain barrier (BBB) (Galván-Arzate et al., 2000) and placenta (Hoffman, 2000). The placenta is another selective transport interface through which a number of environmental metals have been documented to exert toxicological effects. Heavy metals can pass through the placenta (Caserta et al., 2013) and Tl is one of those metals (Hoffman, 2003).

6.3. Metabolism

Metallothionein (MT) is a cysteine-rich (20 residues) metal-binding protein comprising 61–68 amino acids that is synthesized in hepatocytes following heavy metal exposure (Nordberg and Nordberg, 2000). Its possible biological role lies in metabolizing and neutralizing heavy metals (Klaassen and Liu, 1998; Sugiura and Yamashita, 2000) and scavenging free radicals. Kiliç and Kutlu (2010) suggested that exogenous MT acts as a scavenger of Tl and defends against reactive oxygen species (ROS) in rat liver intraperitoneally exposed to CH_3COOTl.

6.4. Excretion

Large amounts of Tl are excreted in the urine approximately 24 h after exposure; thereafter, excretion from the urine slows and the feces may then become an important route of excretion (Goyer and Clarkson, 2001). Overall, 51 % of Tl is eliminated through the bile and feces, while 26 % is excreted in the urine (Mulkey and Oehme, 1993). In humans, Tl is also excreted in sweat, saliva, tears, and breast milk (Rodríguez-Mercado and Altamirano-Lozano, 2013). Richelmi et al. (1980) reported that salivary Tl levels were 5–15 times higher than those of urine during the first 2 weeks and that the time-course change in Tl concentrations was quite similar to that in urine in a 28-year-old woman who ingested Tl_2SO_4. Deposition in the nails and hair is also a key route of slow Tl elimination because the keratin in nails and hair has a high cysteine content and cysteine has a high affinity for Tl. Tl excreted slowly from the body explains its large distribution volume (a term used for quantifying the distribution of Tl between plasma and the rest of the body). Accordingly, Tl is retained in tissues for a long period and can be detected months or even years after exposure. Liu and Liao (2021) detected Tl in the blood and urine of a patient as for up to 21 months after the ingestion of Tl_2SO_4 (Table 1). The slow excretion rate enables the accumulation of Tl even at low exposure levels (Cvjetko et al., 2010). The half-life of Tl depends on the dose and the nature of exposure (route, acute, or chronic). The elimination half-life of Tl in humans has been reported to be as long as 30 days (Goyer and Clarkson, 2001), and Tl remains in the body for days or even months, leading to prolonged neurological insufficiency or permanent damage.

7. Toxicological effects of Tl

7.1. Short-term effects following acute poisoning

Acute Tl poisoning, that is, single ingestion of large amount of Tl in a short time, will usually cause gastrointestinal symptoms, which emerge within the first few hours (John Peter and Viraraghavan, 2005; Cvjetko et al., 2010). When a lower amount of Tl is ingested, symptoms usually develop within 1–2 days. Severe abdominal pain is observed, with vomiting, nausea, and diarrhea. Tl specifically affects the nervous system (sensory and motor changes) (ATSDR, 2015). In humans, acute exposure to Tl leads to critical damage in the central, peripheral, and autonomic nervous systems (Galván-Arzate et al., 2005; John Peter and Viraraghavan, 2005). Rapid progressive and painful peripheral neuropathy development is observed within 2–3 days of exposure (Reed et al., 1963; Malbrain et al., 1997; Rusyniak et al., 2002). Symptoms

