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Review Article

Review of Toluene Actions: Clinical Evidence, Animal Studies, and Molecular Targets*

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Abstract It has long been known that individuals will engage in voluntary inhalation of volatile solvents for their rewarding effects. However, research into the neurobiology of these agents has lagged behind that of more commonly misused drugs such as psychostimulants, alcohol, and nicotine. This imbalance has begun to shift in recent years as the serious effects of misused inhalants, especially among children and adolescents, on brain function and behavior have become appreciated and scientifically documented. In this review, we discuss the physicochemical and pharmacological properties of toluene, a representative member of a large class of organic solvents commonly used as inhalants. This is followed by a brief summary of the clinical and preclinical evidence showing that toluene and related solvents produce significant effects on brain structures and processes involved in the rewarding aspects of drugs. This is highlighted by tables summarizing toluene's effect on behaviors (e.g., reward, motor effects, learning, etc.) and cellular proteins (e.g., voltage and ligand-gated ion channels) closely associated with the actions of misused substances. This review not only demonstrates the significant progress that has been made in understanding the neurobiological basis for solvent misuse but also reveals the challenges that remain in developing a coherent understanding of this often overlooked class of drugs of abuse.

Keywords inhalants; solvents; molecular targets; behavioral effects; sites of action

1. General

Toluene (also known as toluol, methylbenzene, and phenylmethane) is an organic solvent widely used in many industrial processes including plastic production, chemical synthesis, and gasoline manufacturing. A volatile liquid (i.e., it becomes vapor at room temperature), toluene produces psychoactive effects when intentionally inhaled in pure form or from numerous commercial products (e.g., solvents, gasoline, paints, varnishes, paint thinners, adhesives, inks, among other products) [7].

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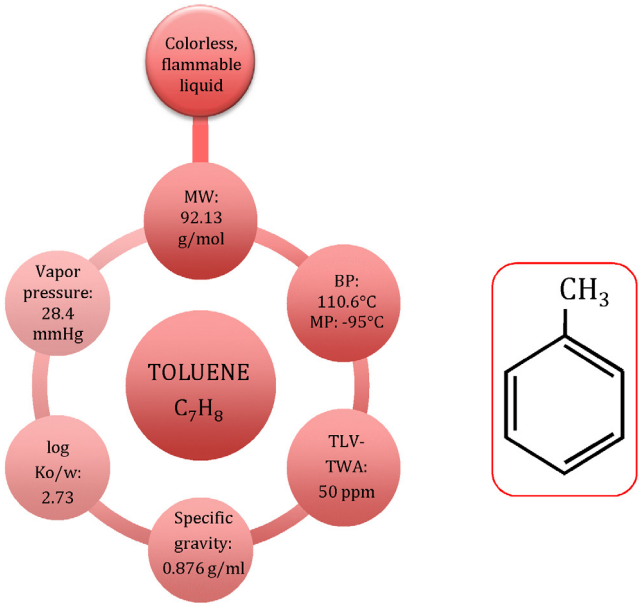

Figure 1: Chemical and physical properties of toluene. BP: boiling point; MP: melting point; TLV-TWA: threshold limit value–time-weighted average: an allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek; log Ko/w: octanol/water partition coefficient.

1.1. Physicochemical properties

Toluene's structure and physicochemical properties are shown in Figure 1. An aromatic hydrocarbon, toluene is lighter than water in its liquid form, but three times heavier than air as a vapor, has a high affinity for lipids (log octanol/water partition coefficient = 2.73), and is flammable with a low flash point (the lowest temperature at which it can vaporize to form an ignitable mixture in air) of 4.4 °C [1].

1.2. Exposure

Individuals can be exposed to low toluene concentrations when they use household/school products or fill the car with gasoline, but these activities generally do not pose significant health risks when performed in well-ventilated areas. Occupational exposure in workplaces such as factories, workshops or refineries usually occurs several hours a day, five days a week. Regulations exist to prevent physiological and behavioral adverse consequences and although they vary among countries, safe exposure limits are usually in the range of 10–100 ppm. The immediately dangerous to life and health limit (IDLH) has been estimated at 500 ppm [72]. In spite of this, people who misuse toluene-based products are exposed to concentrations of several thousands ppm following an intermittent pattern of inhalation [68, 84].

