Development and Characterization of a New Model of Tacrine-Induced Hepatotoxicity: Role of the Sympathetic Nervous System and Hypoxia-Reoxygenation

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ABSTRACT

Tacrine is an acetylcholinesterase inhibitor approved for the treatment of Alzheimer’s disease. Unfortunately, reversible hepatotoxicity in about 30% of patients at therapeutic doses limits clinical use. The purpose of this study was to develop and characterize a model of tacrine hepatotoxicity to begin to understand the mechanisms of injury. Rats were given tacrine (10–50 mg/kg, intragastrically) and killed 24 hr later. An increase in serum aspartate aminotransferase was observed up to 35 mg/kg and histology revealed pericentral necrosis and fatty changes. Aspartate aminotransferase was increased from 12 to 24 hr and returned to control values by 32 hr. Livers were perfused in a nonrecirculating system to measure oxygen uptake and trypan blue was infused at the end of each experiment to evaluate tissue perfusion. Time for trypan blue to distribute evenly throughout the liver 3 hr after tacrine treatment was significantly increased (6.9 ± 1.3 min) compared to controls (1.0 ± 0.3 min) reflecting decreased tissue perfusion. Tacrine also significantly increased the binding of a hypoxia marker, pimonidazole, in pericentral regions almost 3-fold, and increased portal pressure in vivo significantly. It is hypothesized that tacrine, by inhibiting acetylcholine breakdown in the celiac ganglion, increases sympathetic activity in the liver leading to vascular constriction, hypoxia and liver injury. To test this hypothesis, the hepatic nerve was severed and animals were allowed to recover before tacrine treatment. This procedure significantly reduced serum aspartate aminotransferase, time of dye distribution, pimonidazole binding and portal pressure. Furthermore, a free radical adduct was detected with spin trapping and electron spin resonance spectroscopy 8 hr after tacrine treatment, providing evidence for reoxygenation. When catechin (100 mg/kg, i.p.), a free radical scavenger, was given before tacrine, injury was decreased by about 45%. Furthermore, feeding 5% arginine in the diet significantly reduced portal pressure and time of dye distribution. These data are consistent with the hypothesis that tacrine hepatotoxicity is a hypoxia-reoxygenation injury mediated through the sympathetic nervous system.

Alzheimer’s disease affects about 4 million people in the United States and is characterized by a degradation of cholinergic nerves in the cerebral cortex and hippocampus leading to a decrease in cholinergic transmission (Owens, 1993). Drug therapy to increase cholinergic transmission has been one strategy used to combat the symptoms of Alzheimer’s disease (Starr, 1992; Volger, 1991). Tetrahydroaminoacridine (also known as THA, tacrine, and Cognex) is the first agent approved by the Food and Drug Administration for treatment of Alzheimer’s disease. Tacrine acts as an acetylcholinesterase inhibitor to block the degradation of acetylcholine in the neurons of cerebral cortex thereby increasing cholinergic transmission (Wu and Yang, 1989; Hunter et al., 1989). Preclinical trials showed that many Alzheimer’s patients had a significant improvement in symptoms when tacrine (2–3 mg/kg/day) was administered on a daily basis (Farlow et al., 1992; Gamzu et al., 1990; Summers et al., 1981). However, prolonged use of tacrine has proven to be hepatotoxic in about 30% of the patients (Elinder et al., 1989; Ames et al., 1990; Forsyth et al., 1989b; Hammel et al., 1990; Marx, 1987; O’Brien et al., 1991; Summers et al., 1981; Summers et al., 1989) by unknown mechanisms.

Liver injury due to tacrine is characterized by an elevation of the liver-specific enzyme AST (Summers et al., 1989). Histopathology, documented by liver biopsy, revealed pericentral necrosis and fat accumulation in midzonal regions as well as a few cases of drug-induced granulomatous hepatitis (Waktins et al., 1994; O’Brien et al., 1991; Ames et al., 1990;...
Materials and Methods

