α-Thujone (the active component of absinthe): γ-Aminobutyric acid type A receptor modulation and metabolic detoxification.

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See commentary “Absinthe and γ-aminobutyric acid receptors” on page 4417.

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ABSTRACT

α-Thujone is the toxic agent in absinthe, a liqueur popular in the 19th and early 20th centuries that has adverse health effects. It is also the active ingredient of wormwood oil and some other herbal medicines and is reported to have antinociceptive, insecticidal, and anthelmintic activity. This study elucidates the mechanism of α-thujone neurotoxicity and identifies its major metabolites and their role in the poisoning process. Four observations establish that α-thujone is a modulator of the γ-aminobutyric acid (GABA) type A receptor. First, the poisoning signs (and their alleviation by diazepam and phenobarbital) in mice are similar to those of the classical antagonist picrotoxinin. Second, a strain of Drosophila specifically resistant to chloride channel blockers is also tolerant to α-thujone. Third, α-thujone is a competitive inhibitor of [3H]ethynylbicycloorthobenzoate binding to mouse brain membranes. Most definitively, GABA-induced peak currents in rat dorsal root ganglion neurons are suppressed by α-thujone with complete reversal after washout. α-Thujone is quickly metabolized in vitro by mouse liver microsomes with NADPH (cytochrome P450) forming 7-hydroxy-α-thujone as the major product plus five minor ones (4-hydroxy-α-thujone, 4-hydroxy-β-thujone, two other hydroxythujones, and 7,8-dehydro-α-thujone), several of which also are detected in the brain of mice treated i.p. with α-thujone. The major 7-hydroxy metabolite attains much higher brain levels than α-thujone but is less toxic to mice and Drosophila and less potent in the binding assay. The other metabolites assayed are also detoxification products. Thus, α-thujone in absinthe and herbal medicines is a rapid-acting and readily detoxified modulator of the GABA-gated chloride channel.

Absinthe was a popular emerald-green liqueur in the 19th and early 20th centuries. It was commonly imbibed by artists and writers including Vincent van Gogh, Henri de Toulouse-Lautrec, and Charles Baudelaire, often inducing fits and hallucinations and sometimes contributing to psychoses and suicides (1–5). Absinthe became an epidemic health problem and was banned in many countries early in the 20th century, but its use continues legally or illicitly even now (6, 7). The toxic properties of absinthe are attributable to wormwood oil used in making the beverage. Wormwood oil is in itself a prevalent herbal medicine for treating loss of appetite, dyspeptic disorders, and liver and gallbladder complaints (8, 9).

α-Thujone (Fig. 1) generally is considered to be the principal active ingredient of wormwood oil and toxic principle in absinthe (2). The content of β-thujone often exceeds that of α-thujone depending on the plant source, but the β-diastereomer (Fig. 1) is generally of lower toxicity. α-Thujone also is reported to have antinociceptive activity in mice (10). This monoterpenoid occurs in many plants, including Artemesia species, sage, and the Thuja tree (4). Extracts of wormwood were used to control gastrointestinal worms with records back to ancient Egyptian times (4). Artemesia absinthium and wormwood oil have insecticidal properties (11), and α-thujone was one of the two most toxic monoterpenoids tested against western corn rootworm larvae (12). Public mistrust of synthetic pharmaceuticals and pesticides has led to the increasing popularity of herbal medicines and botanical insecticides even though they have not been subjected to the same rigorous tests of safety and evaluation of toxicological mechanisms (13–15).
α-Thujone (the active component of absinthe): γ-Aminobutyric acid type... 

The toxic effects of α-thujone in mammals are well established but the mode of neurotoxic action is poorly understood. It is porphyrogenic, possibly thereby contributing to the absinthe-induced illness of Vincent van Gogh (5, 16). α-Thujone is neurotoxic in rats (17), and ingestion of wormwood oil containing α-thujone recently resulted in human poisoning (18). The hypothesis that α-thujone activates the CB₁ cannabinoid receptor, based on the structural similarity of thujone enol with tetrahydrocannabinol (19), was not supported experimentally (20). The convulsant action led to multiple speculations on mechanisms, one of which was antagonism of the γ-aminobutyric acid (GABA) receptor system (20), a proposal that was not explored further. α- and β-Thujone are reduced in rabbits from the ketones to the corresponding alcohols (thujol and neothujol) (21) of unknown toxicity but no other metabolites are identified.

