Ultrastructural Appearance of Glycogen in the Hypothalamus of the Rabbit Following Chlorpromazine Administration

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Received April 1, 1969

Summary. The tuber cinereum of hypothalamus, cerebral cortex, cerebellar cortex and caudate nucleus of rabbits were examined under the electron microscope following intramuscular administration of chlorpromazine with special consideration of ultrastructural changes in amount and distribution of glycogen granules in their hypothalamus. In these regions, normal astrocytes and their processes contain glycogen granules diffusely scattered in the cytoplasm. In the neurons of the normal hypothalamus and cerebellar cortex, glycogen granules are seen in some presynaptic endings and distal parts of dendrites but not in the perikaryal cytoplasm. In the tuber cinereum of the hypothalamus, after chlorpromazine administration, abundant glycogen granules accumulate at the postsynaptic sites, especially in peripheral parts of dendrites, and clusters of glycogen granules appear in the perikaryal cytoplasm of the nerve cells. These findings are interpreted as an increase of glycogen in these cellular regions and the suggestion is made that chlorpromazine inhibits the glycolytic metabolism in the distal parts of dendrites, particularly at postsynaptic sites and in the perikarya of nerve cells of the hypothalamus.

Key Words: Chlorpromazine — Rabbit hypothalamus — Glycogen — Electron microscopy

Introduction

Since chlorpromazine was utilized for psychiatrical therapy by Delay et al. (1952), it has been known clinically as an effective antipsychotic drug for the treatment of schizophrenia and other psychoses. As to the basic studies on the mechanism of chlorpromazine as a psychotrophic agent in the central nervous system, much has been done by many investigators in the field of neuropharmacology, neurophysiology, and neurochemistry. However, a morphological or ultrastructural approach to the effect upon the central nervous system of psychotrophic drugs, including chlorpromazine, has been attempted in a few instances only. Wilke and Iizuka (1960) demonstrated ultrastructural changes in mitochondria, axons, and dendrites in the cerebral cortex of the mouse after administration of chlorpromazine. Shimizu and Ishii (1964) reported that glycogen granules within the cytoplasm of the astrocytes of the area postrema and the hypothalamus of the rabbit have increased in number after reserpine injection. Dom (1967) observed light microscopically local glial changes in the limbic system of the rat after administration of haloperidol. Wolff (1968) demonstrated that glycogen in the wall
of the recessus infundibularis in the hypothalamus was increased following Mega-phen (chlorpromazine) administration.

In the present investigation we have attempted to study the fine structural changes in various regions of the central nervous system after administration of psychotropic agents. The results will be presented in a series of papers of which this is the first. Here we present the ultrastructural appearance of glycogen in the hypothalamus of the rabbit following chlorpromazine administration.

Materials and Methods

The material presented was taken from six experimental male rabbits and six untreated control male rabbits, weighing from 2.5—3.0 kg. Each control rabbit was anesthetized by an intravenous injection of 25 mg of Nembutal per 1.0 kg body weight just before perfusion. Experimental rabbits in the neuroleptic comatose state three hours after the intramuscular injection of 10—125 mg of chlorpromazine per 1.0 kg body weight were perfused with Ringer solution followed by 3.6% glutaraldehyde (Sabatini et al., 1963) buffered with phosphate at pH 7.4—7.6 (Millonig, 1961a) through the ascending aorta (Palay et al., 1962). Blocks of tissues obtained from four parts of the brain — cerebral cortex, cerebellar cortex, tuber cinereum of hypothalamus, and caudate nucleus — were postfixed in fresh cold 1% phosphate-buffered osmium tetroxide solution for 2—3 hours (Millonig, 1961a). After complete dehydration in ascending concentrations of ethanol, tissue blocks were embedded in Epon 812 (Luft, 1961). After polymerisation, ultrathin sections were made with a glass knife by aid of the Porter-Blum MT-1 microtome. The sections were mounted on collodion-coated copper grids, and were stained with lead tartrate (Millonig, 1961b). Sections were examined with the Hitachi HS-7 electron microscope. Primary magnifications were 4,600 diameters and subsequently photographs were enlarged as desired.

Observations

1. Glycogen Granules in the Normal Brain

Glycogen granules can be identified on the basis of their size, shape and affinity for lead staining (Revel et al., 1960). Normal astrocytes and the processes in the cerebral cortex, cerebellar cortex, caudate nucleus and tuber cinereum of the hypothalamus generally contain glycogen granules, which are diffusely scattered through the cytoplasm as reported by Maxwell and Kruger (1965). In the neurons of the hypothalamus and the cerebellar cortex, however, glycogen granules are found in some presynaptic axon terminals and dendrites (Fig. 1). Few glycogen granules are seen in the neurons of cerebral cortex and caudate nucleus as far as examined. The type of glycogen granules in the brain is predominantly that of single particles (β-type), 200—400 Å in diameter. But sometimes compound particles (α-type) can be observed (Drochmans, 1962; Revel, 1964).

2. Glycogen Granules in the Hypothalamus Following Chlorpromazine Administration

In the case of chlorpromazine administration, no remarkable alterations are noted in the cytoplasmic organelles of nerve cells or glial cells in the brain. One of the most impressive findings in this study, however, is the accumulation of glycogen granules in the postsynaptic regions (Fig. 2) mainly in smaller dendrites of the tuber cinereum of the hypothalamus. Another finding is the appearance of clusters of glycogen granules in the perikaryal cytoplasm of nerve cells in the same region (Fig. 3). Such accumulations of glycogen granules cannot be seen in the