Chemicals. Tacrine (9-amino-1,2,3,4-tetrahydroacridine hydrochloride, catalog #A3773), trypan blue (#T0776), and catechin (#C1251, 98% pure) were purchased from Sigma Chemical Company (St. Louis, MO). α(4-pyridyl-1-oxide)-N-tetra-butylammonium (4-PBON, #P-0020) was purchased from OMRF Spin Trap Source (Oklahoma City, OK). Pimonidazole hydrochloride was synthesized according to published procedures (Smithen and Hardy, 1982) and characterized using standard chromatographic, elemental analysis and spectrographic techniques. Chemicals for the preparation of formalin-fixed, paraffin-embedded tissue sections were reagent grade purity from local suppliers. Vector Laboratories Inc. (Burlingame, CA) supplied the ABC peroxidase Vectastain kit, avidin-biotin blocking kit, rat adsorbed horse-antimouse antibodies and the DAB peroxidase substrate. The antibody to pimonidazole (Raleigh and Koch, 1990) was isotyped using a Clonotyping System/AP kit purchased from Fisher Scientific Company (Pittsburgh, PA).

Experimental animals. Female Sprague-Dawley rats (weight range 175–225 g) were given food and water ad libitum and treated intragastrically with up to 50 mg/kg tacrine dissolved in saline. Animals were anesthetized with sodium pentobarbital (50 mg/kg) or methoxyflurane before all surgical procedures. Blood was drawn from the descending vena cava for enzyme analysis and the liver was perfusion-fixed with 10% formalin, in accordance with institutional guidelines.

Micsrovascular sympathectomy in the liver. Rats were anesthetized and maintained with methoxyflurane. The peritoneum was opened and the portal vein, hepatic artery and bile duct were exposed. A 3-mm wide region of tissue around the vessels and bile duct was removed to cut the sympathetic nerve (Cucchiara et al., 1990). Additionally, ligaments surrounding the liver were also severed to remove sympathetic nerves entering via this route. Sham operations were also performed by opening the abdomen and exposing the portal vein for 10 min. The incision was closed and the rat was allowed to recover at least 72 hr before tacrine treatment.

Liver perfusion. Livers were perfused with Krebs-Henseleitbicarbonate buffer (pH 7.4, 37°C) saturated with an oxygen-carbon dioxide mixture (95:5) in a nonrecirculating system as described elsewhere (Scholz et al., 1973). Perfusate leaving the liver was allowed to flow past a Clark-type oxygen electrode shielded by Teflon (Instech Laboratories, Plymouth Meeting, PA) to measure oxygen content in the perfusate. Oxygen uptake was calculated from the difference between oxygen concentration in the perfusate entering and leaving the system, the flow rate and the liver weight. Oxygen uptake values were used to assess tissue viability during perfusion.

Trypan blue distribution. Trypan blue infusion has been used to assess changes in tissue perfusion (Beckh et al., 1985; Ji et al., 1984; Zhong et al., 1996). A 0.5 mM trypan blue solution (Sigma) in Krebs-Henseleit-bicarbonate buffer saturated with an oxygen-carbon dioxide mixture (95:5) was infused into the perfused liver for up to 15 min at the end of each perfusion experiment (Belinsky et al., 1984). The time for trypan blue to distribute evenly to all regions of the liver was recorded to assess changes in tissue perfusion.

Use of pimonidazole to detect hypoxia in the liver. One hour after treatment with tacrine (35 mg/kg) or saline, animals received pimonidazole (120 mg/kg i.p.) (Arteel et al., 1995, 1996). Pimonidazole detects hypoxia in vivo by binding in cells at oxygen concentrations of 14 µM or less (Raleigh and Koch, 1990). After 2 hr, animals were anesthetized with pentobarbital (50 mg/kg i.p.) and livers were isolated surgically. The liver was perfusion-fixed with 10% formalin, and tissue sections were collected from the right lobe for immunohistochemical analysis of pimonidazole adduct binding.