The goals of this study are to define the mechanism of neurotoxicity of α-thujone and identify its major metabolites (Fig. 1) and their role in the poisoning process. Emphasis is placed on the hypothesis that the convulsant action is caused by modulating the GABA-gated chloride channel.

MATERIALS AND METHODS

Chemicals.

Sources were: α-thujone (≥99% purity) from Fluka; wormwood oil (3.2% α- and 35% β-thujone) from Lhasa Karnak (Berkeley, CA) and absinthe with 0.4 ppm α-thujone, 5 ppm β-thujone, and 50% (vol/vol) ethanol labeled Herrling Absenta (Zaragoza, Spain) with concentrations based on analyses in this laboratory; picrotoxinin, diazepam, and sodium phenobarbital from Sigma; dieldrin and α-endosulfan from Chem Service (West Chester, PA); [3H]ethynylbicycloorthobenzoate ([3H]EBOB) (38 Ci/mmol) from NEN. Although not detailed here, 7-hydroxy-α-thujone, 4-hydroxy-α-thujone, 4-hydroxy-β-thujone, 7,8-dehydro-α-thujone, and a thujol/neothujol mixture were synthesized as standards for comparison with metabolites.

Toxicity to Mice.

Male albino Swiss–Webster mice (22–28 g) were treated i.p. with the test compound by using propylene glycol (2 µl/g body weight) as the carrier vehicle. Prophylactic i.p. treatments also were examined for their effect on α-thujone toxicity (100 mg/kg) individually with ethanol (0.5 or 1.0 g/kg as 20% and 40% solutions in saline, 20 min pretreatment), diazepam (1 mg/kg, 15 min pretreatment), or phenobarbital (15 mg/kg, 15 min pretreatment).

Toxicity to Drosophila.

Fruit flies (Drosophila melanogaster) were used in two types of assays: comparing two strains known to be different in sensitivity to insecticidal chloride channel blockers and comparing α-thujone and its metabolites for toxicity to the susceptible strain. The median lethal concentration (LC₅₀) was determined for α-thujone and dieldrin with two strains of Drosophila: a dieldrin-resistant Rdl⁻/Rdl⁻ strain (22, 23) (obtained from the Bloomington Drosophila Stock Center at Indiana University, Bloomington) and the Canton-S, wild-type sensitive (S) strain. The test chamber was a glass tube (12 × 75 mm) containing a filter paper strip (Whatman no. 1, 8 × 65 mm). Five adult flies were placed in the tube, which then was closed with a single layer of parafilm. A solution of α-thujone or dieldrin in propylene glycol (5 µl) was injected with a 103µl syringe through the parafilm onto the filter paper after which the tube was covered with a second piece of parafilm. Mortality was recorded after 8 h at 25°C as flies that could not move. The experiment was repeated four times to prepare dosage mortality curves for calculation of resistance ratios (LC₅₀ Rd/LC₅₀ S).

Effect on [3H]EBOB Binding in Mouse Brain Membranes.

Mouse brain membranes were prepared and depleted of GABA as described (24). For inhibitor potency assays, the membranes (200 µg protein) were incubated with the test compound (added in DMSO, final concentration 1%) and [3H]EBOB (0.7 nM) in 1.0 ml of 10 mM sodium phosphate, pH 7.5 buffer containing 200 mM sodium chloride at 37°C for 70 min (25). Scatchard analyses were performed with no inhibitor and with 5 and 25 µM α-thujone by using [3H]EBOB at 0.08–26 nM. The inhibitory potency also was measured for ethanol and absinthe (based on ethanol content) with that for ethanol containing 5 µM α-thujone. The incubated mixtures were filtered through GF/C glass fiber filters, then rinsed twice with 5 ml of ice-cold 0.9% sodium chloride, by using a cell harvester. Specific binding was considered to be the difference between total binding and nonspecific binding determined in the presence of 5 µM α-endosulfan (a potent GABA type A (GABAₐ) receptor antagonist and specific inhibitor of [3H]EBOB binding).

Effect on GABA-Induced Whole-Cell Currents.

