ANTITHYROID ACTION OF TETRAETHYLTHIURAM DISULFIDE

BY ARTHUR W. WASE AND JENS CHRISTENSEN

(From the Divisions of Biological Chemistry and Pharmacology, Hahnemann Medical College, Philadelphia, Pennsylvania)

(Received for publication, April 12, 1954)

Tetraethylthiuram disulfide (Antabuse) has been demonstrated to be clinically useful in treating alcoholism (1). The compound has been shown to inhibit the oxidation of acetaldehyde (2) and, further, to inhibit the action of rat liver xanthine oxidase to the extent of 71 per cent, and the succinoxidase system 100 per cent (3).

Examination of the chemical structure of Antabuse indicates that it contains two atomic groupings found in many antithyroid drugs, i.e. \(-\text{N}-\text{C}^-\). This study indicates that Antabuse possesses some antithyroid action in the rat and reacts readily with I\(_2\) in vitro.

EXPERIMENTAL

Eight adult (190 to 210 gm.) male Wistar rats were given Antabuse by intubation, 0.5 gm. per kilo per day, for 3 days. A 0.1 per cent suspension in 1 per cent gum acacia was employed. Sham treatment was received by eight comparable control rats. Food and water were permitted ad libitum during the experiment. 24 hours after the last dose of the drug, the animals were given an intraperitoneal injection of 1 \(\mu\)c. of carrier-free I\(^{131}\), as iodide. Control rats were treated likewise at the same time. 4 hours after injection, the animals were sacrificed by exsanguination, preceded by light ether anesthesia. The entire thyroids were removed, weighed, and prepared for radioassay as described elsewhere (5). The results shown in Table I indicate thyroid activity, as measured by I\(^{131}\) uptake per unit mass of tissue, to be markedly impaired in the animals treated with Antabuse.

Since many of the antithyroid drugs react readily with iodine (6), it was decided to study such a reaction with Antabuse. Preliminary findings showed Antabuse, in CHCl\(_3\), to react rapidly with I\(_2\), forming a violet-brown-colored complex, the absorption spectrogram of which is indicated in Fig. 1. A preparation of 0.01 M Antabuse dissolved in 2 per cent sorbitan monooleate reacted quite rapidly with 0.01 N I\(_2\). Concentrations of I\(_2\) greater than this resulted in the formation of a dark brown precipitate in the reaction vessels. The rate of reduction of I\(_2\) to I\(^-\) was measured by titration with 0.01 N \(\text{Na}_2\text{S}_2\text{O}_3\) at timed intervals. The temperature was
**Table I**

Effect of Tetraethylthiuram Disulfide on $^{131}I$ Uptake of Thyroid from Eight Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Thyroid activity</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>126.4 ± 7.5*</td>
<td>100.0</td>
</tr>
<tr>
<td>Antabuse-treated</td>
<td>56.2 ± 6.8*</td>
<td>44.8</td>
</tr>
</tbody>
</table>

*Mean value ± standard error of the mean.

![Absorption spectrogram of $I_2$, Antabuse, and $I_2$ plus Antabuse. Curve A indicates the formation of a complex substance.](image)

**Fig. 1.** Absorption spectrogram of $I_2$, Antabuse, and $I_2$ plus Antabuse. Curve A indicates the formation of a complex substance.

![Reaction rate of the reduction of $I_2$ by aqueous suspension of Antabuse](image)

**Fig. 2.** Reaction rate of the reduction of $I_2$ by aqueous suspension of Antabuse.
maintained at 22.4 ± 0.1°C. The reaction appears to be of the first order, as shown in Fig. 2, where log [I2] is plotted against time. Reaction flasks that were allowed to stand overnight invariably contained a white precipitate which has not yet been identified.

DISCUSSION

The present data indicate that Antabuse inhibits the iodine-trapping mechanism of the rat thyroid and reacts with I₂ in a manner common to many antithyroid compounds (4). The mechanism of the inhibition may involve the oxidation of I⁻ to I₂, followed by the reaction of the I₂ with -SH to form -S-S-, after some shifting of valence bonds of the Antabuse molecule to provide reactive -SH groups. A reaction of I₂ with Antabuse to form a complex substance has been indicated, and it is not improbable that this could occur in the organism, thereby rendering the I₂ inaccessible for synthetic purposes by the thyroid. Furthermore, since Cu²⁺ appears to be an important factor in the iodide metabolism of the thyroid gland¹ (7), and since Antabuse has been shown to react readily with Cu⁺ to form stable complexes (8), it is possible that Antabuse may impair the I²⁻ uptake by effectively removing Cu⁺ from the biological system responsible for the oxidation of I⁻ to I₂. The inhibition of xanthine oxidase by Antabuse (3) may be related to the above facts, this enzyme system being quite probably involved in thyroid iodine metabolism (9). These assumed modes of action are presently under investigation.

It has been shown that Antabuse prolongs thiopental anesthesia (10). Previous findings (11) indicate thiopental to have a marked antithyroid action. Hence, it is quite possible that the antithyroid properties of both of these drugs are complimentary, especially in view of studies made in these laboratories which indicate anesthesia to be prolonged in thyroidectomized animals.

SUMMARY

1. Antabuse reduced the thyroid I¹³¹-trapping activity of the rat to 44.8 per cent of that of control animals.
2. Antabuse reacts with I₂ to form a complex substance.
3. Iodine is reduced by Antabuse in an aqueous medium.

BIBLIOGRAPHY


¹ Sherman, R. L., and Wase, A. W., unpublished data.
ANTITHYROID ACTION OF TETRAETHYLTHIURAM DISULFIDE
Arthur W. Wase and Jens Christensen

J. Biol. Chem. 1954, 211:75-78.

Access the most updated version of this article at http://www.jbc.org/content/211/1/75.citation

Alerts:
• When this article is cited
• When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 0 references, 0 of which can be accessed free at http://www.jbc.org/content/211/1/75.citation.full.html#ref-list-1