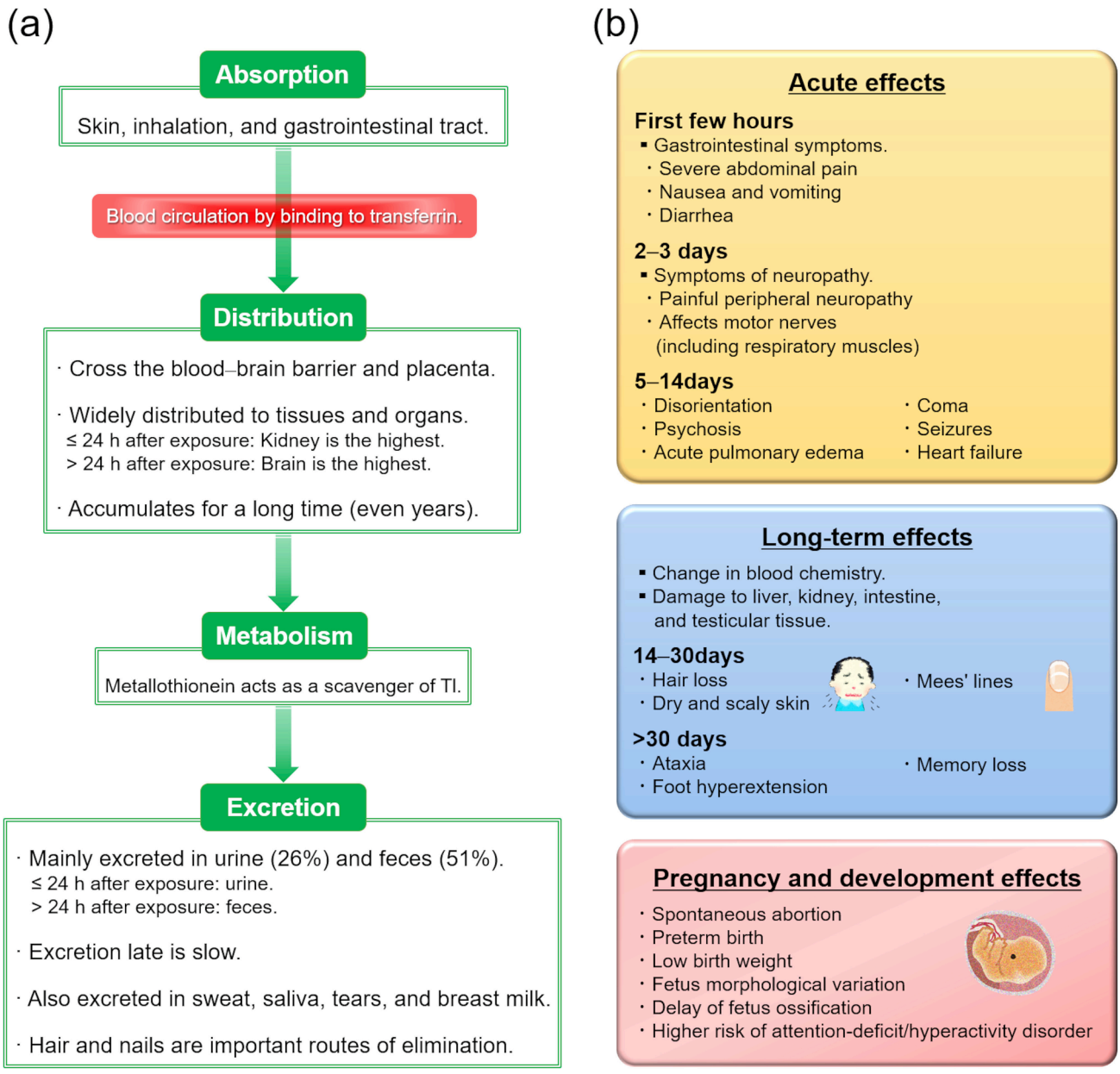

Fig. 2. Biological fate (a) and toxicological effects (b) of thallium.

