Effect of Mecloqualone on the Oxygen and Glucose Uptake by Brain Tissue in vitro

Mecloqualone is a hypnotic drug from the 2,3-substituted quinazolone group, which was introduced by GUJRAL et al.[1,2]. Mecloqualone is twice as active but not more toxic than Methaqualone, the latter being the most studied drug from that group[3-5]. Our paper deals with the effect of Mecloqualone on the oxygen and glucose utilization by brain tissue in vitro.

Table I. Effect of Mecloqualone on oxygen and glucose uptake by brain slices

Drug concentration	Potasium concentration	Oxygen (µl/100 mg wet tissue/h)	Glucose (mg/100 mg wet tissue/h)
Control	5 mM	71.40±4.31 (10)	0.72±0.06 (10)
	100 mM	81.43±2.97 (18)	1.21±0.08 (12)
$1\times10^{-3}M$	5 mM	47.10±5.70 (8)[b]	1.06±0.11 (8)[a]
	100 mM	59.95±2.93 (8)[c]	1.07±0.04 (12)
$1\times10^{-4}M$	5 mM	44.60±3.12 (8)[b]	0.96±0.12 (8)
	100 mM	75.66±5.63 (8)	1.09±0.07 (12)

[a] $P<0.02$; [b] $P<0.01$; [c] $P<0.001$. The figures are means±S.E.M. In brackets the number of slices.

Table II. Effect of Mecloqualone on oxygen utilization by brain homogenates

Drug concentration	No. of experiments	Oxygen uptake (µl/100 mg wet tissue/h)
Control	21	72.64±2.46
$1\times10^{-3}M$	8	56.47±5.67[a]
$1\times10^{-4}M$	8	65.88±1.95

[a] $P<0.01$. The figures are means ±S.E.M.

Material and methods. Adult male albino rats were used to prepare brain slices, as described by MCILWAIN and BUDDLE[6], and brain homogenates. The slices were incubated in Krebs-Ringer phosphate medium (pH 7.4), which contained glucose (10 mM) and 5 mM or 100 mM potassium. Whole brain homogenates were prepared in 0.25 M sucrose, 0.1 M phosphate buffer (pH 7.4). Oxygen utilization was determined by the manometric technique of Warburg[7], and glucose uptake was estimated by measuring the glucose concentration in the medium at the end of incubation with a glucose oxidase method[8].

Results and discussion. It is known that some central nervous system depressors inhibit oxygen uptake by the brain tissue (QUASTEL[9], MCILWAIN[10]) and this effect is more evident when the tissue respiration has been stimulated by a high potassium concentration in the medium (GHOSH and QUASTEL[11], TAMARIT[12]). The data of Tables I and II show that Mecloqualone inhibits oxygen utilization by brain slices and brain homogenates, but it can be seen in Table I that the inhibition is roughly the same at potassium concentrations of 5 mM and 100 mM.

Table I shows also that glucose uptake by the tissue is enhanced in the presence of the drug, but this effect is only apparent at the lowest potassium concentration.

Resumen. La mecloqualona inhibe in vitro, la respiración de cortes y homogenizados de cerebro, incrementando el consumo de glucosa; este último efecto no se produce cuando al medio de incubación se añaden 100 mM de potasio.

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Storing of Secretory Material Inside the Perinuclear Space

Conspicuous dilatations and inclusions of the rough endoplasmic reticulum (RER) are known from many types of cells. Only a few papers report on dilatations of the perinuclear space (PS). WILLIAMS and JEW[1] observed pockets between the inner and outer nuclear membranes in fibroblasts surrounding the sympathetic ganglia of young cats. Large cisternae within the PS of subcommissural cells – specialized ependymal cells in the diencephalic brain – were also demonstrated[2,3]. We could observe large dilatations of the PS in 2 different cell types. As the investigations had another purpose, these findings will be only briefly reported.

The results were obtained in material prepared with normal methods for electron microscopy after immersion or perfusion fixations. 1. Cells of the subcommissural organ of untreated rats (Wistar): These secretory cells have large nuclei with deeply folded surfaces or more or less segmentated nuclei (Figure 1). The PS is quite normal in regions without or with scattered nuclear pores. In regions with numerous pores, conspicuous dilatations of the PS may be present. There are pockets between two pores or large cisternae bridging over some pores. The volumes of the cisternae may amount to nearly a quarter of the volumes of the nuclei itself. In the basal region of the cisternae small strands of cytoplasm penetrate the cisternae in a gratelike manner. The contents of the dilatations are very finely flocculated after fixation in osmium tetroxide solution.

