Toluene Inhalation Increases Extracellular Noradrenalinne and Dopamine in the Medial Prefrontal Cortex and Nucleus Accumbens in Freely-Moving Rats

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Abstract

Toluene is a major component of thinner, which can cause intoxication with inhalation. Until recently, there were little experimental data focusing on the neuropharmacological effects of toluene. In this study, central effects caused by toluene were examined. Noradrenalinne and dopamine levels in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAcc) were studied in freely-moving rats during exposure to inhaled toluene, using in vivo microdialysis.

Toluene inhalation at 7,000 ppm increased extracellular noradrenalinne and dopamine levels in both the mPFC and the NAcc. In the NAcc, noradrenalinne and dopamine increased to 210 % and 178 % of their respective baseline values. In the mPFC, noradrenalinne and dopamine increased to 306 % and 183 %, respectively. At both sites, the increase of noradrenalinne was greater than that of dopamine. Toluene inhalation at 1,000 ppm and 3,000 ppm did not significantly affect extracellular noradrenalinne and dopamine levels.

It became clear that toluene inhalation was involved in the mesolimbic dopamine system which plays an especially important part in the drug dependence. These results also suggest that exposure to toluene by inhalation enhances excitability of noradrenergic neurons.

Key words: Toluene/Noradrenaline/Dopamine/Microdialysis
Introduction

Toluene is widely used as an organic solvent in commercial products, such as paint lacquers, paint thinners and adhesives. Because easily obtainable, it is frequently abused by inhalation, and causes social problems and easily opens the gateway for other drugs of abuse among children and adolescents.

Following exposure, toluene enters lipid-rich regions of the body, for example the brain\(^7\). Until recently, toluene is merely regarded as a nonselective lipid soluble agent, so there are little experimental data focusing on the neuropharmacological effects of toluene and therefore the mechanism of its effects remains unclear.

Recently, an electrophysiological study that investigated the effect of toluene on dopaminergic neurons found that exposure to toluene by inhalation initially stimulates and ultimately attenuates firing of the dopaminergic neurons in the ventral tegmental area (VTA)\(^2\), much as other drugs of abuse do\(^9\).

In studies using microdialysis, Stengard et al. (1994)\(^6\) observed increases of extracellular dopamine in the rat striatum following toluene inhalation concomitant with locomotor activity changes. Gerasimov et al. (2002)\(^5\) also indicated that toluene inhalation in rats resulted in specific regional changes in extracellular dopamine, suggesting that toluene exhibits selective effects on neuronal output. Conversely, Kondo et al. (1995)\(^6\) reported that toluene did not affect extracellular dopamine levels in the rat striatum following intraperitoneal injection, despite the fact that locomotor activity was clearly affected. Thus, it would appear that the route of the administration and/or the method of toluene vaporization significantly affects the results.

The mesolimbic dopamine system associated with the nucleus accumbens (NAcc) is well known to play an important role in reinforcement through positive emotion (i.e., a rewarding system), and in the development of psychological dependence\(^7\). In addition, the mesocortical dopamine system projecting to the medial prefrontal cortex (mPFC) is also considered to be a component of the rewarding system. Some reports suggest that abuse drugs have preferential effects on dopamine neurons in the NAcc rather than on those in the mPFC\(^8\). Therefore, measurement of neurotransmitter levels in the NAcc and mPFC at the same time may provide some clues to identify which regions in the central nervous system are influenced by abuse drugs.

The noradrenaline nervous system is tightly correlated to the dopamine nervous system. It has been suggested that the function of the noradrenaline neurons is related to behavior, cognitive function with respect to ambient attention, anxiety, etc. In particular, the mPFC may play an important role in emotional representation and cognition. It has also been suggested that this noradrenaline system may be involved in the expression of withdrawal symptoms associated with opiate drugs\(^10\). However, no study to date has assessed brain noradrenaline levels *in vivo* during toluene inhalation. Therefore, to investigate the brain region specificities and monoamine specificities related to the acute effect of toluene
inhalation exposure, we examined noradrenaline and dopamine concentrations in the NAcc and mPFC in rats. We implanted dual probes into the mPFC and NAcc to simultaneously monitor dopamine and noradrenaline levels and to compare the effects of toluene in these two regions.

