vessels were numerous, and they were separated from the ventricle only by a thin ependymal cover in some places.

The chrome-haematoxyphilous substance and the aldehyde-fuchsin-positive substance showed identical distribution in this region. Its abundance was extraordinarily high as compared with animals of other species. It occurred in profusion subependymally, in the ependymal cell interstices and also within the third ventricle. Its location was identical with that of the hyaline material demonstrated by haematoxylin. The material staining by the selective methods, i.e., by chrome-haematoxylin and aldehyde-fuchsin, partially occurred as a fine, granular mass, partially as typical Herring bodies. In the places where this selective material projected into the third ventricle through the interstices of ependymal cells, it formed club-shaped protuberances.

The location of the secretory material in the ependymal ridge of the recess seems to indicate that, in the camel, it is transferred into the third ventricle in great quantities in this area. According to some investigations, neurosecretory material could be released to a certain extent also into the third cerebral ventricle in some species[2-6]. The structure of the ependyma, which is here strikingly different from the usual ependyma in the camel, as well as in some other animals[7], might also point to such transfer. Of course, the possibility has to be considered that the secretory material observed in the third ventricle might be an artifact; but such material was also encountered in sections with absolutely intact ependymal cover. The profuse occurrence of the material around the subependymal vessels is difficult to explain except by assuming that also release of the material into the circulation occurs here, as it obviously does also in the distal part of the neurosecretory system, in the neurohypophysis[8].

*Zusammenfassung.* Es wird gezeigt, dass bei Kameliden das Ependym auf dem Boden des Recessus infundibularis aus platten Zellen besteht. Im Ependymbereich und in Zellinsterstitien findet sich in reichlichem Masse hyaline Masse, die durch selektive, Neurosekretion anzeigende intensive Färbung dargestellt wird. Die Lokalisation des Materials deutet auf eine Ausschüttung des Neurosekrets in den dritten Gehirnventrikel hin.

S. Talanti and E. Kivalo

*Department of Anatomy, Veterinary College Helsinki (Finland), The Research Department of Rinnekoti, Institute of Mental Deficiency, Helsinki (Finland), April 18, 1961.*

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## Antagonism Against the Arecoline Tremors of Oxyphenonium and its Tertiary Analogue after Intravenous and Intracerebral Administration in Mice

It is well known that the peripheral anticholinergic action of the quaternary ammonium compounds is much higher than that of their tertiary analogues. This is probably due to the great importance of the cationic 'head' in the interaction of drugs with cholinergic receptors[1-3]. Central effect of quaternary compounds is, however, much weaker than that of their tertiary analogues[4-10].

Since the specific mediator for the cholinergic receptors in the periphery as well as in the central nervous system is the quaternary fully ionized substance, acetylcholine[3,11-15] it is likely that the cationic 'head' of the drug is important for the interaction with central as well as peripherical cholinergic receptors.

It is believed that the low central effect of quaternary compounds may be explained by the difficulty with which the fully ionized quaternary compounds[13,16-23] penetrate the blood-brain barrier.

Therefore it is possible to suppose that the quaternary compounds would be at least as active on the central as on the peripheral cholinoreceptors, if they could get into the central nervous system through the blood-brain barrier[3].

It has been established in our preliminary experiments in rabbits that the quaternary analogue of nicotine, which was without convulsive effect intravenously, caused in suboccipital administration convulsions in doses even lower than those of nicotine[10].

The aim of the present report is an investigation of the central anticholinergic effects of oxyphenonium and its tertiary analogue, compound VUFB-3100, after intravenous and intraventricular administration in mice, as evidenced by the ability to prevent tremors caused by intravenous injection of arecoline[24] (Formulae).

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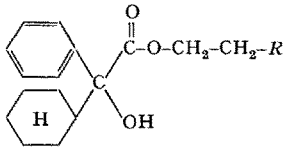
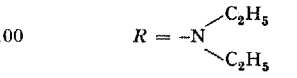
In the case of intraventricular administration, the drugs were dissolved in the Tyrode solution, coloured by addition of Evans blue and injected into the lateral cerebral ventricle in a volume of 0.01 ml, according to the method described by HALEY[25], and using the apparatus constructed by VANĚČEK and KREBS[26]. The accuracy of the localisation of injection was always checked after each experiment. In control experiments intraventricular injection of Tyrode solution with Evans blue had no influence on arecoline tremors. The interval between the administration of the drug tested and the injection of arecoline (5 mg/kg) was 10 min in the intraventricular administration and 5 min in the intravenous administration.