Several methods are used for voluntarily inhaling toluene-based products: "huffing" refers to breathing fumes from a solvent-soaked rag or tissue paper that is held in a hand and placed near the nose and mouth, "sniffing" is the direct nasal inhalation from containers, "bagging" refers to breathing fumes from substances placed in a bag, and "cuffing" means inhaling vapors from cuffs or sleeves soaked with solvents and raised to the mouth and nose [33]. In Australia, "chroming" is used as synonymous with inhaling paint sprays, which contain toluene and propellant gases [88]. Using any of these methods, inhalant effects appear very quickly, usually within seconds, and they last from 15 min to 60 min. In order to increase the duration of effects, users repeat the exposure to maintain the desired level of intoxication.

1.3. Metabolism

Toluene is rapidly absorbed through the lungs. Gastrointestinal and dermal absorption also occurs. Once absorbed, it is distributed to highly perfused lipid-rich organs. Because of its high affinity for lipids, toluene can readily cross the brain blood barrier and the placenta. As perfusion in the brain is very high, the brain's toluene concentration is also high in this region. Most inhaled toluene (95%) is metabolized in the liver first to benzyl alcohol which is by turn oxidized to benzoic acid that is then conjugated with glycine to form hippuric acid. Conversion to cresol is a minor pathway [2]. Hippuric acid is dissociated in hippurate anions and protons. Protons are titrated by bicarbonate and some of the anions are excreted in the urine with ammonium. After binge toluene exposure, there is an excess of hippuric acid, which can produce the excretion of not only ammonium, but also sodium and potassium combined with hippurate anions, resulting in a metabolic acidosis and hypokalemia. Low levels of potassium are associated with weakness, muscle spasticity, cardiac arrhythmias, and other serious complications. The rate-limiting step in toluene metabolism is conversion to benzyl alcohol through cytochrome P450 in the liver. Several P450 isoenzymes are involved in toluene metabolism, among which CYP2E1 has been described as the most active in forming benzyl alcohol [71] and one which can be induced by repeated toluene exposure [70].

Table 1: Effects of toluene exposure.

Acute effects	Chronic effects
– Irritation of eyes and respiratory pathways – Initial euphoria; excitation – Emotional liability: sudden mood changes – Dizziness – Slurred speech – Blurred vision – Lack of motor coordination – Illusions; hallucinations – Muscle spasticity	– Cognitive impairments (e.g., memory loss, difficulty in concentrating, and attention deficit) – Diffuse cerebellar atrophy – White matter abnormalities, particularly around brain ventricles – Ventricular enlargement – Loss of muscle strength – Cerebellar ataxia which leads to impaired motor coordination – Hearing loss; sight impairment; nystagmus

2. Effects: the clinical evidence

Toluene is the most commonly misused solvent and also the best studied, both in terms of behavioral effects and action mechanisms. Acute and chronic effects of toluene are summarized in Table 1. Briefly, toluene intoxication resembles ethanol intoxication in some aspects because toluene produces an initial euphoria and excitation, followed by a more prolonged inhibition. Motor incoordination, dizziness, relaxation, and lightheadedness are also characteristic of toluene intoxication. Unlike other central nervous system (CNS) depressant drugs, toluene produces illusions and hallucinations [34, 66]. Of particular concern is that even acute inhalation can lead to life threatening conditions due to poor oxygenation, cardiac arrhythmias, and other complications associated with hypokalemia. "Sudden sniffing death" has been documented since the 1970s [8, 20] and can be caused by cardiac arrhythmias, hypothermia, hypoxia or a combination of these factors [16].

Long-term effects of toluene inhalation vary depending on age, patterns of use (duration and frequency), misused products, and concomitant exposure to other drugs. Chronic irritation of eyes and respiratory airways is common. Heavy long-term toluene abuse has been associated with general cognitive impairments (e.g., memory deficits, difficulty to concentrate, etc.), decreased IQ, increased impulsivity, and impaired judgment [53, 99]. Imaging studies have shown that toluene chronic exposure can lead to neurobiological abnormalities, which have been related to white matter damage (leukoencephalopathy). Interestingly, in a study using proton magnetic resonance spectroscopy, axonal damage, rather than demyelination, was found [3].