**Materials and Methods**

**I. Animals and surgery**

Male Wistar rats weighing 260 g to 320 g were obtained from Charles River Japan. Rats were placed in a stereotaxic instrument (David Kopf Instruments, USA) under anesthesia with pentobarbital (40 mg/kg i.p.). Two guide cannulas (Microbritech, Sweden), each with a dummy probe, were implanted into the brain and fixed to the skull with dental cement. Based on the atlas of the rat brain\(^5\), one guide cannula was implanted into the NAcc (anterior–posterior \(+1.6\) mm, medial–lateral \(\pm 0.8\) mm, dorsal–ventral \(-8.0\) mm to bregma) and the other was implanted into the mPFC (anterior–posterior \(+2.5\) mm, medial–lateral \(\pm 2.0\) mm \(14^\circ\) inclination, dorsal–ventral \(-6.0\) mm to bregma) respectively (Fig. 1 and Fig. 2). The dummy probes were left in the brain until the dialysis experiment was started. The procedures applied in this study were approved by the Animal Experiment Committee, Kyushu Dental College and conducted in accordance to the Guidelines for Animal Experiments of the Kyushu Dental College.

**Fig. 1** Diagram of the dialysis probes implanted at the medial prefrontal cortex (mPFC) and at the nucleus accumbens (NAcc).

**Fig. 2** Diagram of coronal sections from rat brain indicating placement of dialysis probes adapted from Paxinos and Watson (1982). A, the medial prefrontal cortex; B, the nucleus accumbens.
II. Microdialysis

Extracellular noradrenaline and dopamine levels were measured one or two days after surgery. The dummy probes were removed from the guide canulas and microdialysis probes (MAB4, Microbiotech, Sweden) (cut off 6 kD, OD 0.24 mm, membrane length 4.0 mm for the mPFC, 2.4 mm for the NAcc) were gently inserted into the guides. The microdialysis probes were perfused with perfusion medium (artificial cerebrospinal fluid) before insertion into the mPFC and NAcc. The perfusion medium consisted of Ringer's solution containing NaCl (140 mM), CaCl₂ (2.3 mM), MgCl₂ (1.0 mM) and KCl (3.0 mM). The perfusion rate was 4.0 µl/min. Dialysate samples were collected every 15 min. After the stable baseline values of noradrenaline and dopamine were determined, the rats were exposed to toluene. The dialysate samples were collected at least 45 min (three samples) before and 75 min (five samples) after the exposure to toluene.

Dialysate samples were injected with an auto sampler (model 231XL, Gilson, France) kept at 4°C to 6°C. Noradrenaline and dopamine concentrations in the samples were determined by high-performance liquid chromatography (HPLC) (LC-10AD pump, Shimadzu, Kyoto, Japan) with electrochemical detection (Coullochem II, ESA Biosciences Inc., USA) using a reversed phase column (C₁₈, 4.6 mm × 150 mm, Cosmosil, Nacalai, Japan). The mobile phase was composed of 4.1 g sodium acetate adjusted to pH 6.0, 100 ml methanol, 50 mg ethylenediaminetetraacetic acid and 150 mg octane sulfonate in 900 ml H₂O, and was degassed by purging with He gas. The column was placed within a column oven (GL Sciences Inc., Japan) maintained at 25°C. The data were analyzed using a Chromelon data analysis system (Dionex Corp., USA). After the experiment, the rats were sacrificed with an overdose of chloral hydrate. The brains were removed and sliced to microscopically confirm the proper localization of the probes.

III. Exposure to toluene

Exposure to toluene (HPLC grade, Wako Pure Chemical Industries, Japan) was conducted in a gas exchange chamber (300 mm × 280 mm × 280 mm), with inlet and outlet ports (Fig. 3). The chamber was set onto a turntable so as to turn with the swiveling of a rat. Constant airflow was 1 l/min. The flow rate was increased to 6 l/min, only when vaporized toluene was added to the inlet air. A feely-moving rat was exposed to toluene for 30 min. The concentration of toluene was calibrated during preliminary investigations with gas chromatography.

A vaporizer (Vapor19.3, Dräger, Germany) normally used for inhalational anesthesia was adjusted for toluene and was used for the vaporization of toluene. When the dial of the vaporizer was adjusted to the approximate required concentrations with gas detector tubes (Kitagawa124SH, Komyo Rikagaku Kogyo, Japan) for toluene, the toluene concentrations were precisely quantified by gas chromatograph.