begin in the feet and legs and extend to the hands (Rusyniak et al., 2010). Motor nerves are affected, including those innervating respiratory muscles (Hologgitas et al., 1980; Rusyniak et al., 2002). Tl poisoning can sometimes be misdiagnosed as Guillain–Barré syndrome due to similar symptoms of neuropathy (Mulkey and Oehme, 1993). Moreover, disorientation, coma, psychosis, seizures, acute pulmonary edema, and heart failure are observed 5 h to 14 days after poisoning (Meggs et al., 1994; Hoffman et al., 1999; Rusyniak et al., 2002). Psychiatric disorders such as psychosis, depression, aggressiveness, hallucinations, cognitive disorders, and emotional disorders have been reported in patients with acute Tl intoxication (Cavanagh et al., 1974; Zavaliy et al., 2021). Disorientation and generalized slowing on electroencephalography is observed with acute Tl poisoning (McMillan et al., 1997). This acute cardiovascular effect may result from competition of Tl^+ with K^+ for membrane transport systems, which leads to inhibited oxidative phosphorylation in mitochondria and disrupted protein synthesis (Goyer and Clarkson, 2001).

7.2. Long-term effects following acute poisoning

In the long term, Tl alters the blood chemistry, damages the liver, kidney, intestine, and tissue in the testes, and causes hair loss (Das et al., 2006). Elevated levels of aspartate transaminase and alanine transaminase have been reported (Zhao et al., 2008; Al Hammouri et al., 2011; Riyaz et al., 2013; Li et al., 2015; Lin et al., 2019; Wang et al., 2021), as well as elevated CK-MB (Wang et al., 2021) and lactate dehydrogenase (Al Hammouri et al., 2011). Alopecia is the best-known symptom of Tl poisoning (Galván-Arzate and Santamaría, 1998; Rusyniak et al., 2002). Tl poisoning specifically induces active hair loss >100 hairs/day in the 2–4 week period after poisoning and often presents as diffuse alopecia 2–3 weeks after Tl exposure (Cvjetko et al., 2010; Yu et al., 2018). Mees' lines (transverse white lines in the nails) are observed about 1 month after Tl poisoning due to impaired fingernail growth (Zhao et al., 2008). Additionally, dry and scaly skin is observed 2–4 weeks after the poisoning, and ataxia, foot hyperextension, and memory loss have been reported more than 30 days after exposure to Tl

(Meggs et al., 1994; Hoffman et al., 1999; Rusyniak et al., 2002). Chronic exposure to Tl results in alterations to the brain, spinal cord, and peripheral nerves (Galván-Arzate et al., 2005). The toxicological effects of Tl are summarized in Fig. 2b.

7.3. Toxicological effects of prenatal and postnatal exposure

As mentioned above, Tl can easily be transported via the placenta to the fetus. Rapid uptake and retention of Tl occurred in both the maternal and fetal organs following oral exposure to Tl_2SO_4 in pregnant rats (Sabbioni et al., 1982). Prenatal exposure increases the risk of spontaneous abortion (Hoffman, 2000) as well as preterm birth and low birth weight (Qi et al., 2019; Wu et al., 2019; Zhou et al., 2021; Chen et al., 2022). Alopecia has been observed in children exposed to Tl during the fetal stage, although some children were born grossly normal or with limited poisoning manifestations even though their mothers exhibited symptoms of severe Tl poisoning (Hoffman, 2000). Álvarez-Barrera et al. (2019) demonstrated that intraperitoneal injection of CH_3COOTl to pregnant mice induced morphological variations in the fetus and a delay in fetal ossification. Moreover, recent studies have reported that high levels of Tl exposure during pregnancy are related to a higher risk of attention-deficit/hyperactivity disorder and lower full-scale intelligence (Tong et al., 2020).

Infants are also at risk of Tl exposure via breastfeeding. Previous quantitative evidence has confirmed that Tl is eliminated in breast milk (Hoffman, 2000). Johnston et al. (1996) reported ^{201}Tl concentrations in the breastmilk of a female brain-tumor patient administered ^{201}Tl for a brain scan at 2–500 h after administration. To our knowledge, no studies have investigated the effects of Tl on infants exposed through breast milk. The toxicological effects of Tl during pregnancy are summarized in Fig. 2b.