A well-described complication of toluene exposure is renal tubular acidosis. Although it can happen after an acute binge episode of intentional toluene inhalation, it is

more frequent in chronic users [70]. Renal failure can also occur, and it is attributed to acute tubular necrosis caused by hypotension or possibly rhabdomyolysis. Liver toxicity may also be a consequence of toluene exposure [67].

Toluene produces tinnitus and can cause hearing loss after chronic exposure. Hearing frequencies affected by toluene are different from those affected by noise but both factors can act synergistically to diminish hearing [42].

Due to its lipophilic nature, toluene crosses biological membranes easily, including the placental barrier. If inhalation occurs during pregnancy, the fetus can be affected with developmental disorders, physical malformations or even death. A fetal solvent syndrome (FSS), analogous to the fetal alcohol spectrum disorder (FASD), has been described. Thus, infants born from mothers who misused toluene-based products can have smaller heads, a thin upper lip, lower set ears, and other signs similar to what has been described for FASD. Follow-up studies of children exposed during gestation to solvents show growth retardation, language impairment, and cerebellar dysfunction (reviewed in [16,50]).

Although the clinical effects of toluene are relatively well known, many studies have analyzed the damages caused by inhalation of toluene-based products rather than toluene itself. Human studies are limited by ethical concerns and the occurrence of confounding variables such as malnourishment and concomitant use of other drugs. Because of this, animal studies have been very valuable to determine the cause-effects relationships between toluene exposure, behavior, and sites of action. Also, under controlled experimental conditions, it has been possible to establish concentration-dependent effects.

3. Preclinical evidence

3.1. Neurobehavioral studies

Most behavioral studies have been done in rodents. Of special interest for this review are those that used binge patterns of toluene exposure either acutely or chronically, but many of these effects have also been described for conditions of prolonged exposures to low toluene concentrations. Some of the most representative studies are summarized in Table 2.

Being a misused drug, toluene has reinforcing effects. This has been shown using the conditioned preference place procedure [43,46,58], intravenous self-administration [13], and intracranial self-stimulation [91]. Inhaled toluene acts as a robust discriminative stimulus [85,86] and also produces CNS depressant-like [15,45,77], amphetamine-like [14], and PCP-like discriminative effects [25]. Similar to other CNS depressant drugs, toluene has anxiolytic-like properties [24,63,74], anticonvulsant effects [26,29,31,35,96], and impairs locomotor coordination [28,89]. It also exerts antidepressant-like actions [39] and a biphasic locomotor response; that is, increased and decreased activity at low and high concentrations, respectively [9,17,27,78]. The detrimental effects on learning, short-term and long-term memory produced by toluene are also well documented [54, 60,61,69,94]. A species-specific effect is observed regarding nociception because toluene increases the response to a noxious stimulus in mice [38], but has antinociceptive effects in rats [54]. Hypothermia [30,48,73] and tachycardia have also been described after toluene exposure [49].

There are relatively few studies concerning tolerance development and sensitization after chronic toluene exposure. The most consistent finding is sensitization to hyperlocomotion effects [9,23,61]. As in humans, prenatal exposure to toluene has been associated with malformations [18], growth retardation [55], delayed reflexes [51], and attention deficit in pups [62]. Some of these deleterious effects of prenatal toluene exposure can be enhanced by stress [52,87]. Exposure to toluene during gestation also results in deficient body weight gain and poor lactation in dams [87].