Quantitative analysis of toluene was performed in Nishinihon Occupational Health Service Center. The measurement conditions for the flame-ionization-detection equipped gas chromatograph (GC-17A, Shimadzu, Japan) were as follows, column size: 0.53 mm × 30 mm,
carrier gas: He, column temperature: 70 °C. Toluene (Wako Pure Chemical Industries, Japan) was used as a standard for the calibration curve. Samples were collected from the chamber outlet into an exclusive sampling container. From the sampling container, a 1 ml sample was collected and injected into the gas chromatograph using a gas-tight syringe. After repeating this procedure several times, we marked the vaporizer dial at toluene concentrations of 1,000 ppm, 3,000 ppm and 7,000 ppm as low, intermediate and high concentrations in consideration of limits of the vaporizer.

IV. Expression of results and statistics

All values are expressed as a percentage relative to control values. The mean concentration of three stable baseline samples was defined as 100% before toluene exposure. Statistical analyses were performed using one-way analysis of variance (ANOVA) with repeated measures and Dunnett's multiple comparison tests for post-hoc determination of significance. $p$-values < 0.05 were considered significant.

Results

Basal extracellular concentrations of noradrenaline and dopamine before exposure were $21.5\pm1.6$ fmol/sample and $18.1\pm2.1$ (mean ± S.E.M.) fmol/sample in the mPFC, $12.4\pm1.3$
Fig. 4 Changes in HPLC chromatograms of noradrenaline (NA) and dopamine (DA) before (A) and after (B) exposure to inhaled toluene (7,000 ppm) in the nucleus accumbens.

fmol/sample and 23.6±2.7 fmol/sample in the NAcc, respectively (n=18).

The HPLC chromatograms are shown in Fig. 4. The effects of inhalation exposure to toluene (1,000 ppm to 7,000 ppm) are shown in Figs. 5 and 6.

In the NAcc, toluene inhalation exposure did not affect extracellular noradrenaline and dopamine levels at 1,000 ppm and 3,000 ppm (Fig. 5A and Fig. 5B). However, at 7,000 ppm, toluene exposure elicited significant increases of both noradrenaline and dopamine (Fig. 5C). The noradrenaline and dopamine increased to 210 % and 178 % above their baseline values, respectively. The dopamine levels in the NAcc remained at 156 % one hour after the end of the toluene exposure.

In the mPFC, toluene inhalation exposure did not significantly increase extracellular dopamine and noradrenaline levels at 1,000 ppm and 3,000 ppm (Fig. 6A and Fig. 6B). However, both neurotransmitters increased significantly at 7,000 ppm (Fig. 6C), to 306 % and 183 %, for noradrenaline and dopamine respectively. Furthermore, the percentage increase of noradrenaline was significantly greater than that of dopamine at the same timepoint.
Fig. 5 Changes of extracellular noradrenaline and dopamine in the nucleus accumbens in response to a 30-min toluene inhalation (black bar). Concentrations of toluene were 1,000 ppm (A), 3,000 ppm (B) and 7,000 ppm (C). Data are presented as percentages relative to basal values ± S.E.M. (n=5-6). *p<0.05 compared with basal values.
Fig. 6 Changes of extracellular noradrenaline and dopamine in the medial prefrontal cortex in response to a 30-min toluene inhalation (black bar). Concentrations of toluene were 1,000 ppm (A), 3,000 ppm (B) and 7,000 ppm (C). Data are presented as percentages relative to basal values ± S.E.M. (n=5–6). *p<0.05 compared with basal values.
Discussion

Repeated use of toluene evokes central nervous system (CNS) symptoms, such as euphoria, hallucination, and psychological dependence. The conditioned place preference procedure has been used to demonstrate that inhalation of toluene produces the rewarding effect, that is, it utilizes the same route as abuse\(^{10}\). Administration of toluene by inhalation is a desirable method when the action of toluene is investigated with an animal because it closely resembles intake of this volatile organic solvent when it is abused by humans. Various vaporization methods were used in previous research with toluene. These methods included paving the animal chamber with hygroscopic paper and allowing toluene to soak into that paper\(^{10}\), or vaporization of toluene by heating to its boiling point\(^{10}\). However, in the former method, an animal must be removed from the chamber to stop toluene inhalation. In the latter method, time is required for the toluene concentration to reach a constant density.

In the present study, a vaporizer normally used for inhalational anesthesia was used for vaporizing toluene. Concentrations were calibrated with gas chromatography so that the toluene level could be adjusted to 1,000 ppm, 3,000 ppm or 7,000 ppm in advance and maintained at that level to assure consistency of exposure throughout the experiment.