8. Toxicological mechanism

The toxicological mechanisms of Tl are shown in Fig. 3. One proposed mechanism of Tl toxicity is the similarity of the ionic radius of Tl^+ to that of K^+ (Rusznyák et al., 1968). In addition, they are both univalent ions (John Peter and Viraraghavan, 2005). In the reduced state, the ionic radius for Tl^+ is 1.76 Å while that of K^+ is 1.60 Å (Rader et al., 2019; Rinklebe et al., 2020). K^+ can easily be replaced with Tl^+ and Tl^+ can mimic the biological behavior of K^+ (Diwan and Lehrer, 1977) and interfere with vital potassium-dependent processes. A low level of serum potassium (3.3 mEq/L) was reported in a Tl poisoning case (Tanaka et al., 1978). Tl^+ may replace K^+ in Na^+/K^+ ATPase and thereby inhibit Na^+/K^+ ATPase activity (John Peter and Viraraghavan, 2005; Cvjetko et al., 2010). In the rabbit kidney, the affinity of Tl^+ for activating Na^+/K^+ ATPase has been reported to be 10 times greater than that of K^+ (Britten and Blank, 1968). In addition to ATPase, Tl^+ replaces physiological K^+ in monovalent cation-activated enzymes such as pyruvate kinase and aldehyde dehydrogenase (John Peter and Viraraghavan, 2005).

Another mechanism of Tl toxicity is its ability to react with thiol (-SH) groups of proteins and mitochondrial membranes, similar to other heavy metals (John Peter and Viraraghavan, 2005; Cvjetko et al., 2010). Tl has a high affinity for S ligands because it has empty *d*-orbitals in its electronic configuration (Cvjetko et al., 2010). Tl poisoning may be

