Z. Rechtsmedizin 70, 89—92 (1972)


# Antagonism of Pyrithinol-HCl to Ethyl Alcohol at a Spinal Cholinergic Synapse

R. Benecke, J. Meyer-Lohmann, R. Hagenah, and C. Hellweg

Physiologisches Institut der Universität Göttingen, Lehrstuhl II, Göttingen (BRD)

Received October 8, 1971

*Summary.* Pyrithinol-HCl (40 mg/kg i.v.) decreased in cats the activity of individual Renshaw cells in the spinal ventral horn which are known to be excited via typically cholinergic motor axon collaterals. On the other hand this substance prevented the excitatory action which ethyl alcohol (0.8—1.6 g/kg i.v.) normally exerts upon the Renshaw cells. No protective effect of pyrithinol-HCl was found against the alcohol induced depression of gamma motoneurones. It is assumed from the results that pyrithinol-HCl exerts its protective action specifically upon cholinergic systems.

*Zusammenfassung.* „Antagonistische Wirkung von Pyrithinol-HCl gegenüber Äthylalkohol, untersucht an einer cholinergen Synapse im Rückenmark."

1. An decerebrierten oder narkotisierten (Pentobarbital) Katzen wurde die Wirkung von Pyrithinol-HCl allein und in Verbindung mit Äthylalkohol auf die Aktivität einzelner Renshaw-Zellen (RZ) nach antidromer Reizung untersucht.

2. Durch Pyrithinol-HCl (40 mg/kg i.v.) wurde die RZ-Aktivität vermindert.

3. Nach vorheriger Gabe von Äthylalkohol (1,6 g/kg i.v.), die eine starke RZ-Aktivierung hervorrief, bewirkte Pyrithinol-HCl (40 mg/kg i.v.) eine Verminderung der RZ-Aktivität bis unter den Ausgangswert vor der Alkoholgabe.

4. Gabe von Alkohol (0,8 g/kg i.v.) nach Pyrithinol-HCl (40 mg/kg i.v.) bewirkte an der RZ keine Aktivitätssteigerungen mehr.

5. Da an Gamma-Motoneuronen die stark drosselnde Wirkung von Alkohol durch Pyrithinol-HCl nicht aufgehoben wurde, ist anzunehmen, daß Pyrithinol-HCl im Rückenmark eine Schutzwirkung gegenüber Alkohol speziell an der cholinergen RZ-Synapse entfaltet.

*Key words:* Ethyl Alcohol, Antagonism of Pyrithinol-HCl — Alcohol Intoxication.

It has been demonstrated — with recordings of EEG and cortical evoked respones — that pyrithinol-HCl exerts an antagonism against acute alcohol intoxication (Teijeira and Martinez-Lage, 1961; Dolce, 1970; Tan-eli, 1971). However, there are only speculations about the mechanism of its protective action. It has been reported that ethyl alcohol has at least two modes of basic action upon nervous structures: firstly, it facilitates cholinergic synaptic transmission (Feng and Li, 1941; Larrabee and Posternak, 1952; Okada and Adachi, 1961; Gage, 1965; Okada, 1967; Hagenah *et al.*, 1971; Meyer-Lohmann *et al.*, 1971); secondly, in some cases it has a depressive effect on a neurone's activity, either due to a change in ionic permeability of its membrane (Eidelberg and Wooley, 1970) or to a reduction of its excitatory input. We therefore investigated