Analysis of tissue-bound pimonidazole by immunohistochemistry. Paraffin blocks of formalin-fixed liver tissue were sectioned at 6 µm and pimonidazole adducts were detected with a biotin-streptavidin-peroxidase indirect immunostaining method modified for rat livers (Arteel et al., 1995). Sections were hydrated and treated briefly with 0.01% protease (pronase E) and exposed to mouse antipimonidazole IgG antibody in PBS-Tween for 2 hr at 37°C. Rat adsorbed horse anti-mouse antibody was then applied to the sections for 30 min. Once the antibody-biotin-peroxidase complex was formed, DAB chromogen was added as the peroxidase substrate. After the immunostaining procedure, a light counterstain of hematoxylin was applied followed by mounting with crystal mount solu-
Detection of free radical adducts. To assess free radical formation after tacrine treatment, the spin trapping reagent 4-POBN (250 mg/kg, dissolved in saline) was injected into the tail vein 7 hr after tacrine treatment. The abdomen was opened while the rat was under ether anesthesia and bile was collected for 1 hr via a cannula (polyethylene tubing #50) placed in the common bile duct into 50 μl dipyrild on ice to prevent ex vivo free radical formation and stored on dry ice until analysis (Knecht et al., 1990). Bile samples were then thawed, placed in a quartz ESR cell, and scanned. Free radical adducts were detected with a Bruker ESP 106 ESR spectrometer. Instrument conditions were as follows: 20-mW microwave power; 1.007-G modulation amplitude and 80-G scan range.

Histology and serum enzymes. One centimeter thick sections of liver were placed in 1% paraformaldehyde for at least 24 hr. The fixed tissue was embedded in paraffin, prepared for light microscopy and stained with hematoxylin and eosin. Blood was collected from the descending vena cava or tail vein, placed in 1.5-ml plastic tubes and allowed to clot. Serum was separated by centrifugation (500 × g and stored at -20°C until AST activity was measured by standard enzymatic methods (Bergmeyer, 1983).

Statistics. All data are presented as mean ± S.E.M. Comparisons between groups were performed by Student’s t test, analysis of variance or repeated measures analysis of variance followed by Bonferroni’s post hoc test for multiple comparisons. The criterion for significance of P < .05 was selected before the study.

Results
Characterization of tacrine-induced liver injury. Animals were treated with 10 to 50 mg/kg tacrine or a comparable amount of saline intragastrically 24 hr before serum was collected for measurement of AST as described in “Materials and Methods.” Tacrine caused a significant increase in serum AST activity at 35 mg/kg (table 1). Animals treated with a higher dose of tacrine (50 mg/kg) died within 4 hr of acute cholinergic toxicity as evidenced by salivation, tremor and difficult breathing (Taylor, 1990) without any liver pathology; therefore, 35 mg/kg was selected for all subsequent studies.

 Twenty four hours was selected as an end point for dose-response experiments described above out of convenience. To determine the complete time course, rats were sacrificed every 4 hr for up to 32 hr after tacrine treatment and serum AST measured (fig. 1). From 0 to 8 hr, there was a steady increase in AST. At 12 hr, AST reached a plateau (~120 U/liter) which remained about double the control value for up to 24 hr. By 32 hr, values had returned to control levels (~50 U/liter).

Histology from animals treated with 35 mg/kg tacrine for 24 hr and saline-treated controls is shown in figure 2. Livers from untreated rats were normal (fig. 2A). In livers from the tacrine-treated rats (fig. 2B), necrosis was detected in midzonal and pericentral regions of the liver lobule accompanied by fatty changes.

Role of hypoxia and the sympathetic nervous system in tacrine-mediated hepatotoxicity. To determine if tacrine caused cell death, livers were perfused and then infused with trypan blue at the end of the perfusion. About 10% of the cells in the pericentral region stained positive for trypan blue in histology. Yet, during perfusion, it was observed that the distribution of trypan blue in the circulation of the tacrine-treated liver was significantly impaired. Not only can trypan blue be used in histologically to stain dead cells in the liver (Belinsky et al., 1984; Zhong et al., 1996), but time for vital dye to distribute evenly can be used to detect changes in intrahepatic perfusion (Beckh et al., 1984; Ji et al., 1984; Zhong et al., 1996). Therefore, the time for trypan blue to distribute evenly in the perfused liver was used as an index of changes in intrahepatic distribution of flow (fig. 3). Overall, there was a significant, nearly 7-fold increase in the time for trypan blue to distribute when tacrine-treated animals (6.9 ± 1.7 min) were compared to controls (1.0 ± 0.3 min), showing decreased

![Fig. 1. Time course of AST release after tacrine administration. Blood was drawn from the tail vein every 4 hr for 32 hr after tacrine (35 mg/kg) treatment for determination of AST as described in “Materials and Methods.” Values are the mean ± S.E.M. (n = 4). Representative error bars are shown.](image-url)
tissue perfusion. However, there was no significant difference in the oxygen uptake of perfused livers ex vivo from tacrine-treated animals (112 ± 10 μmol/g/hr) compared to controls (105 ± 7 μmol/g/hr). When the hepatic nerve, which is known to control liver microcirculation, was severed 72 hr before tacrine treatment, the increase in trypan blue distribution time by tacrine was prevented.