2. Neurosecretory cells of *Triturus vulgaris* (the animals were treated in 1% NaCl solution for 3 h). The neurons of the praeoptic nucleus are big cells with neurosecretory electron dense vesicles. After treatment in hypertonic solution, the PS of some nuclei is partly very much enlarged (Figure 2). On the outer membrane of the dilatations, an incomplete coating of ribosomes, and on the base of the cisternae, penetrating strands of the cytoplasm could be observed. The outer parts of the cisternae separate themselves and build up big vacuoles. The cisternae and vacuoles occupy a fine-particulated

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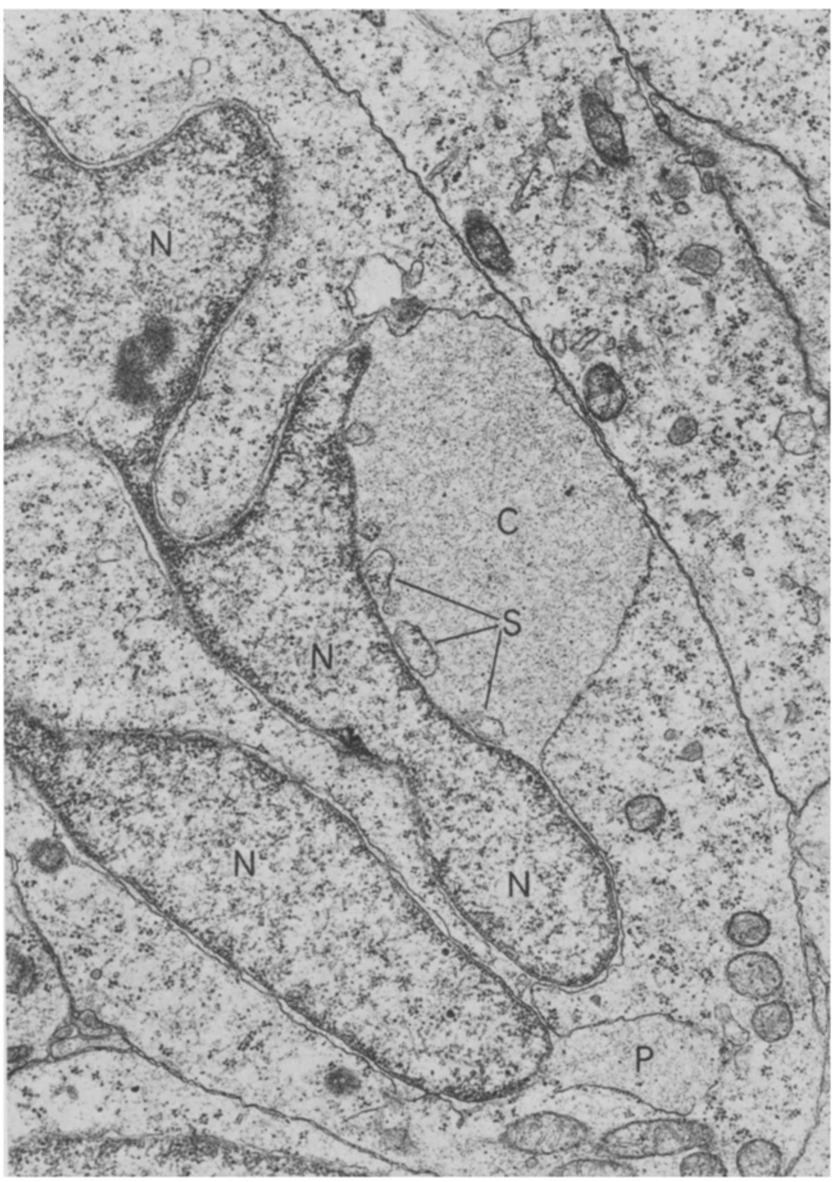

Fig. 1. Segmentated nucleus (N) of a subcommissural cell of the rat with dilatations of the perinuclear space. C, cisterna; P, pocket; S, strands of the cytoplasm. ×32,300.