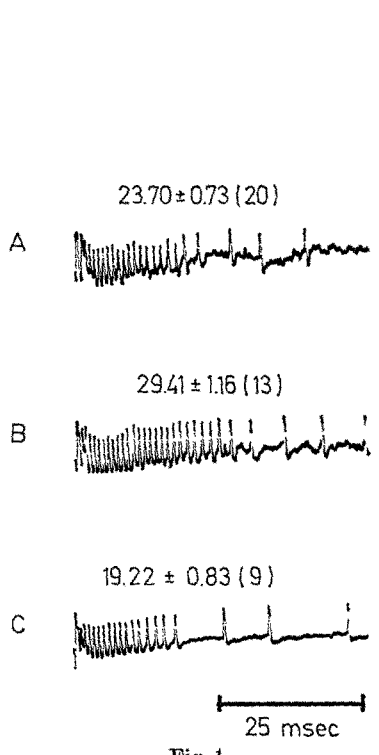


Fig. 1

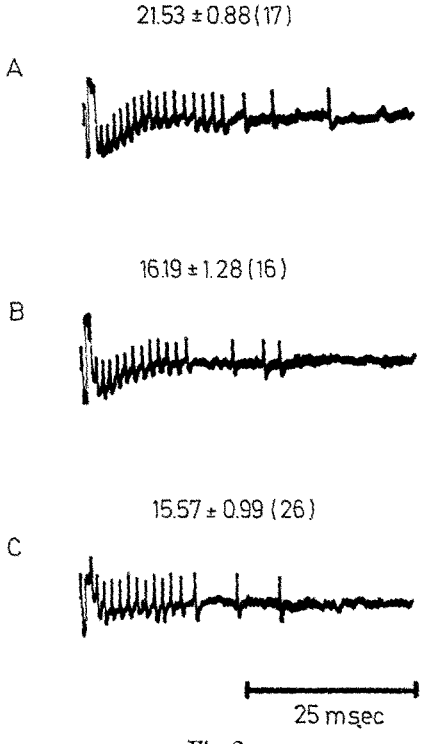


Fig. 2

Fig. 1A—C. The excitatory effect of ethyl alcohol (1.6 g/kg i.v.) on the discharge of a Renshaw cell activated by supramaximal antidromic stimulation of the ventral root $L_7$ in a pentobarbital cat, and the antagonism of pyrithinol-HCl (40 mg/kg i.v.). A Control. B 3 min after the injection of ethanol. C 8 min after the injection of pyrithinol-HCl. Time between B and C: 15 min. The mean count of spikes per antidromic volley during the first 50 msec (23.70, 29.41, 19.22, respectively) and the standard deviation of their individual values ($\pm$ 0.73, $\pm$ 1.16, $\pm$ 0.83, respectively) are shown above the records. In brackets the number of trials is given from which the results were computed in each case

Fig. 2A—C. The action of pyrithinol-HCl (40 mg/kg i.v.) and of ethyl alcohol (0.8 g/kg i.v.) upon the responsiveness of a Renshaw cell to supramaximal stimulation of the ventral root $L_7$. A Control. B 5 min after the injection of pyrithinol-HCl. C 2 min after the application of ethanol. Time between B and C: 16 min. For the meaning of numbers, see legend of Fig. 1. Decerebrated cat

the effect of pyrithinol-HCl, both alone and in combination with ethyl alcohol, on the activity of cat's Renshaw cells which are excited via cholinergic synapses by recurrent collaterals of spinal alpha motoneurones. For comparison, we observed the reactions of spinal gamma motoneurones which are very sensitive to depressive drug actions (Schomburg, 1968), but receive much less Renshaw inhibition than the alpha cells (Ellaway, 1971).

Pyrithinol-HCl (40 mg/kg in Ringer's solution) was slowly (over 2—5 min) injected intravenously. Further details for the methodical procedure are described elsewhere (Meyer-Lohmann *et al.*, 1971).

Fig. 1A shows the response of an individual Renshaw cell to a single antidromic volley in ventral root $L_7$, recorded by conventional microtechniques. An intravenous injection of ethyl alcohol (1.6 g/kg) caused a highly significant increase ($p < 0.001$) of the response of the Renshaw cell (Fig. 1 B). We have recently described this typical effect in detail (Hagenah *et al.*, 1971; Meyer-Lohmann *et al.*, 1971). By pyrithinol-HCl (40 mg/kg i.v.) the excitatory effect of alcohol is abolished (Fig. 1C), the Renshaw cell's response is now even reduced in comparison to the control ($p < 0.001$). In Fig. 2 the sequence of drug application was reversed. Pyrithinol-HCl (40 mg/kg i.v.) was given first, causing a highly significant decrease ($p < 0.001$) of the response of the Renshaw cell (Fig. 2A and B). In general, this decrease was maximal within 5—10 min after the drug's application, whereas control conditions were apparently reestablished after about 1 hr. An application of ethyl alcohol (0.8 g/kg i.v.), 21 min after the injection of pyrithinol-HCl, was now unsuccessful in increasing the responsiveness of the Renshaw cell (Fig. 2C). Even 1 hr after pyrithinol-HCl application no significant increase in the Renshaw cell's activity could be seen.