Rat dorsal root ganglion neurons were prepared and cultured as described (26). Currents were induced by 10-msec pulses of 300 µM GABA and recorded by using the whole-cell patch clamp technique. The GABA-induced inward current of this preparation was carried by chloride ions through open chloride channels (27). Each cell was tested for the degree of suppression caused by bath application of α-thujone to determine the concentration for 50% inhibition (IC₅₀).

GC-MS Identification and Analysis of α-Thujone and Metabolites.

Standard analytical methods of GC-MS and derivatization of alcohol and ketone functionalities were applied to...
α-Thujone (the active component of absinthe): γ-Aminobutyric acid type...
α-Thujone Modulation of the GABA<sub>A</sub> Receptor-Chloride Channel.

The currents induced by 300 µM GABA are suppressed with 30 µM bath-applied α-thujone and there is full reversal on washing with α-thujone-free solution (Fig. 4 A and B). The IC<sub>50</sub> for α-thujone is 21 µM in suppressing the GABA-induced currents (Fig. 4C).

**Figure 4**

Suppression of GABA-induced peak currents by bath application of α-thujone. Currents were induced by 300 µM GABA (10 msec) pulses. The peak amplitude of current decreased with 30 µM α-thujone and recovered after washing with α-thujone-free solution. (A) Time course of 30 µM α-thujone-induced changes in peak current amplitude. (B) Representative current records. (C) Concentration-response relationship (mean ± SD, n = 4–5).

Absinthe, Ethanol, and Ethanol Containing α-Thujone as Inhibitors of [<sup>3</sup>H]EBOB Binding.

The inhibitory effects on [<sup>3</sup>H]EBOB binding were compared for absinthe, ethanol, and ethanol containing α-thujone to help understand their independent and combined actions on the chloride channel. The IC<sub>50</sub> for absinthe (based on ethanol content) is 263 ± 47 mM and for ethanol is significantly higher at 370 ± 4 mM (Fig. 5A). There is no significant interaction between the effects of ethanol and α-thujone (Fig. 5B), i.e., α-thujone (5 µM) inhibition is 20–30% independent of ethanol concentration up to 300 mM.

**Figure 5**

Absinthe, ethanol, and ethanol containing α-thujone inhibit [<sup>3</sup>H]EBOB binding to mouse brain membranes. (A) Comparison of an absinthe preparation (based on ethanol content) with ethanol (average of duplicate measurements or mean ± SD, n = 6). (B) Comparison of ethanol with ethanol containing 5 µM α-thujone (average of duplicate measurements).

Metabolism of α-Thujone by Liver Enzymes.

Incubation of α-thujone with rabbit (but not mouse) liver cytosol gives thujol and neothujol, identified by GC-MS comparison with authentic standards per se and by forming trimethylsilyl (but not methyloxime) derivatives. This enzymatic reduction depends on NADPH but occurs in small yield. Metabolism in mouse liver microsomes is a much more facile reaction and gives no thujol or neothujol but instead different products. α-Thujone is stable on incubation with mouse liver microsomes alone but is almost completely metabolized when NADPH (but not NADP, NADH, or NAD) also is added. Six NADPH-dependent microsomal metabolites are evident by GC-MS, each at higher retention time than the parent α-thujone (Fig. 6). The first-eluting metabolite is identical in GC and MS features to synthetic 7,8-dehydro-α-thujone. The next five metabolites each are converted to trimethylsilyl and methyloxime derivatives, indicating the presence of both an alcohol substituent and a ketone functionality. Synthesis of various hydroxythujones and their comparison with the metabolites (directly, and as trimethylsilyl ethers and methyloximes) identifies the major product as 7-hydroxy-α-thujone and two minor metabolites as the diastereomers of 4-hydroxythujone.