3.2. Sites of action for toluene

The molecular and cellular targets for abused inhalants including toluene have been investigated using a variety of in vitro and in vivo preparations. Not surprisingly, many of these studies have focused on defining the effects of toluene on ion channels that are critically involved in regulating neuronal excitability. As summarized in Table 3, results from these studies indicate that both voltage-gated and ligand-gated ion channels are affected by concentrations of toluene associated with voluntary inhalation of these substances. In addition, these studies suggest that toluene and other related solvents possess a surprising degree of selectivity given their rather simple chemical structure. For example, toluene was shown to significantly inhibit the NMDA subtype of glutamate-activated ion channels while having little effect on the closely-related AMPA subtype of ionotropic glutamate receptors [6,36]. Moreover, within the NMDA family, receptors composed of the GluN2B subunit were considerably more sensitive to toluene inhibition than other NMDA receptor subtypes. A similar effect was observed for nicotinic acetylcholine receptors (nAchRs), where $\alpha_4\beta_2$ receptors were much more sensitive to toluene inhibition than α_7 nAchRs [5]. Amongst the P2X family of ATP-gated channels, toluene inhibits the function of some subtypes (P2X2, P2X4) but enhances currents through P2X3 containing receptors [98]. These findings suggest that there are distinct sites of action for toluene on individual channel subunits and that regional and anatomical differences in subunit expression are important determinants of solvent action.

After the identification of some of toluene's molecular actions, several research groups studied metabolic and neurochemical changes associated with toluene exposure. For example, using microPET [82], it has been shown that

Table 2: Preclinical studies on toluene's effects.

Acute effects	Preparation	Species	Refs.
Reinforcing properties	Intravenous self-administration	Mice	[13]
	Conditioned place preference	Rats	[46]
		Mice	[43]
Discriminative stimulus effects	Toluene acts as a discriminative stimulus	Mice	[85,86]
	Amphetamine-like effects	Mice	[14]
	CNS depressant-like effects	Mice	[15,77]
Anxiolytic-like	Burying behavior test (decreased cumulative time burying the prod)	Mice	[63,74]
	Elevated plus maze (increased number of entries and time spent in open arms)	Mice	[24]
	Geller-Seifter conflict test (active response reinstatement after punishment)	Rats	[45,96]
Motor incoordination	Rota rod test	Rats	[61]
Anticonvulsant	PTZ-induced seizures (decreased percentage of convulsing animals)	Rats	[96]
	NMDA-induced seizures (decreased percentage of convulsing animals; protection against death)	Mice	[29,35]
	Nicotine-, picrotoxin- and bicuculline-induced seizures (increased seizure threshold)	Mice	[29]
Antidepressant-like	Forced swimming test and tail suspension test (decreased immobility)	Mice	[39]
Altered locomotion	Open field test	Rats	[9,17,49,54,78]
	Low concentrations: increased locomotion		
	High concentrations: decreased locomotion		
Impaired learning and memory	Passive avoidance test (long-term memory)	Rats	[54]
	Novel object recognition test (reduced novel object exploration)	Rats	[54]
		Mice	[60,94]
Pronociception	Hot plate and tail flick tests (increased latency to response)	Mice	[38,74]
Antinociception	Foot-shock test (increased threshold to elicit a response	Rats	[54]
Impulsivity-like	Waiting-for-reward task	Mice	[21]
Social interaction	Social interaction test (reduced contact with a partner)	Mice	[60]
Chronic exposure			
Impaired learning and memory	Morris water maze; object recognition, passive avoidance test	Rats	[54,92]
Sensitization to hyperlocomotion	Open field test	Mice	[22]
Prenatal exposure			
Increased locomotor activity	Open field test	Rats	[51]
Delayed reflexes	Postnatal test battery (surface righting, air righting, auditory startle)	Rats	[51]
Impulsivity-like	Waiting-for-reward task	Rats	[21]
Sensitization to hyperlocomotion	Open field test (amphetamine induced locomotion)	Rats	[19]

acute and repeated toluene exposure markedly reduces the metabolic function in rat brain. This effect was regionally specific, with the hippocampus, pons, and thalamus as the more affected areas. Other researchers have found that toluene produces increases in dopamine release and dopaminergic neurons' activity [10,47,79,80,97], regional brain changes in glutamate, glutamine, and monoamine levels [57,76,95], as well as changes in NMDA and $GABA_A$ receptor densities or subunit composition [32,59,93]. Toluene's apoptotic effects have also been described [100] and, interestingly, these actions can be lessened by placing animals in enriched environments [75]. Recent studies show that repeated toluene exposure also results in epigenetic changes that might have a long-term impact on gene expression and behavior [54,81]. Other effects of toluene such as increased oxidative stress seem to contribute to the detrimental effects of prolonged toluene exposure [56].