The activity of gamma motoneurones, recorded from ventral root filaments in decerebrated cats, decreased after an injection of alcohol (0.8 mg/kg); total silence was usually reached within 1 min. This effect took place independent of whether pyrithinol-HCl had been given before or not.

Provided that the actions of ethyl alcohol on spinal nervous structures are restricted to the two mechanisms mentioned above, it may be concluded from these results that pyrithinol-HCl exerts its protective effect specifically upon cholinergic systems.

The authors thank the E. Merck Company (Darmstadt, Germany) for a gift of pyrithinol-HCl (Encephabol®).

## References

Dolce, G.: Beeinflussung der akuten alkohol-bedingten Veränderungen des EEG, der evoked potentials sowie des Verhaltens bei der Katze durch Pyrithioxin. Prag: C. I. N. P. 1970.

Eidelberg, E., Wooley, D. F.: Effects of ethyl alcohol upon spinal cord neurones. Arch. int. Pharmacodyn. **185**, 388—396 (1970).

Ellaway, P. H.: Recurrent inhibition of fusimotor neurones exhibiting background discharges in the decerebrate and the spinal cat. J. Physiol. (Lond.) **216**, 419—439 (1971).

Feng, T. P., Li, T. H.: Studies on the neuro-muscular junction. XXV. Eserine-like actions of aliphatic alcohols and ketones. Chin. J. Physiol. **16**, 317—340 (1941).

Gage, P. W.: The effect of methyl, ethyl and N-propyl alcohol on neuromuscular transmission in the rat. J. Pharmacol. exp. Ther. **150**, 236—243 (1965).

Hagenah, R., Meyer-Lohmann, J., Hellweg, C., Benecke, R.: The action of ethyl alcohol on the recurrent inhibition in the feline lumbosacral cord. Proc. int. Un. Physiol. Sci. **9**, 229 (1971).

Larrabee, M. G., Posternak, J. M.: Selective action of anesthetics on synapses and axons in mammalian sympathetic ganglia. J. Neurophysiol. **15**, 9—114 (1952).

Meyer-Lohmann, J., Hagenah, R., Hellweg, C., Benecke, R.: The action of ethyl alcohol on the activity of individual Renshaw cells. Naunyn-Schmiedebergs Arch. Pharmacol. **272**, 131—142 (1972).

Okada, K.: Effects of alcohols and acetone on the neuromuscular junction of frog. Jap. J. Physiol. **17**, 245—261 (1967).

— Adachi, M.: Effects of ethyl alcohol on the end-plate potential. J. Physiol. Soc. Jap. **23**, 655—664 (1961).

Schomburg, E. D.: Fusiomotorische Förderung und Hemmung bei Pinna-Reizung in Abhängigkeit vom zentralnervösen Zustand. (Fusimotor excitation and inhibition by pinna stimulation dependent upon different central nervous states.) Pflügers Arch. **304**, 164—182 (1968).

Tan-eli, B.: Alcohol effects on cortical evoked responses in humans related to subchronic oral or acute intravenous administration of pyrithioxin. V. World Congress of Psychiatry, Mexico 1971.

Teijeira, J., Martinez-Lage, J. M.: Antagonismo entre piridoxina y disulfuro de piridoxina y alcohol etilico. Rev. esp. Fisiol. **17**, 11—26 (1961).

Dr. J. Meyer-Lohmann
Physiologisches Institut der Universität
(Lehrstuhl II)
D-3400 Göttingen
Germany