**Figure 6**

Representative GC-MS- selected ion monitoring chromatograms for α-thujone and metabolites extracted from the mouse liver microsome-NADPH (P450) system and the brain of α-thujone-treated mice (50 mg/kg, i.p., 10 min after treatment). The major metabolite is 7-hydroxy-α-thujone. Four minor hydroxythujone metabolites are as follows: 1) 4-hydroxy-α; 3) 4-hydroxy-β; 2 and 4) others. Dehydro refers to 7,8-dehydro-α-thujone. Shaded peaks not derived from α-thujone are an endogenous substance (end) and the internal standard (IS). All thujone-derived metabolites fall within the chromatographic region shown.
α-Thujone (the active component of absinthe): γ-Aminobutyric acid type


discriminating levels used were 50 mg/kg i.p. for mice and 50 µg/tube for the S strain of Drosophila. With mice, α-thujone is lethal, whereas 7-hydroxy-α-thujone, dehydro-α-thujone, and thujol/neothujol are not lethal. With Drosophila, α-thujone gives complete mortality, dehydro-α-thujone gives 70% mortality, and 7-hydroxy-α-thujone and thujol/neothujol give about 30% mortality. In the [3H]EBOB binding assay, 7-hydroxy-α-thujone gives an IC50 value of 730 ± 265 µM versus 13 ± 4 µM for α-thujone (Fig. 3A), whereas the value for dehydro-α-thujone is 149 ± 10 µM (inhibition curve not shown).

DISCUSSION

This study establishes that α-thujone modulates the GABA<sub>A</sub> receptor based on four observations. Comparison with picrotoxinin, the classical GABA<sub>A</sub> receptor antagonist, revealed similar poisoning signs and in both cases alleviation of the toxicity by diazepam, phenobarbital, and ethanol (28, 29). Drosophila with a single point mutation in the Rdl GABA receptor subunit of Ala<sup>303</sup> to Ser conferring resistance to dieldrin (22, 23) is also resistant to α-thujone, albeit to a lesser degree. α-Thujone is a competitive inhibitor of [3H]EBOB binding, i.e., of the noncompetitive blocker site of the GABA-gated chloride channel (25). Most importantly, electrophysiological studies establish that in dorsal root ganglion neurons α-thujone is a reversible modulator of the GABA<sub>A</sub> receptor.

Absinthe and wormwood oil contain not only α-thujone as their purported active ingredient but also many other candidate toxins, including β-thujone and ethanol in the case of absinthe. β-Thujone is less toxic than α-thujone to mice (19) and Drosophila and in addition is 2.3-fold less potent in the [3H]EBOB assay (this investigation). Ethanol also enhances neuronal GABA<sub>A</sub> receptor function (30) and therefore might suppress the blocking action of α-thujone in absinthe. However, ethanol does not alter the inhibitory action of α-thujone on [3H]EBOB binding. The α- and β-thujone content of the absinthe sample examined here (0.4 and 5 ppm or 2.6 and 33 µM, respectively) may be a contributing factor in the somewhat greater potency of absinthe (based on ethanol content) than of ethanol per se in the [3H]EBOB assay. However, the 10 ppm (66 µM) upper limit of the European Commission (6) and particularly the 260 ppm (1710 µM) thujone content of old absinthe (6) would give a detectable to major inhibitory effect beyond that of the ethanol content. Current low levels of α- and β-thujone in absinthe are of much less toxicological concern than the ethanol content (6).

α-Thujone as other monoterpenes is easily metabolized. The single report on metabolism identifies thujol and neothujol probably as conjugates in the urine of thujone-treated rabbits (21). We find enzymatic reduction (possibly by a cytosolic ketone reductase) (31) of α-thujone to thujol and neothujol in low yield by rabbit but not mouse liver cytosol with NADPH. The mouse liver microsomal P450 system rapidly converts α-thujone to 7-hydroxy-α-thujone (major), the diastereomers of 4-hydroxythujone (minor), and other hydroxythujones (minor). Interestingly, the major sites of P450 hydroxylation at the 4- and 7-positions are those involving
intermediate tertiary radicals that are more stable than secondary and primary radicals. Dehydro-\(\text{\textalpha{}}\)-thujone also is observed and may arise from dehydration of the 7-hydroxy compound as a biological reaction because this possible conversion is not an artifact during the extraction and analysis procedure. The various hydroxythujones probably are not the terminal metabolites because they are expected to undergo conjugation and excretion. However, the presence of hydroxythujones in the brain suggests their potential importance in the neurotoxicity.