To test the hypothesis that redistribution of hepatic flow caused by tacrine leads to hypoxia, the hypoxia marker pimonidazole was injected and 2 hr later livers were harvested and pimonidazole adduct binding was quantitated (Arteel et al., 1995, 1996). Tacrine significantly increased pimonidazole binding nearly 3-fold in pericentral regions of the liver lobule (fig. 4). To determine if the hepatic nerve is involved in the mechanism of hypoxia, some rats underwent hepatic sympathectomy or sham operation and were allowed to recover for 72 hr before tacrine administration. Sham operation alone had no significant effect on the binding of pimonidazole after tacrine treatment; however, sympathectomy significantly reduced pimonidazole binding. Most important, in animals treated with tacrine, sympathectomy 72 hr before tacrine treatment significantly decreased pericentral binding of pimonidazole compared to treated sham-operated animals.

There was a significant increase in portal pressure after treatment with 35 mg/kg tacrine in unoperated and sham-operated animals compared to saline-treated controls (fig. 5). Cutting the sympathetic hepatic nerve completely blocked the tacrine-mediated increase in portal pressure in vivo.

The ultimate test of the hypothesis that the hepatic nerve is involved in tacrine-mediated hepatotoxicity is to show that severing the nerve blocks damage. Accordingly, blood was drawn 24 hr after tacrine treatment for measurement of AST (fig. 6). As before, tacrine caused a significant increase in AST compared to controls. Sham operation had no effect on serum AST; however, cutting the sympathetic nerve before tacrine treatment prevented the increase in serum AST.

**Prevention of tacrine hepatotoxicity by hepatic denervation is not due to inability to regulate body temperature.** Because tacrine is extensively metabolized by the liver and hepatotoxicity has been proposed to be caused by production of toxic metabolites, one possible explanation for the observations in these studies is that severing the hepatic nerve may decrease body temperature and inhibit metabolism of tacrine. Accordingly, the time course of changes in body temperature was measured after tacrine treatment (fig. 7). As with other acetylcholinesterase inhibitors (Kooka et al., 1987), tacrine treatment caused a significant decrease in body temperature of about 3°C at 4 and 8 hr that was unaffected by prior surgery. Body temperature returned to near pretreatment values at 24 hr in all groups.

**Evidence for free radical production and reperfusion injury after tacrine treatment.** It is possible that the injury due to tacrine treatment is not the result of prolonged hypoxia but instead occurs upon reperfusion when the vas-
cular space increases (i.e., after tacrine is metabolized) and oxygen reenters previously hypoxic cells leading to the production of free radicals that cause cell injury. Using the spin trapping technique, a free radical adduct was detected in the bile of tacrine-treated animals 8 hr after treatment (fig. 8). The radical spectrum simulated as a mixture of two radical species (species I: $a^{\Delta} = 15.8$ and $a^{\beta H} = 2.1$, species II: $a^{\Delta} = 15.6$ and $a^{\beta H} = 3.4$). The coupling constants of species I is consistent with a carbon-centered free radical while species II is consistent with an oxygen-centered free radical.

Dietary arginine has been shown to prevent reperfusion injury in the perfused rat liver (Jones and Thurman, 1996). A diet high in the arginine (5% w/w), which is known to improve the hepatic microcirculation most likely by increasing nitric oxide production, or a control diet was fed to rats for 3 days before tacrine treatment. Dietary arginine prevented the increases in portal pressure and time of vital dye distribution caused by tacrine (table 2).

To determine if free radical production plays a role in tacrine hepatotoxicity, the free radical scavenger catechin (100 mg/kg) or saline vehicle was administered 1 hr before tacrine treatment (fig. 9). Catechin prevented the increase in AST observed with tacrine treatment ($P < .05$).