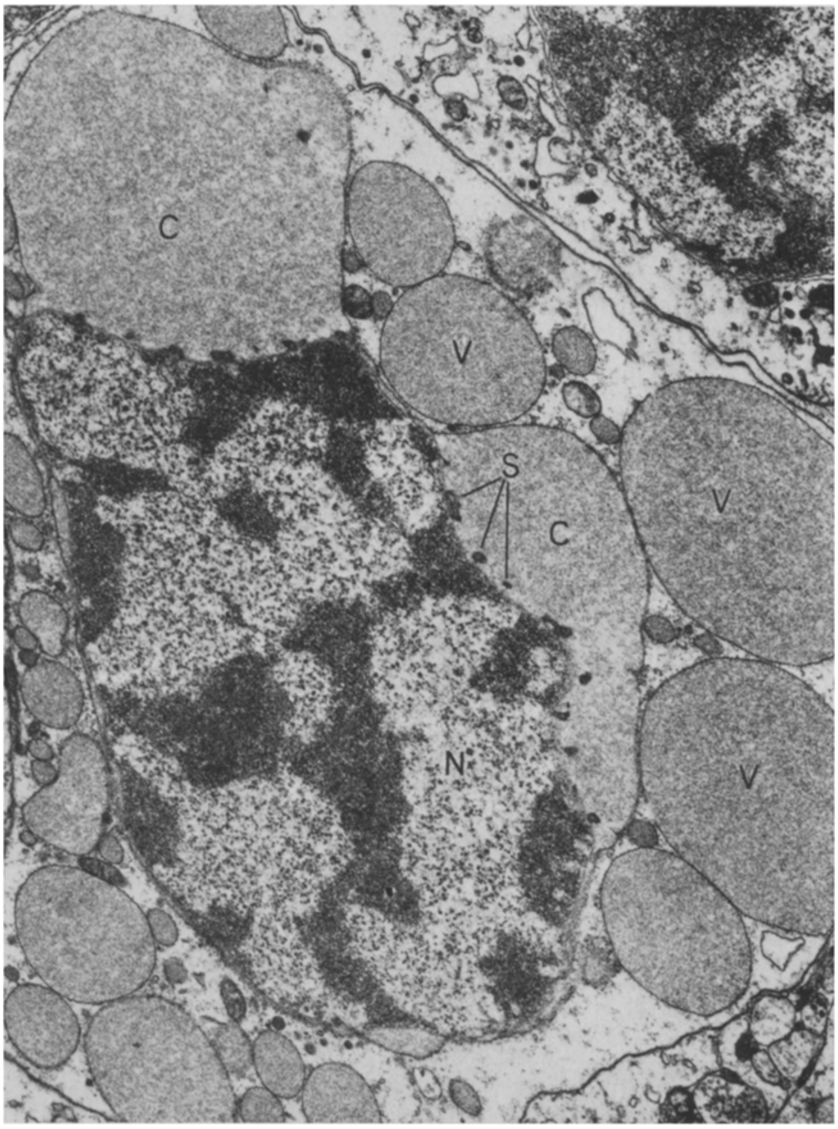

Fig. 2. Nucleus (N) of a praeoptic neuron with large cisternae (C) in the perinuclear space. S, strands of cytoplasm; V, vacuoles. ×13,000.

material of moderatly electron density. The cisternae are not artefacts.

Discussion. Both cell types are secretory ones, their secretion is rich in protein. The PS belonging to the endoplasmic reticulum is limited by 2 membranes. The outer one is more or less surrounded by a coating of ribosomes and participates in protein synthesis. We consider two possibilities for the accumulation of material in the PS: 1. In loco production or overproduction by the RER and transportation of the surplus into the PS: not very likely.

2. Production of proteins or oligopeptides inside the nucleus and storing these products in the PS. Protein synthesis has been found in isolated nuclei of Hela-cells[4]. SADOWSKI et al.[5] demonstrated polysomes within isolated nuclei of rat liver. We assume nuclear synthesis of proteins to be also a normal process in the secretory cells of the subcommissural organ and the praeoptic nucleus. Piling up secretory material in the PS for a limited time will be possible if the protein synthesis inside the nucleus is higher than the available energy for continuous transportation of the products into the cytoplasm, that means, the accumulation may be a disregulation of a normal homeostatic mechanism.

Zusammenfassung. In Zellen des Subcommissuralorgans unbehandelter Wistar-Ratten und in neurosekretorischen Zellen NaCl-belasteter Teichmolche wurden voluminöse Erweiterungen der Perinuclearzisterne beobachtet, die beim Teichmolch zur Ausbildung grosser Vakuolen führen können. Perinuclearzisterne und Vakuolen enthalten ein feingranuläres, mässig elektronendichtes Material (proteinreiches Sekret). Es wird eine intranucleäre Synthese von Oligopeptiden oder Proteinen für möglich gehalten.

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