Lipidosis-like ultrastructural alterations in rat tissues induced by an antidepressant drug (iprindole)

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Iprindole has been reported to cause ultrastructural alterations in rat lung tissue. They consist of the occurrence of lamellated cytoplasmic inclusions (myeloid figures) within epithelial cells and in alveolar macrophages, which were rich in phospholipids (Vijeyaratnam & Corrin, 1972). Identical alterations have been observed in lungs and in other tissues of the rat after treatment with the anorectic drug chlorphentermine (Lüllman-Rauch, Reil, Rossen & Seiler, 1972; Lüllmann, Lüllmann-Rauch & Reil, 1973; Lüllmann-Rauch & Reil, 1973). On the basis of ultrastructural, biochemical and physicochemical findings these alterations have been interpreted to reflect a generalized phospholipidosis, which is the result of an association of the amphiphilic chlorphentermine molecules to phospholipids (Lüllmann, Lüllman-Rauch & Wassermann, 1973; Seydel & Wassermann, 1973). Iprindole also is an amphiphilic compound, due to its hydrophobic tricyclic moiety and its hydrophilic side chain. The present study was designed to investigate whether iprindole, in addition to the reported pulmonary changes, causes similar alterations in other tissues, thus fitting into the proposed concept of a generalized phospholipidosis induced by amphiphilic drugs.

Iprindole (50 to 125 mg/kg) was orally administered to male Wistar rats for 5 to 25 days. Tissues were fixed with glutaraldehyde and OsO^4, and were further processed for electron microscopy. The basic cellular alterations in the tissues mentioned below consisted of the appearance of numerous membrane-bound cytoplasmic inclusions, which had a crystalloid or a lamellated internal structure with a periodicity of 45 Å, suggesting the presence of polar lipids. After nine days of drug treatment the majority of cells in the following tissues was affected: lung, liver, adrenal cortex and medulla, lymph nodes, spleen, kidney, salivary glands, testicular Leydig' and Sertoli' cells, thyroid gland, vascular endothelium, retinal pigment epithelium. After 25 days of treatment numerous inclusions were found also in retinal ganglion cells, dorsal root ganglion cells, and in nerve cells of various regions of the central nervous system, such as spinal cord, cerebellar and cerebral cortex.

These cellular alterations, which are identical with those induced by chlorphentermine, are interpreted as supporting the concept of a drug-induced generalized lipidosis, which is related not to one group of drugs but rather to a certain physicochemical character of drug molecules, i.e. the amphiphilia.

While there is so far no clear experimental evidence concerning the pathological significance of the alterations induced by the two drugs discussed in the present study, there are reports from Japan (Shikata, Kanetaka, Endo & Nagashima, 1972) on severe human cases of generalized phospholipidosis induced by the coronary dilatator 4,4'-diethylaminoethoxy-hexestrol, which also is an amphiphilic compound. Thus it might be useful for the design and evaluation of the new drugs to keep in mind the possibility of this side effect.

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