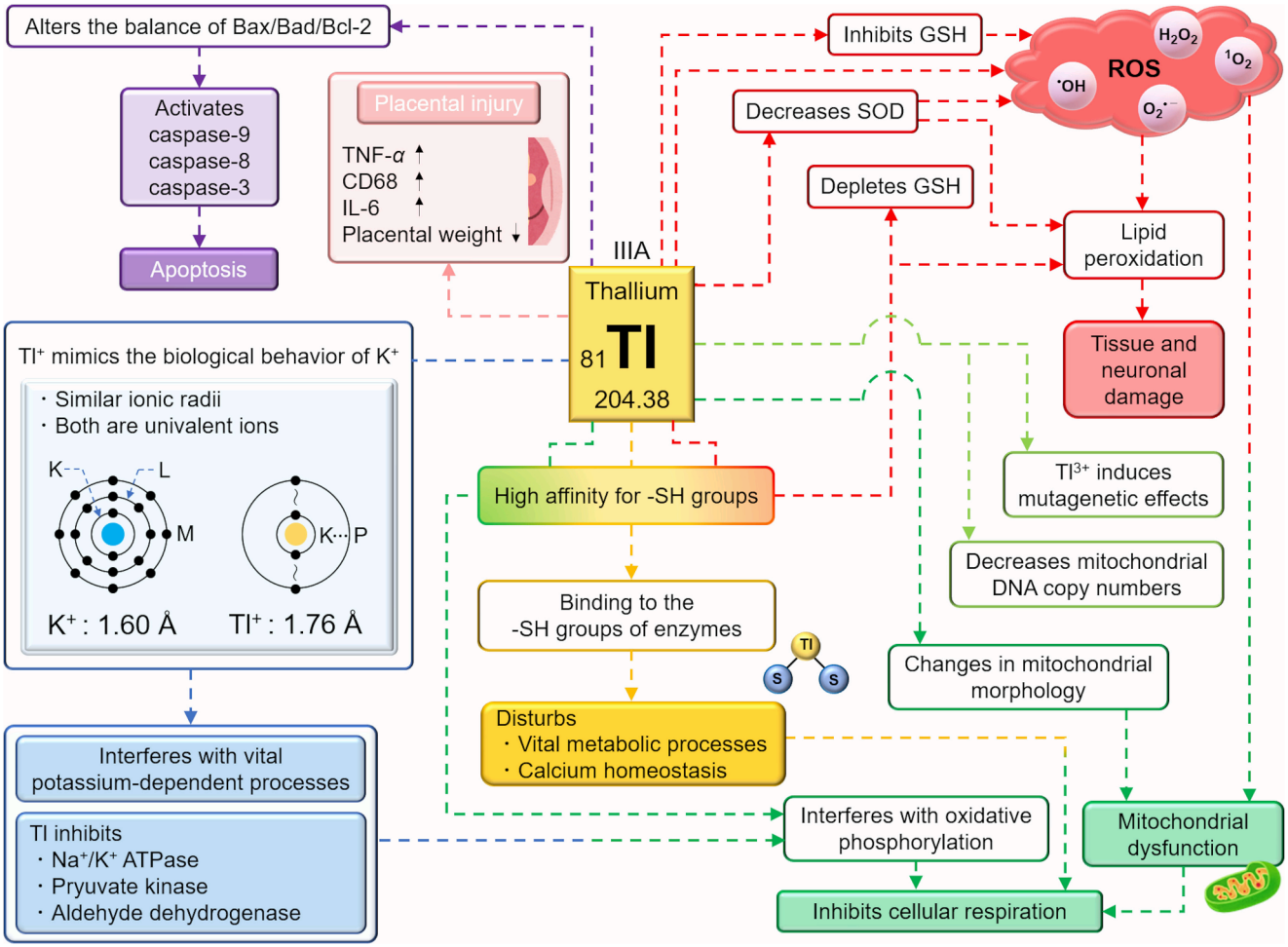

Fig. 3. Schematic of the toxicity mechanism of thallium. GSH, glutathione; ROS, reactive oxygen species; SOD, superoxide dismutase.

induced by inhibition of a variety of enzyme reactions as a result of -SH group binding, which disturbs vital metabolic processes (Ramsden, 2002). Tl may exert toxicity by inhibiting cellular respiration, interacting with riboflavin and riboflavin-based cofactors, and disrupting calcium homeostasis (Mulkey and Oehme, 1993). In addition to competing with K^+, Tl binds to -SH groups in mitochondria and interferes with oxidative phosphorylation. The affinity of Tl for -SH groups may also lead to lipid peroxidation and intracellular glutathione depletion (Goyer and Clarkson, 2001) and disruption of calcium homeostasis (Kiliç and Kutlu, 2010). Intra-subunit disulfide bonds of Cu-Zn superoxide dismutase (SOD), which remove superoxide anions from living organisms, may also be a target of Tl. In the rat, Cu-Zn SOD activity is significantly decreased by Tl administration (Galván-Arzate et al., 2005). In addition, hair loss, the main symptom of Tl poisoning, is caused by its binding to the -SH groups of hair keratins and its disruption of hair shaft formation (Kanwar and Narang, 2013). Moreover, Tl toxicity is related to the effect of Tl on glutathione (GSH) activity: GSH inhibits heavy metal toxicity by binding heavy metals through -SH groups (Genchi et al., 2021). Oxidative stress may be increased by the inhibition of enzymes containing cysteine residues in the active site as a result of GSH modification (Mulkey and Oehme, 1993).

Tl toxicity is also related to the generation of ROS, which cause tissue damage and dysfunction (Villaverde et al., 2004; Galván-Arzate et al., 2005; Hanzel et al., 2005; Eskandari et al., 2015; Kiliç and Kutlu, 2010; Anaya-Ramos et al., 2021). Eskandari et al. (2015) demonstrated that Tl^+ increases ROS production by impairing the electron transfer chain in isolated rat liver mitochondria, activating the cell death signaling pathway. Lipid peroxidation and hydrogen peroxide (H_2O_2) have been shown to be suitable markers of ROS involvement in Tl toxicity (Galván-Arzate et al., 2005; Hanzel and Verstraeten, 2006). Lipid peroxidation by ROS formation due to Tl exposure induces tissue damage and organ dysfunction in the brain and liver tissue (Galván-Arzate et al., 2000; Maya-López et al., 2018). Furthermore, Tl increases neural lipid peroxidation, which damages neurons (Hasan and Ali, 1981). A recent study found that Tl induces ROS generation and mitochondrial dysfunction in primary hippocampal neurons from Wistar rat embryos (Lin et al., 2020). It has also been reported that the Tl-mediated disruption of mitochondrial function is related to Tl toxicity. Changes in the morphology of mitochondria, such as swelling, have been reported (Herman and Bensch, 1967; Spencer et al., 1973). Tl affects isolated mitochondrial function by opening transition pores and uncoupling the respiratory chain (Bragadin et al., 2003; Korotkov and Lapin, 2003).