In conclusion, the last 15 years have provided extensive evidence of the molecular, cellular, and systemic actions of toluene and have firmly established solvents as important drugs of abuse. Despite these advances, it remains an interesting challenge to identify the most relevant molecular mechanisms that underlie the specific effects of toluene and related solvents. There is a recent evidence indicating that different neurotransmitter systems are activated at different doses/concentrations of toluene [73] and it is likely that similar differences exist regarding acute versus chronic exposures to these solvents. Of particular interest in understanding the long-term effects of inhalant use is how exposure to these agents during adolescence impacts normal brain development, cognition, and behavior in adults. This is especially relevant for frontal cortical areas that undergo significant maturation during the time that many solvent users are experimenting with these agents. In addition, there

Table 3: Summary of the effects of toluene on recombinant and native ion channels.

Receptor name	Subunit composition	Effect	Ref.
AMPA	GluA1; GluA1/2	None	[36]
	GluA6	Increase	[36]
	Native neuron	None/decrease[a]	[6,11]
NMDA	GluN1/N2A	Decrease	[36]
	GluN1/N2B	Decrease	[36]
	GluN1/N2C	Decrease	[36]
	Native neuron	Decrease	[4]
GABA	$\alpha_4\beta_2$	Increase	[12]
	Native neuron	Increase[b]	[11,64,65]
Glycine	α_7	Increase	[12]
5HT$_3$	5HT$_3$	Increase	[64]
nAchR	$\alpha_4\beta_2$	Decrease	[5,4]
	$\alpha_4\beta_2$	Decrease	[5]
	$\alpha_4\beta_2$	Decrease	[5,4]
	$\alpha_4\beta_2$	Decrease	[5]
	α_7	Decrease	[5,4]
	Native neuron	Decrease	[5]
ATP	P2X2	Increase	[98]
	P2X2/3	Increase	[98]
	P2X3	Decreased	[98]
	P2X4	Increase	[98]
	P2X4/6	Increase	[98]
Sodium channels	Nav1.5 (cardiac)	Decrease	[37]
	Native cardiac	Decrease	[37]
	Nav1.4 (skeletal)	Decrease	[44]
	Native neuron	None	[11]
Ca^{++} channels	Cav1/Cav2	Decrease	[83,90]
	Native neuron	Decrease	[83]
K$^+$ channels	mSlo	Decrease	[40]
	Girk2	Decrease	[40]
	Girk1/2; Girk1/4	None	[40]
Gap junction	Native (HEK cell)	Decrease	[41]

[a]Toluene inhibition of AMPA EPSCs [11] was endocannabinoid dependent.
[b]Toluene enhanced the frequency but not amplitude of GABA IPSCs [65].

is a clear evidence that stress affects these same frontal areas suggesting that the deleterious effects of inhalants may be exacerbated by environmental and psychosocial factors (e.g., homelessness, poor family structure, etc.) often associated with the use of abused inhalants. From an experimental standpoint, there is also a need to conduct studies utilizing relevant mixtures of solvents. To date, most animal-based reports have used single compounds with toluene being considered the representative volatile solvent. But it is clear that many individuals who misuse inhalants are exposed to complex mixtures of solvents that may produce effects that are different from those observed with toluene alone. While this presents a more challenging experimental design, it is likely to be more informative and may identify novel sites or mechanisms of action that would not be revealed with studies of single solvents. Finally, efforts are needed to better understand how other commonly used drugs of abuse may affect the actions of abused inhalants. With the recent discovery of the neural targets of toluene and related solvents, it is clear that there is a substantial overlap in the cellular and molecular actions of these agents with other drugs such as alcohol, nicotine, and marijuana. These findings suggest that the effects of abused inhalants on brain circuits that underlie reward, cognition, and behavioral control may be amplified or altered by chronic use of these other commonly abused substances.

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