Discussion

Development and characterization of a new model of tacrine-induced liver injury. In this study, a new model has been developed in the rat to study the hepatotoxicity of tacrine. Tacrine caused a significant increase in serum AST, a specific marker for liver toxicity (table 1), and injury in midzonal and pericentral regions of the liver lobule as well as fatty changes (fig. 2) at 35 mg/kg. Lower doses, as reported by others (Hunter et al., 1989), do not cause significant liver injury. This pattern of injury 24 hr after 35 mg/kg tacrine is...
similar to that observed with hypoxia (Lemasters et al., 1981). Additionally, it resembles the pathology observed in the clinic when patients are given tacrine chronically (Waktkins et al., 1994; O’Brien et al., 1991; Ames et al., 1990; Forsyth et al., 1989a; Hammel et al., 1990). Furthermore, tacrine decreased tissue perfusion (fig. 3), increased portal pressure in vivo (fig. 5) and increased pimonidazole adduct binding in the pericentral region of the lobule (fig. 4) providing evidence that tacrine causes hypoxia in the liver by altering intrahepatic blood flow and decreasing tissue perfusion. Collectively, these data support the hypothesis that acute tacrine treatment causes hypoxia.

Role of the sympathetic nervous system in the mechanism of tacrine-induced hepatotoxicity. It is well known that the sympathetic nervous system plays an important role in control of the microcirculation in the liver (Lautt, 1980; Gardemann et al., 1992). The pathway by which the liver is innervated is shown schematically in figure 10. The sympathetic nerve controlling the liver vasculature originates from the cholinergic celiac ganglion. Acetylcholine is released in the celiac ganglion and causes an action potential that propagates through the hepatic nerve, which is the afferent, sympathetic pathway to the liver. It is postulated that norepinephrine is released directly onto endothelial cells and stellate cells in periportal regions of the liver, decreasing sinusoidal vascular space and tissue perfusion (Gardemann et al., 1992). Infusion of noradrenaline or electrical stimulation of the sympathetic pathway in the perfused liver alters the distribution of trypan blue in the liver and decreases surface oxygen tension (Beekh et al., 1985; Ji et al., 1984). Prolonged hypoxia is known to cause cell death; therefore, it was hypothesized that tacrine, by increasing acetylcholine at the celiac ganglion, would increase sympathetic activity via the hepatic nerve and release norepinephrine in the liver causing injury. To test this hypothesis, the sympathetic afferent to the liver was severed. Hepatic sympathectomy prevented the decrease in tissue perfusion (fig. 3), the increase in portal pressure (fig. 5), and the increase in binding of the hypoxia marker pimonidazole in pericentral regions of the liver.
liver (fig. 4). The increase in AST (fig. 6) caused by tacrine was also reduced significantly by cutting the sympathetic hepatic nerve. These data support the hypothesis that the sympathetic hepatic nerve plays a central role in the mechanism of tacrine-induced liver injury.

Several years ago, it was shown that severing the spinal cord just above the branch to the celiac ganglion, which controls the sympathetic hepatic nerve, prevented carbon tetrachloride toxicity (Calvert and Brody, 1960; Brody et al., 1961). It was proposed that CCl₄ toxicity occurred through the sympathetic nervous system by altering liver hemodynamics. In an elegant study, however, Larson and Plaa (1965) showed that cordotomy decreased body temperature in the rat thereby decreasing bioactivation of CCl₄ explaining why injury was prevented (Larson et al., 1964). Therefore, it was possible that cutting the sympathetic hepatic nerve would decrease core body temperature thereby decreasing bioactivation of tacrine and preventing hepatotoxicity by a similar mechanism. However, the decrease in tacrine-induced liver injury after hepatic sympathectomy was not due to the inability of animals to regulate body temperature (fig. 7). There was no difference in body temperature in any group before tacrine treatment. Moreover, tacrine treatment caused only about a 3°C decrease in core body temperature that was independent of prior surgery. In the studies with CCl₄, there was about a 10°C decrease in body temperature when the drug was administered. Therefore, it is concluded that hepatic denervation has little effect on body temperature compared to cordotomy. Furthermore, it is concluded that the decrease in tacrine toxicity after hepatic denervation is not due to inability of animals to regulate body temperature.