Tl induces apoptosis (Bragadin et al., 2003). Tl also alters the balance of Bax/Bad/Bcl-2 proteins and activates caspase-9, caspase-8, and caspase-3 in mitochondria, leading to apoptotic death (Osorio-Rico et al., 2017). It has been suggested that the toxicity is due to DNA damage (Nishioka, 1975). However, the genetic effects of Tl have not been fully elucidated. Tl^+ is known to be molecularly more stable than Tl^{3+}, which has strong oxidizing capacity (Harris and Messori, 2002). Sánchez-Chapul et al. (2023) demonstrated that the DNA double helix and its oxidization were not altered by Tl^+. In contrast, Nowicka et al. (2013) showed that Tl^+ is oxidized to Tl^{3+} by experimental UV irradiation and the presence of oxygen and that Tl^{3+} oxidizes guanine residues in DNA to 8-oxoguanine, inducing DNA breaks and exerting mutagenic effects. They also demonstrated that Tl interacts with oligonucleotide gene sequences in human 8-oxoguanine DNA glycosylase (*hOGG1*), which is responsible for repairing DNA damage. Recently, Wu et al. (2019) reported decreased amounts of mitochondrial DNA copy numbers and shortened neonatal telomere length due to epigenetic changes in proteins of H3 and H4 histones in the urine of pregnant women exposed to environmental Tl. They also revealed that prenatal Tl exposure shortened neonatal telomere length (Wu et al., 2021).

Few studies have investigated the toxicological mechanisms of prenatal thallium exposure and whether the effect of Tl on fetal development is direct or indirect. Zhou et al. (2021) suggested that prenatal exposure to Tl is negatively associated with birth weight and that this association may be mediated by decreased placental weight. Zhu et al. (2020) reported that prenatal Tl exposure in a Chinese population induced an inflammatory response in the placenta and found that serum Tl levels in pregnant women were positively associated with CD68, TNF-α, and Il-6. Based on the findings of the above studies, the effect of Tl on the fetus is considered to be indirect, via placental injury.

As previously mentioned, Tl causes the most severe damage in the central nervous system. ROS formation, disruption of K^+-regulated homeostasis, mitochondrial dysfunction, excitotoxicity, and apoptosis are all considered to be mechanisms of Tl neurotoxicity. In particular, the brain is sensitive to oxidative damage because it contains high levels of unsaturated lipids and it has a high rate of oxidative metabolism (Chevalier et al., 1994; Goering et al., 2002). The inhibition of Na+/K+ ATPase activity may disturb neurotransmission, while that of Na+/K+ ATPase and pyruvate kinase activities induces excitotoxicity due to ATP depletion (Maya-López et al., 2018). Maya-López et al. (2018) suggested that energy depletion (mitochondrial dysfunction), inhibition of Na^+/K^+ ATPase activity, and lipid peroxidation (oxidative damage) might account for the toxic pattern elicited by Tl^+ in the nerve terminals of rat brains. Aldehyde dehydrogenase catalyzes the production of retinoic acid from retinol (vitamin A), and endogenous retinoic acid is essential for embryonic development and adult physiological processes (Wang et al., 2023). Retinoic acid also plays an important role in the development of the BBB in humans and mice (Mizee et al., 2013), and its signaling is a critical process for neurodevelopment (Cho et al., 2021; Menegola et al., 2021). The inhibition of aldehyde dehydrogenase by Tl^+ exposure may prevent the development of the BBB as well as neurodevelopment by decreasing retinoic acid levels. The toxicological mechanisms of neuro-damage by Tl are shown in Fig. 4.