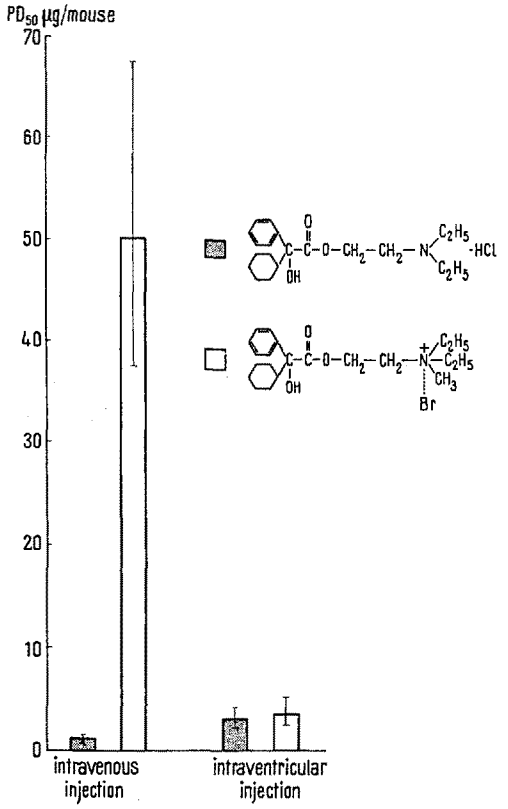


Oxyphenonium $R = -N^{+}(C_2H_5)(CH_3)(C_2H_5)$ $Br^-$



VÚFB-3100 $R = -N(C_2H_5)(C_2H_5)$ HCl

| Mode of administration | Drug injected | $PD_{50}$ | Fiducial limits for $P = 0.05$ |
|---|---|---|---|
| intravenous | oxyphenonium | 2.52 mg/kg | 1.88 –3.88 |
| intravenous | VÚFB-3100 | 0.052 mg/kg | 0.039–0.068 |
| intraventricular | oxyphenonium | 3.4 µg/mouse | 2.26 –5.1 |
| intraventricular | VÚFB-3100 | 2.9 µg/mouse | 2.07 –4.06 |




Central antiarecoline effect of oxyphenonium and its tertiary analogue (compound VÚFB-3100) in intravenous and intraventricular administration. Ordinate: Dosage of the drugs in µg/mouse. White columns: oxyphenonium, shaded columns: its tertiary analogue.

The results are summarized in the Table. $PD_{50}$, i.e. the dose preventing the arecoline tremors in 50% of mice was 48.5 times higher for oxyphenonium in intravenous administration than that for compound VUFB-3100 (fiducial limits 32.7–72.5).

In contrast to this, there was no significant difference between the action of these drugs in administration into the cerebral ventricle.

This difference could be explained on the basis of difficult penetration through the blood-brain barrier for the fully ionized oxyphenonium. To compare the absolute values of the doses of tested drugs in intravenous and intraventricular administration, the intravenous doses were converted to µg/mouse, i.e. for 20 g of the body weight (Figure). It is conceivable that it is necessary to take this calculation with caution, since in the intravenous administration the drug is distributed in the whole body, while in the intraventricular administration the whole amount of drugs comes directly into contact with the brain in a high concentration.

It is obvious that the drug injected directly into the ventricle would be effective in a smaller dose than when injected intravenously. However, as is shown in the Figure, that is true only for oxyphenonium, which was 14.8 times stronger in intraventricular administration than intravenously (fiducial limits 9–24.4). On the other hand, the compound VUFB-3100 was 2.79 times stronger intravenously than intraventricularly (fiducial limits 1.8–4.33). It is therefore possible that compound VUFB-3100, which is partly present in blood as a base and probably easily penetrates the blood-brain barrier, reaches the brain cholinergic receptors better when injected intravenously than from absorption from the inside of the ventricle.

Therefore it is likely that the wall of the ventricle, which is a certain barrier also for the penetration of the tertiary compound, will be an even greater barrier for the penetration of the quaternary oxyphenonium, which has a positive charge. It is possible that it may explain the fact why oxyphenonium injected into the ventricle has an equal effect as compound VUFB-3100 and not stronger, as in the effect on peripheric cholinoreceptors.

*Zusammenfassung.* Die zentrale anticholinergische Wirkung von Oxyphenonium und seinem Analogon, der Substanz VUFB-3100, die tertiären Stickstoff im Molekül enthält, wurde bei intravenöser und intraventrikulärer Applikation geprüft. Die Wirkung von Oxyphenonium war bei intravenöser Verabreichung 48,5mal schwächer als diejenige von VUFB-3100, während bei Einführung der Substanz direkt in die laterale Hirnkammer nur unbedeutende Wirkungsunterschiede erzielt werden konnten.

Die Resultate passen zur Hypothese, wonach die schwächere zentrale anticholinergische Wirkung des Oxyphenoniums wahrscheinlich mit seiner schlechten Penetration durch die hämato-enzephalische Barriere zusammenhängt.

E. V. ZEJMAL[27] and Z. VOTAVA

*Research Institute for Pharmacy and Biochemistry, Prague (Czechoslovakia), May 9, 1961.*

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