The data generated in these studies are consistent with the hypothesis that increased stimulation of the sympathetic pathway in the liver, mediated through the action of tacrine at the celiac ganglion, causes hypoxia in the liver that plays a major role in the mechanism of tacrine hepatotoxicity.

Reperfusion injury occurs after tacrine. As tacrine is metabolized, it is proposed that resistance in the sinusoids decreases because of diminishing stimulation of the sympathetic hepatic nerve. Blood flow to the liver increases, restoring oxygen to previously hypoxic cells (fig. 10). Reperfusion of the liver after hypoxia could result in production of free radicals by activated Kupffer cells or xanthine oxidase leading to parenchymal cell injury (Lemasters and Thurman, 1993). Indeed, we have detected two free radical species 8 hr after tacrine treatment by spin trapping and ESR spectroscopy (fig. 8). Furthermore, the free radical scavenger catechin

The effect of dietary arginine on in vivo portal pressure and vital dye distribution in perfusion after tacrine treatment

<table>
<thead>
<tr>
<th>Diet</th>
<th>Treatment</th>
<th>Portal pressure (cm Water)</th>
<th>Time of vital dye distribution (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Tacrine</td>
<td>7.9 ± 0.7</td>
<td>5.6 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>Arginine Tacrine</td>
<td>5.4 ± 0.7ª</td>
<td>1.0 ± 0.1ª</td>
<td></td>
</tr>
</tbody>
</table>

ª Rats were fed a semisynthetic powdered diet containing 5% arginine or isonitrogenous control diet for 3 days (Jones and Thurman, 1996). Animals were given 35 mg/kg tacrine intragastrically and in vivo portal pressure and time of vital dye distribution during perfusion were determined three hours later as described in "Materials and Methods." Values are the mean ± S.E.M. (n = 4).

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Fig. 8. Detection of free radical adducts in the bile after tacrine treatment. Tacrine (35 mg/kg) was given intragastrically. After 7 hr, rats were anesthetized and 4-POBN (250 mg/kg) was injected i.v. Bile was collected for the next hour into dipyrrolid to prevent ex vivo radical formation, and free radical adducts were detected by ESR as described in "Materials and Methods." Data shown are of a typical spectrum.

Fig. 9. Effects of catechin treatment on tacrine-induced liver injury. Catechin (100 mg/kg, i.p.) or a comparable amount of saline was administered 1 hr before treatment with tacrine (35 mg/kg, intragastrically). Sixteen hours after drug treatment, blood was collected and AST determined as described in "Materials and Methods." Values are mean ± S.E.M. (n = 4). Statistical comparisons were made using analysis of variance and Bonferroni’s post hoc test. a, different from saline-treated control. b, different from tacrine-treated animals.
was shown to decrease hepatotoxicity resulting from tacrine treatment (fig. 9). Collectively, these data are consistent with the hypothesis that a significant component of tacrine-mediated hepatotoxicity may not be prolonged hypoxia per se, but rather the result of increased free radical formation upon reperfusion of previously hypoxic tissue.

Even though sympathectomy before tacrine treatment prevents hepatotoxicity in this model, surgery is not a viable alternative to prevent tacrine-induced liver injury in the clinic. The hypoxia–reperfusion mechanism of tacrine-induced liver injury proposed here predicts that drugs which block increases in cholinergic transmission in the ganglion or prevent constriction of the microvasculature in the liver could be useful in preventing tacrine-induced liver injury. Indeed, arginine, which is known to provide substrate for nitric oxide synthesis and cause vasodilatation (Jones and Thurman, 1996), blunts increases in portal pressure and nitric oxide synthesis (Jones and Thurman, 1996), blunts increases in portal pressure and nitric oxide synthesis (Jones and Thurman, 1996).

Fig. 10. Proposed mechanism of tacrine-induced hepatotoxicity. The sympathetic, afferent nerve bundle of the liver is illustrated. Based on data from this new model of tacrine-induced liver injury, it is hypothesized that tacrine acts at the celiac ganglion to increase sympathetic activity to the liver leading to diminished sinusoidal space, decreased blood flow and hypoxia. As tacrine is metabolized, free radicals are formed leading to reperfusion injury as oxygen delivery increases in previously hypoxic cells. AR, Acetylcholine release; NE, noradrenaline release.

References


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