We used microdialysis to examine the effects of toluene. This method is widely used to study neurotransmitters in the CNS in vivo. A microdialysis probe is implanted in tissue and constantly perfused with artificial cerebrospinal fluid. The advantage of in vivo microdialysis over post-mortem analysis of the brain is that in vivo microdialysis can monitor the movement of substances in the extracellular fluid in an awakened freely-moving animal. In vivo substances in the extracellular fluid are collected in accordance with the concentration gradient through a dialysis membrane. This enables measurement to extracellular concentrations immediately after the collection. The amount of extracellular monoamine can be inferred to be the quantity acting at the synapse in the living body, and the movement of monoamine is important. Furthermore, by implanting several probes in a brain, it is possible to simultaneously track monoamine levels over time. We used dual probe implantation into the mPFC and NAcc to monitor and compare drug effects in the two regions.

Toluene inhalation increased extracellular noradrenaline and dopamine levels in both the mPFC and NAcc. While both synaptic neurotransmitters increased in response to toluene, the overall increases of noradrenaline were significantly greater compared with those of dopamine.

Noradrenergic and dopaminergic neurons exist under different circumstances in the NAcc and mPFC. For example, it is known that basal extracellular dopamine levels are greater than the noradrenaline levels in the NAcc. In the NAcc, baseline extracellular dopamine concentration obtained before toluene inhalation was 23.6±2.7 fmol/sample. This baseline dopamine concentration was greater than that of noradrenaline, which was 12.4±1.3
fmol/sample in the NAcc. By contrast, noradrenergic innervation is well known to be greater in the mPFC than in the NAcc. Baseline extracellular noradrenaline concentration was larger in the mPFC compared with that in the NAcc, 21.5±1.6 fmol/sample versus 12.4±1.3 fmol/sample, respectively. Interestingly, in the present investigation, extracellular noradrenaline levels increased to a greater degree than dopamine in both the NAcc and the mPFC following inhalation exposure to 7,000 ppm toluene. The higher percentage increases of noradrenaline in both sites suggest enhanced excitability of noradrenergic neurons.

I. In the NAcc

There have been several reports on the effects of toluene on dopamine release in the NAcc that discuss the potential for psychological dependence. However, this is the first report to simultaneously examine the effects of toluene on noradrenaline and dopamine release in the NAcc. The present finding that toluene inhalation at 3,000 ppm did not exhibit any significant effect on dopamine in the NAcc is consistent with the findings reported by Gerasimov et al. following exposure to toluene at 3,000 ppm for 40 min\(^9\).

It has been suggested that dopamine release in the NAcc is related to the drug reward mechanism, and that the reinforcing efficacy of drugs of abuse is related to their ability to increase extracellular dopamine in the NAcc\(^10\). The dopaminergic projection from the VTA to the NAcc is the most crucial pathway in the rewarding system. Many studies have shown that the VTA–NAcc pathway has been implicated in the mechanism of excitation\(^3\)\(^-\)\(^9\). The mesocorticolimbic dopamine system originates from the VTA and its dopamine activity is regulated in a complex manner by both gamma-aminobutyric acid-ergic (GABAergic) and glutamatergic input. It is commonly believed that abuse drugs have an impact somewhere within the circuit of the rewarding system, but the specific mechanism(s) of action may be different. Consequently, enhancement of dopamine neurotransmission within this circuit is proposed to underlie the reinforcing properties of toluene. Consistent with dopamine increases in response to abuse drugs, extracellular dopamine levels in the present study were increased by 7,000 ppm toluene inhalation in the NAcc.

An electrophysiological study in ketamine-anesthetized rats demonstrated that inhaled toluene exposure initially stimulated and ultimately attenuated dopamine neuronal firing in the VTA\(^10\). Furthermore, toluene exhibits a biphasic dose–response relationship on locomotor activity. At low concentrations, toluene increases locomotor activity in rats, whereas at higher concentrations locomotor activity is decreased\(^6\)\(^,\)\(^7\). This toluene-induced locomotor hyperactivity was attenuated significantly by administration of a dopamine D\(_3\) receptor antagonist or 6-hydroxydopamine-induced lesions of the NAcc\(^10\). These findings imply that toluene exposure stimulated dopaminergic neurons within the mesolimbic reward pathway\(^6\) and that expression of this dopamine system is important in the enhancement of locomotor activity.

