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SHORT COMMUNICATIONS

Distribution in the brain of ^{14}C-benzenehexachloride: Autoradiographic study

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THROUGH the administration of various isomers of benzenehexachloride (BHC), it was found possible to produce resistance to numerous convulsion-inducing agents[1, 2, 3, 4]. In further investigations this effect was more closely analysed [5–7]. In a study of the distribution of α- and γ-BHC with the help of ^{14}C-labeled compounds, it was found that a remarkable accumulation of the drug occurs in certain areas of the central nervous system (CNS).[8] In the investigation reported here we have attempted to obtain further insight into the distribution of α-BHC in the CNS by means of autoradiographic techniques.

METHODS

The ^{14}C-BHC was prepared by Schering A. G., Berlin (sp. act. 3·4 μc/mg).

Female rats weighing from 85 to 100 g were given 200 mg/kg corresponding to 0·68 μ ^{14}C-BHC/g i.p. The rats were killed 24 h after injection by immersion of the whole animal in hexane cooled with solid carbon dioxide to about −70°. Frontal or sagittal sections through the whole head were taken at different levels of the brain. The section thickness was 20μ. Autoradiograms of the frozen-dried sections were made by apposition against Structurix (Gevaert) X-ray film [9, 10]. The exposure time was 90 days.

The sections were stained by Heidenhain's[11] method, giving the myelin sheaths a dark blue color.

RESULTS

The distribution of ^{14}C-BHC in four frontal sections of the brain from the forebrain to the brain stem is illustrated in Fig. [1–5]. Figures 6 and 7 illustrate the distribution of the BHC in two sagittal sections, the line of the section in Fig. 6 being more lateral and in Fig. 7 more medially situated.

The autoradiogram from the most anterior part (Fig. 1) shows a very distinct accumulation in a few restricted areas which correspond to the corpus callosum, commissura anterior, fasciculus opticus, and tractus olfactorius lateralis. The other brain areas show a rather low uptake of radioactive substance. In the next two sections the same findings can be made and, in addition, an accumulation can be seen in the fornix, capsula interna, and corpus striatum.

If the distribution in the autoradiogram (Fig. 2) is compared to the corresponding section (Fig. 3), stained according to Heidenhain,[11] an almost total coincidence can be seen between the regions of high uptake in the autoradiogram and the highly stained areas in the section which are rich in myelin fibres. Also, in the rest of the autoradiograms the radioactivity is found almost exclusively in white matter.

DISCUSSION

From comparison of the specifically stained sections from different levels of the brain to the corresponding autoradiograms, the radioactive substance appears to be almost exclusively located in white matter. This finding is surprising since we have not found a similar distribution described in the literature.

The reason for the pronounced affinity for white matter is not yet known. One possibility to consider is a specific uptake by certain transport mechanisms in border surfaces. The substance might also be bound by certain structures of the white matter. A third possibility is that the localization is a result of an exceptionally high solubility of BHC in white-matter lipids. At present there are no findings which strongly favor one of the suggested processes.

There is also a possibility that radioactive constituents from BHC are taken up by the white matter after structural changes of the BHC molecule. It is known that BHC is transformed in the liver into various chlorophenol derivatives by the splitting off of chlorine and hydrogen and uptake of oxygen. These derivatives, however, could not be found in the CNS[8] and are probably rapidly excreted.

The manner in which BHC enters into the white matter has not yet been studied systematically. Its distribution seems to occur via the blood and not via the cerebrospinal fluid, as is the case with acetazolamide.[12] Nor did we find any typical accumulation in especially well-vascularized areas as Roth and Barlow[13] did with extremely lipoid-soluble substances such as thiopental.

It is not at present possible to relate the anticonvulsive action of BHC to the distribution findings. For this purpose metabolic studies should be made on white matter specifically rather than with homogenates of whole brain.

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Toxicities and myotonic activities of certain polychlorobenzoic acids

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AS PART of a toxicological investigation of the herbicide 2, 3, 6-trichlorobenzoic acid (TBA)[1] and its derivatives, a series of isomeric di-, tri- and tetrachlorobenzoic acids has been examined. They were administered subcutaneously, as 10% aqueous sodium salts, to groups of albino mice, for comparative toxicity assessment. The results are of some interest from the structure-activity aspect.

In addition to non-specific toxic effects including weakness, dyspnoea, prostration, tremors, and terminal coma, certain of the compounds also caused myotonic muscular stiffness and transient spasm, especially marked in the back legs, and on stimulation. This myotonic action is quite characteristic, is produced by a number of hormone weedkillers at high dosages, and has been fully described.[2] The results obtained are summarized in Table 1.