9. Medical treatment of Tl poisoning

Treatment for Tl poisoning patients is performed to eliminate Tl and to prevent further absorption. The most effective antidote is ferric hexacyanoferrate ($Fe_4[Fe(CN)_6]_3$), which is known as Prussian blue (Cvjetko et al., 2010). Prussian blue is orally administered (Galván-Arzate and Santamaría, 1998) and exchanges K for Tl in the gut to increase the fecal excretion of a complex of Tl and Prussian blue (Rusyniak et al., 2010). A recent study demonstrated that MT alone or in combination with Prussian blue plays a cytoprotective role after Tl exposure (Anaya-Ramos et al., 2021). In addition, activated charcoal can be used (Cvjetko et al., 2010; Rusyniak et al., 2010). Hemodialysis and hemoperfusion are also recommended for removing Tl from the blood stream (Malbrain et al., 1997; Thompson, 1981). However, a single antidote is not effective in severe Tl poisoning cases and combinations of different administration have been reported to be effective in a number of cases (Riyaz et al., 2013).

10. Conclusions

Tl is one of the most toxic metals. Because Tl salts are colorless, odorless, and tasteless, it has been used historically in homicides, leading it to be known as “the poisoner’s poison.” Tl is found in the natural environment at low levels, and it has been used as, for example, a rodenticide, semiconductor material, and for myocardial imaging. To diagnose Tl poisoning, confirmation of elevated Tl concentrations in the blood, urine, or hair is indispensable. However, evidence for Tl exposure cannot be rapidly obtained by clinicians because Tl analysis can be performed only in limited laboratories. AAS is the most frequently used method for Tl determination in biological samples, and ICP-MS is the most recently introduced method. Tl^+ is more stable than Tl^{3+}, and Tl^+ salts enter the body through the K^+ uptake mechanism. Tl^+ is rapidly absorbed and is widely distributed to organs. The kidneys show the highest Tl concentration about 24 h after ingestion while the concentration is highest in the brain thereafter. Tl is excreted in the feces and