Repeated toluene exposure enhanced the motor–stimulant response to apomorphine in rats, suggesting that such exposure produced cross-sensitization with a direct dopamine agonist\(^10\). Further investigations in vitro (using Xenopus oocytes) have implicated some degree of
specificity in the mechanism(s) of action of toluene, because receptor specificity of toluene is seen in N-methyl-D-aspartate (NMDA) receptor antagonism and GABA receptor stimulation. In addition, recent studies have shown that the serotonin (5-HT) receptor in the VTA regulates the mesolimbic dopamine system. It has also been reported that toluene activates the function of the 5-HT receptor in vitro. In consideration of both previous investigations and the present findings, it is suggested that toluene inhalation activates the mesocorticolimbic dopamine system, likely through 5-HT, NMDA or GABA receptors.

Extracellular noradrenaline levels increased to a greater degree than dopamine following inhalation exposure to 7,000 ppm toluene. Further research must be conducted to explain the rationale and the function of noradrenaline in the NAcc.

II. In the mPFC

While the mPFC region of the brain is involved in anxiety and negative emotions, this region also communicates with the positive emotional circuit. The mPFC receives inhibitory input from the mesocortical dopamine pathway and gets excitatory input from the mediodorsal thalamic nucleus. The mediodorsal thalamic nucleus catches the output from the NAcc mediated by the ventral pallidum. Therefore, the mPFC is also connected with the NAcc indirectly and thus forms a loop. Interactions of noradrenaline release and dopamine release may occur in the mPFC, since it is known to share monoamine reuptake transporters.

Recent studies have suggested that the mPFC is also involved in the generation of reward. In the mPFC, increases of dopamine and noradrenaline were observed with toluene, similar to those in the NAcc. In contrast to Gerasimov et al., who observed an increase of dopamine following exposure to toluene at 3,000 ppm for 40 min, the present investigation showed no significant increase of dopamine in the mPFC following exposure to toluene at 3,000 ppm. A number of reasons could account for these apparently disparate results. The method used by Gerasimov et al. to vaporize toluene was a heated sand bath perfused with toluene, which was installed in the bottom part of the rat chamber, such that the vapor of toluene was supplied to the rat chamber through holes in the floor. In contrast, our method provided a fixed concentration of toluene to the rat through a vaporizer. Furthermore, there were also differences in the position of insertion of the probe. Although Gerasimov et al. inserted the probe to the mPFC into a position 3.7 mm in front of Bregma, we used on angle of 14° and inserted to a position 2.5 mm in front of Bregma. The mPFC includes the anterior cingulate cortex, prelimbic cortex and infralimbic cortex. Recent studies have suggested that the anterior cingulate cortex is implicated in evaluating how much effort to expand for a larger reward. Gerasimov's probe location into the mPFC mainly included the anterior cingulate cortex area while our probe location mainly included the prelimbic cortex and infralimbic cortex. The differences in probe locations could make a difference in extracellular dopamine levels.

Previous microdialysis studies have demonstrated concomitant release of dopamine and noradrenaline in the mPFC under different conditions, including exposure to foot shock,
atypical antipsychotics, and antidepressants. In this experiment, the inhalation of toluene at 7,000 ppm increased both dopamine and noradrenaline in the mPFC. It is likely that toluene may exhibit effects analogous to those of antipsychotics. Many investigators have reported that antidepressants increase extracellular noradrenaline levels in the mPFC\(^{27}\). However, these drugs have no potential for drug dependence. Increases of dopamine and noradrenaline in the mPFC could provide a mechanism by which environmental stimuli can elicit emotional arousal.

Because the unusual sensations and euphoria caused by toluene provide a motive to maintain the addiction and resemble those induced by ethanol, it has been proposed that toluene may resemble ethanol with respect to the site of action. Ethanol is known to increase noradrenaline levels in the mPFC\(^{30}\). A low dose of ethanol has been shown to increase noradrenaline output to about 160 \% of baseline levels in the mPFC, whereas a higher dose of ethanol inhibited noradrenaline output to about 70 \%\(^{40}\). A similar biphasic effect has been observed for acetylcholine\(^{41}\). Though neurobehavioral studies associating toluene with biphasic changes in the CNS function\(^{14,17}\) have been reported, exposure to 1,000 ppm to 7,000 ppm toluene in this study, noradrenaline levels increased at 7,000 ppm. Biphasic action may be observed if the concentration of toluene is further increased.

