Fragmentation of Mast Cells Caused by Some Phenothiazine Derivatives

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Chlorpromazine has been reported to give rather frequent side effects such as pruritus, dermatitis and other cutaneous reactions, rhinitis and icterus. The side effects have been proposed to be of an allergic nature. If so, the manifestations should be due to or accompanied with release of histamine. As phenothiazine derivatives have a pronounced antihistamine effect, it is, however, difficult to use current methods for biological testing of histamine liberated by these derivatives. Since "histamine releasers" have been observed to disrupt mast cells we have tested some phenothiazine derivatives on their ability to cause disruption of mast cells. A slight modification of the technique described by Norton was used [1].

The disrupting actions of chlorpromazine, chlorpromazine sulfoxide, oxypromazine, promethazine and promazine are compared with that of compound 48/80, a very potent "histamine liberator". All the phenothiazine derivatives except chlorpromazine sulfoxide, the major metabolite of chlorpromazine, have a disrupting action on mast cells, although to a lesser degree than 48/80. The ED_{50} value (50 % disruption of mast cells) is for 48/80 0.32 μg/ml (0.18—0.56), and for chlorpromazine, the most active of the phenothiazine derivatives studied, ED_{50} is 45 μg/ml (42.1—48.2). The log-dose response curve obtained for chlorpromazine is of the same character as that obtained for 48/80, a fact indicating that the mechanism of action on the mast cell membrane is identical for the two substances.

It is of interest to note that chlorpromazine produces an action in cases of essential hyperlipemia similar to that produced by intravenous heparin [2]. The "clearing effect" of chlorpromazine might be explained as the result of its disruptive action on mast cells. These cells contain, at least in some species and in some tissues, not only histamine but also heparin, which substances occur in the blood on fragmentation of the mast cells.

On treatment of mental illnesses it has been proved that chlorpromazine is the most active of the phenothiazine derivatives studied. It can therefore be discussed if not only the side effects but also the clinical effect may be explained partly by the disruption of the mast cells.

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Formic Acid Oxidation in *Aspergillus niger*

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Preformed mycelial pads of *Aspergillus niger* discharge large amounts of oxalate when incubated with sodium formate. Based on this finding Bernhauer postulated a C_1—C_1 condensation to take place in the organism [1]. As noticed by Butkewitsch, oxalate is, however, also produced when the mycelium is incubated on a buffer in the absence of organic carbon [2].

These findings were confirmed in the present investigation. When ^{14}C-labelled formate was employed, a small but significant incorporation into oxalate was observed. This incorporation may well have passed through carbonate as an intermediate, since labelled carbonate was converted to oxalate to the same extent as formate.

Carbonate is readily formed from formate by the organism or extracts thereof, provided the organism has been exposed to formate during growth. The inducible and soluble enzyme catalyzing this reaction has been partly purified and some of its properties studied. It carries out the oxidative decarboxylation of formate with oxygen as the only effective electron acceptor and H_2O_2 as the reaction product together with CO_2. No dialyzable cofactors participate in the reaction. The enzyme has a pH optimum of 6.2 and a Michaelis constant of 0.013 M.

1. Bernhauer, K. and Slalina, F. *Biochem. Z.* **274** (1934) 97.
2. Butkewitsch, W. S. *Biochem. Z.* **276** (1935) 451.