Drug desensitization and cross-desensitization in guinea-pig ileum

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Drug desensitization was assessed in guinea-pig ileum strips suspended in Ringer solution employing isometric recording. An electronic compensating device (Schild & Seaford, 1970) automatically readjusted the length of the muscle thus ensuring a constant initial tension. Desensitizing drugs were administered for a period of 8-10 min in a high concentration (50-100 times that needed to establish a dose-response curve) and the degree of subsequent desensitization was expressed in terms of dose-ratio usually 10 min afterwards.

The main findings were as follows: 1. Degree of desensitization depended on concentration and period of contact with the desensitizing drug. 2. Strong cross-desensitization was seen after acetylcholine desensitization of histamine responses (ACh → Hi); less strongly by Hi → ACh: strong cross-desensitization by Hi → 5-HT; little or none by 5-HT → Hi: strong cross-desensitization by Hi → bradykinin (BK). 3. The degree of desensitization was related to the Ca^{++} content of the Ringer solution *during* the desensitization period (using hepes Ringer, Good, Winget, Winter, Connolly, Izawa & Singh, 1966, which does not precipitate calcium, as the desensitizing solution). When the desensitizing solution contained 4 mM Ca^{++} in place of 0.2 mM Ca^{++}, duration and degree of both auto-desensitization Hi → Hi (Schild, 1973), ACh → ACh, BK → BK and cross-desensitization ACh → Hi, Hi → BK were significantly diminished. 4. Desensitization Hi → Hi was obtainable in the complete absence of calcium in solution suggesting that calcium is not required for the interaction of histamine with receptors.

These findings suggest that drug desensitization in guinea pig ileum may, depending on the drug used, be unspecific or drug-specific and that it is related to the calcium content of the desensitizing solution. It seems possible that the effect of calcium is exerted at a post-receptor level common to different drugs.

References

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The effect of isoprenaline on ^{86}Rb uptake by horse lymphocytes *in vitro*

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Catecholamines affect a number of functions of leucocytes; these functions include inhibition of histamine release (Lichtenstein & Margolis, 1968), inhibition of immune cytolysis (Henney, Bourne & Lichtenstein, 1972) and inhibition of sheep red blood cell plaque formation (Melmon, Bourne, Weinstein, Shearer, Brauminger & Kraur, 1974).

The possible importance of changes in cation distribution during mitogen-induced transformation of lymphocytes (Quastel & Kaplan, 1970; Allwood, Asherson, Davey & Goodford, 1971) led us to carry out a study on the effect of isoprenaline on the uptake of ^{86}Rb by lymphocytes.

Lymphocytes were isolated from horse peripheral blood. To remove granulocytes, the lymphocyte-rich plasma, obtained by gravity sedimentation for 15 min, was passaged through three (7.0 x 1.4 cm) glass wool columns set up in series. The lymphocyte-rich effluent obtained from these columns was run onto a fourth set of (12.0 x 1.4 cm) glass wool columns which were incubated at 37°C for 1 hour. Elution of these latter columns with medium 199 (pH 7.4, gassed with 5% CO_2 in air) followed by lysis of the remaining red cells with 155 mM NH_4Cl gave a fraction of lymphocytes (always greater than 97% pure from other cell types), which were suspended in medium 199 containing 20% heat-inactivated homologous serum at a concentration between 2-10 x 10^6 cells ml^{-1}.

The lymphocytes obtained by this method were maintained on a culture-tube roller, without