Noradrenergic neurons in the mPFC are derived mainly from the locus coeruleus (LC)\(^{27,29}\). The activity of the noradrenergic system in the LC is modified by excitatory or inhibitory input originating in the nucleus paragigantocellularis in addition to modification by noradrenaline itself through the \(\alpha_2\) receptors\(^{31}\). Therefore, noradrenaline level in the mPFC is regulated by various neural networks. It has been well documented that adrenergic activity in the LC is associated with noradrenaline release from the mPFC in response to stress. Extracellular noradrenaline in the mPFC is increased by stress\(^{30,34,35}\) or novelty\(^{35}\), and stress–induced noradrenaline release in mPFC can be attenuated by diazepam\(^{34,35}\) or high–dose ethanol\(^{30}\). In this study, toluene inhalation increased extracellular noradrenaline in the mPFC. The increase of noradrenaline in the mPFC induced by toluene may also be affected through the interneurons around the LC. It is unclear whether the increase in noradrenaline following toluene inhalation is due to activation of the neurons in the LC, or due to direct release from termini in the mPFC. In consideration of toluene's psychological dependence, the neuronal pathways affected by toluene may be different from those of the stress–induced system. However, further research on stress and toluene interactions, including stress–drug sensitization, is necessary.

It is known that dopamine in the mPFC may contribute to working memory, and modulate cognitive functions\(^{39}\). Dopamine stimulation may be beneficial to the mPFC function, whereas excessive dopamine stimulation is detrimental to working memory performance\(^{40}\). As toluene induces dysfunction of memory and recognition\(^{41}\), increased dopamine in the mPFC may be associated with the emergence of these clinical CNS symptoms following toluene inhalation. The dopaminergic system is known to be involved in schizophrenia. Therefore, the potential stimulation of the dopaminergic system by toluene
supports the existence of some correlation of symptoms and neural activity between inhalant abuse and schizophrenia.

Several suggestions have been made for the increases in extracellular neurotransmitters by toluene, including neuronal excitation and inhibition of enzymes or transporters. Very little is known regarding the cellular effects of many other volatile agents of abuse. Since repeated and acute exposure to toluene has been shown to induce cross-sensitization to cocaine in rats, it is apparent that toluene exerts some actions apart from transporter inhibition. Extracellular dopamine and noradrenaline increase by effects of toluene, may likely through 5-HT, NMDA or GABA receptors.

**Conclusion**

Noradrenaline and dopamine release in the mPFC and the NAcc were studied in freely-moving rats during inhalation exposure to toluene using in vivo microdialysis.

1. Exposure to 1,000 ppm and 3,000 ppm toluene did not cause a significant increase of extracellular noradrenaline and dopamine levels in either the mPFC or the NAcc.

2. Toluene inhalation at 7,000 ppm increased extracellular noradrenaline and dopamine levels in both the mPFC and the NAcc.

3. In each on these areas, the increases of noradrenaline were greater than those of dopamine.

These results also suggest that exposure to toluene by inhalation enhances excitability of noradrenergic neurons.

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トルエン吸入が自由行動下ラットの大脳皮質前頭前野と側坐核における細胞外ノルアドレナリンとドパミンを増加させる

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抄録

トルエンはシンナーの主成分で、吸入により酔酔感を得ることができる。近年まで、トルエンの神経薬理学的影響に焦点をあてている実験データは極めて少ない。本研究では、トルエンによる中枢神経系への作用を調べた。自由行動下のラットで、トルエン吸入処理の間の大脳皮質内側前頭前野（mPFC）と側坐核（NAcc）におけるノルアドレナリンとドパミンの濃度変化をin vivoマイクロダイアフリシスを用いて研究した。

7,000 ppmのトルエンの吸入は、mPFCとNAccで細胞外ノルアドレナリンとドパミン濃度を増加させた。NAccにおいて、ノルアドレナリンとドパミンはそれぞれ、306%と183%まで増加した。両方の部位で、ノルアドレナリンの増加は、ドパミンの増加より大きかった。1,000 ppmと3,000 ppmのトルエンの吸入では、細胞外ノルアドレナリンとドパミンの濃度に有意な影響をあたえなかった。

トルエン吸入は、薬物依存に特に重要な役割を果たす中枢神経系ドパミン神経に関与することが明らかになった。これらの結果は、吸入によるトルエンへの曝露がノルアドレナリン動性神経の興奮性を高めることも示唆する。

キーワード：トルエン/ノルアドレナリン/ドパミン/マイクロダイアフリシス