Metabolic detoxification is a dominant feature of \(\text{\textalpha{}}\)-thujone neurotoxicity in mice. There are two principal candidate toxicants, \(\text{\textalpha{}}\)-thujone and its 7-hydroxy metabolite. The 7-hydroxy compound is present in brain at much higher levels than the parent \(\text{\textalpha{}}\)-thujone, suggesting possible conversion in situ, but this oxidation was not observed on incubation of \(\text{\textalpha{}}\)-thujone with brain microsomes and NADPH. \(\text{\textalpha{}}\)-Thujone compared with 7-hydroxy-\(\text{\textalpha{}}\)-thujone is 56-fold more potent in the \([\text{\textH{}}]\text{EBOB}\) binding assay and much more toxic to mice and houseflies. It appears that all of the metabolites studied here are detoxification products, i.e., less toxic than \(\text{\textalpha{}}\)-thujone. However, the level in brain of 7-hydroxy-\(\text{\textalpha{}}\)-thujone is several-fold greater than that of \(\text{\textalpha{}}\)-thujone (e.g., 29 and 11 ppm, respectively, at the time of severe poising signs), suggesting that either one or both may contribute to the toxic manifestations.

This study establishes that \(\text{\textalpha{}}\)-thujone acts at the noncompetitive blocker site of the GABA \(\text{\textgamma{}}\) receptor and is rapidly detoxified, thereby providing a reasonable explanation for some of the actions of absinthe other than those caused by ethanol, and allowing more meaningful evaluation of risks involved in the continued use of herbal medicines containing \(\text{\textalpha{}}\)-thujone.

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**ABBREVIATIONS**

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<th>Abbreviation</th>
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<tr>
<td>EBOB</td>
<td>ethynylbicycloorthobenzoate or 4′-ethyl-4-n-propylbicycloorthobenzoate</td>
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<tr>
<td>GABA</td>
<td>(\gamma)-aminobutyric acid</td>
</tr>
<tr>
<td>GABA(_A) receptor</td>
<td>type A GABA receptor</td>
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<td>LC(_{50})</td>
<td>median lethal concentration</td>
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**FOOTNOTES**

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Article and publication date are at www.pnas.org/cgi/doi/10.1073/pnas.070042397

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Figure 2
α-Thujone (the active component of absinthe): γ-Aminobutyric acid type...
Figure 4

A. Peak current (nA) over time (min) with exposure to 30 μM α-thujone and subsequent washout.

B. Comparison of control and treated conditions with 30 μM α-thujone showing a decrease in peak current.

C. Graph showing peak current (% of control) against α-thujone concentration (μM) with IC₅₀ = 21 μM.
Figure 5

[Diagram A] 
- [3H]EBOB binding (%)
- Axes: Ethanol (mM)
- Two lines: Ethanol and Absinthe

[Diagram B] 
- [3H]EBOB binding (%)
- Axes: Ethanol (mM)
- Three lines: Ethanol alone, Ethanol + 5 μM α-thujone
α-Thujone (the active component of absinthe): γ-Aminobutyric acid type...
α-Thujone (the active component of absinthe): γ-Aminobutyric acid type...

Figure 7

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  (PMID:10781032)

- Detection of errors of interpretation in experiments in enzyme kinetics.
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Genes & Proteins

Found 1 unique Genes closely
related to this citation

Rdl: Resistant to dieldrin
(NCBI gene: 39054)

Found 2 unique Proteins closely related to this citation

Gamma-aminobutyric acid receptor
(FlyBase: Q7JPT1)
Gamma-aminobutyric acid receptor subunit beta
(FlyBase: P25123)

Identified 4 unique Genes/Proteins in the Full Text

Rdl (1)
type A (1)
CB1 (1)
cytochrome P450 (1)

Gene Ontology (GO) Terms

Identified 7 unique GO Terms in the Full Text

binding (17)
microsomes (5)
membranes (5)
cytosol (3)
death (2)
excretion (1)
conjugation (1)

Species

Identified 14 unique Species in the Full Text

mice (29)
mouse
Drosophila (11)
rabbits (5)
flies (3)
rat (3)
houseflies (1)
animals (1)
Drosophila melanogaster (1)
Fruit flies (1)
human (1)
mammals (1)
western corn rootworm (1)
Thuja (1)
plants (1)

Diseases

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psychoses (1)
hallucinations (1)
Chemicals

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