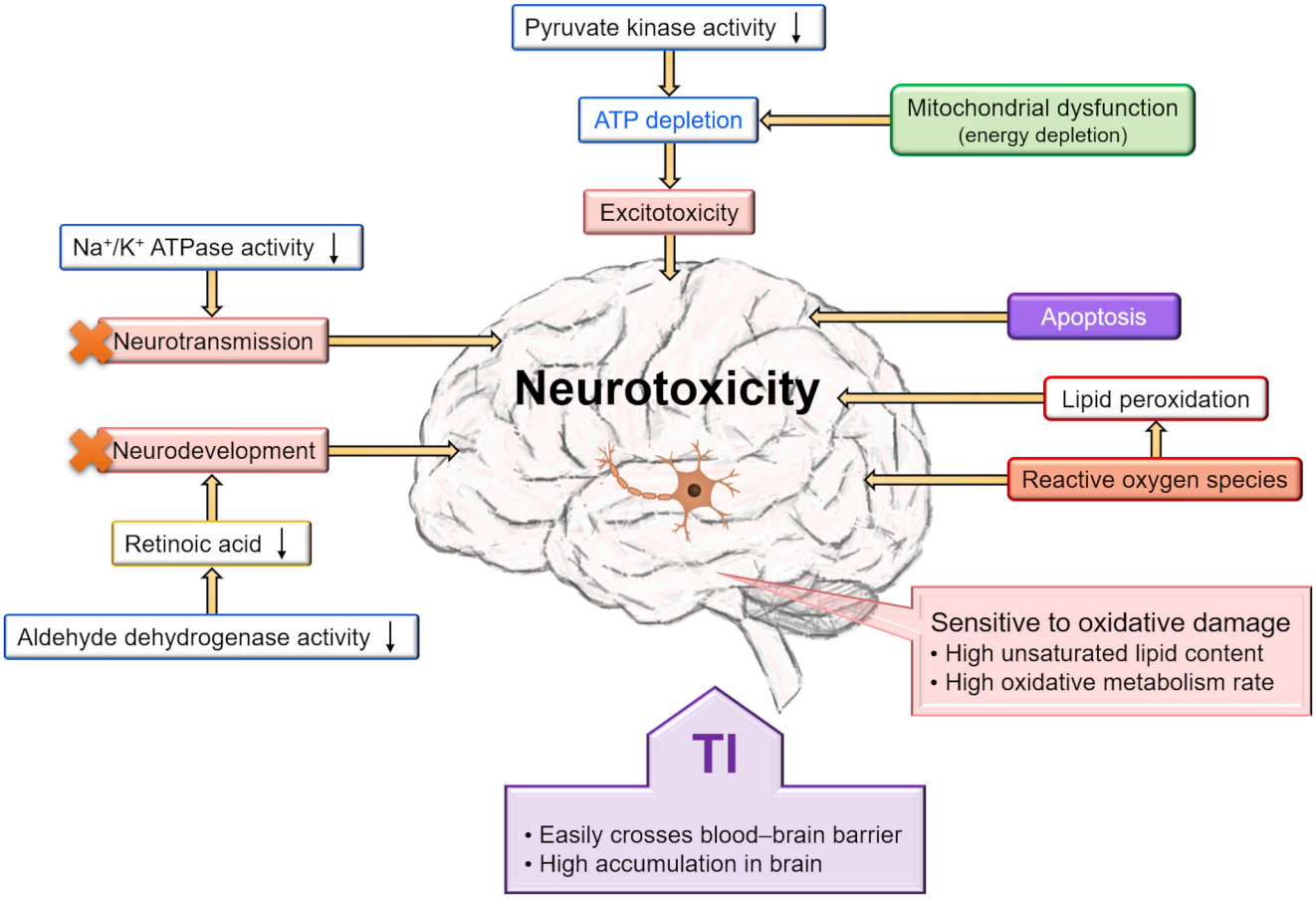

Fig. 4. Schematic of the neurotoxicity mechanism of thallium.

urine. The excretion rate for Tl is quite slow due to the large distribution volume of Tl and it persists for as long as 21 months in untreated Tl poisoning cases. Gastrointestinal symptoms are observed when acute poisoning by ingestion of large amount of Tl. Tl induces neurological dysfunction with similar symptoms to Guillain–Barré syndrome after 2–3 days of exposure. Following 2–4 weeks after exposure, alopecia is observed. Mees' lines, transverse white lines in the nails, are observed about 1 month after Tl poisoning. The toxicological mechanism of Tl is considered to be the ionic radius similarity of Tl^+ to K^+ and the interference of Tl^+ with vital potassium-dependent processes. Another possible mechanism of Tl toxicity is inhibition of enzyme reactions by the binding of Tl to -SH groups, which disturbs vital metabolic processes. Tl toxicity is also related to ROS generation and mitochondrial dysfunction. Tl causes the most severe damage in the central nervous system. The brain is sensitive to oxidative damage and Tl neuro-damage is caused by ROS formation in addition to mitochondrial dysfunction, excitotoxicity, and apoptosis. Placental exposure to Tl can lead to spontaneous abortion, preterm birth, low birth weight, and teratogenicity. The most effective antidote is the ion exchanger Prussian blue, which exchanges K for Tl in the gut to increase the fecal excretion of a complex of Tl and Prussian blue. Recently, it was reported that MT alone or in combination with Prussian blue has cytoprotective effects after Tl exposure. Tl poisoning cases are still reported, and the early detection of Tl in biological samples and its treatment with an antidote are essential.

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CRediT authorship contribution statement

Junko Fujihara: Writing – original draft, Visualization. **Naoki Nishimoto:** Writing – review & editing, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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