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Elevated Blood Glucose after Compound 48/80 Treatment Is Not Related to Hepatic Mast Cell Degranulation in Rats[1,2] (42425)

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Abstract. Blood glucose, hepatic glycogen, and the histological integrity of hepatic mast cells, were evaluated in anesthetized rats receiving iv injections of 0.125 mg/kg body weight compound 48/80 (a mast cell degranulator) and/or of 0.001 to 10.0 mg/kg body weight lodoxamide tromethamine (an inhibitor of mast cell degranulation). A nonglucogenic dose of lodoxamide, 0.001 mg/kg body weight, prevented dissipation of histochemically demonstrable fluorescence in mast cells (degranulation) without inhibiting compound 48/80-induced hyperglycemia and hepatic glycogenolysis. These results suggest that this glucotropic response is independent of compound 48/80-evoked release of mediators such as serotonin from mast cells.

Even though many functions of the mast cell have been identified, the complete scope of its activity remains a mystery and the "riddle of the mast cell" continues unsolved (1). As each component of the mast cell was discovered, the proposed function(s) of these cells was modified (2). In 1938, when heparin was identified as a constituent and widely accepted as the final answer to Ehrlich's "riddle," Michels listed 25 hypotheses of mast cell function (3). With the addition of histamine in 1952 (4) and serotonin in rodents in 1955 (5), the list was revised even further (see 1, 2, 6–9).

Previous studies from this laboratory indicated that compound 48/80, serotonin, or endotoxin produce microvascular constriction and decreased (lobular) perfusion in the liver of rats (10–12). Lodoxamide tromethamine, an inhibitor of mast cell degranulation (13), reversed the compound 48/80- or endotoxin-elicited responses, thereby providing putative evidence, implicating mast cell constituents in the generation of low flow (10–11). The results of these investigations also suggested that mast cells stimulated systemic hyperglycemia by triggering hepatic glycogenolysis during conditions of hypoperfusion (14). Exogenous administration of two mast cell mediators, serotonin or histamine, each elicited hepatic glycogen hypercatabolism with resultant hyperglycemia (15, 16). In addition, the well-known secretogogue, compound 48/80, provoked such glucoregulatory dyshomeostasis (17). These results raised the unresolved question as to whether compound 48/80-induced glycogenolytic responses were mediated by released mast cell constituents (17). The current study was designed to answer this question by utilizing lodoxamide tromethamine to inhibit mast cell degranulation and mediator release.

Materials and Methods. *Animals and pharmacology.* Sixty-one male Sprague–Dawley rats (260–425 g) that had been fed *ad libitum* were anesthetized with intraperitoneal (ip) injections of urethane (2.0 mg/g body wt). One carotid artery was cannulated to collect samples of blood for determinations of glucose. Experimental drugs were given by femoral intravenous infusion in 0.5 ml of Ringer's solution as a carrier per 100 g body weight. Rats were injected twice; the first injection was given 5 min prior to the second. The doses and intervals chosen for injection were based upon results of previous studies (10, 13, 14,

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TABLE I. MEAN BLOOD GLUCOSE, HEPATIC GLYCOGEN, AND NUMBER OF FALCK–HILLARP POSITIVE MAST CELLS IN RATS FOLLOWING INJECTION (iv) WITH RINGER'S SOLUTION (0.5 ml/100 g), LODOXAMIDE TROMETHAMINE (0.001 TO 10.0 mg/kg), AND/OR COMPOUND 48/80 (0.125 mg/kg)[a]

Time (min):		0	5	15	20	25	35	35	35
Treatment									
1st injection (time 0)	Second injection (5 min)	Blood glucose (mg/dl)						Hepatic glycogen (% wet wt)	Mast cells
Ringer's	Ringer's ($n = 5$)	194 (13)	204 (16)	222 (20)	225 (26)	228 (23)	231 (20)	4.19 (0.42)	392 (7)
Lodoxamide (mg/kg)									
0.001	($n = 6$)	117 (4)	182 (10)	176 (6)	178 (7)	180 (7)	192 (8)	4.25 (0.37)	418 (14)
0.01	($n = 5$)	207 (16)	226 (16)	256 (17)	266 (20)	284 (21)	316 (15)	4.29 (0.34)	439 (9)
0.1	($n = 5$)	232 (15)	252 (19)	284 (14)	302 (10)	316 (9)	338 (12)	3.74 (0.55)	425 (12)
1.0	($n = 4$)	168 (12)	188 (21)	230 (32)	228 (31)	248 (37)	256 (43)	5.61 (0.55)	446 (14)
10.0	($n = 5$)	228 (17)	216 (20)	258 (17)	276 (18)	292 (20)	318 (24)	4.70 (0.34)	440 (6)
Ringer's	Compound 48/80 ($n = 6$)	210 (20)	222 (21)	281 (18)	303 (16)	342 (16)	367 (32)	2.41 (0.18)	179 (8)
Loxamide (mg/kg)									
0.001	($n = 7$)	188 (14)	194 (13)	246 (9)	267 (18)	284 (20)	282 (22)	2.87 (0.48)	456 (14)
0.01	($n = 5$)	238 (15)	248 (14)	274 (12)	304 (12)	312 (14)	336 (22)	2.36 (0.53)	396 (18)
0.1	($n = 5$)	196 (13)	204 (15)	212 (16)	242 (17)	270 (18)	286 (12)	3.28 (0.25)	436 (10)
1.0	($n = 4$)	173 (16)	173 (24)	218 (40)	240 (40)	284 (50)	303 (50)	2.95 (0.24)	229 (11)
10.0	($n = 4$)	205 (21)	208 (20)	240 (16)	—	268 (11)	300 (11)	3.36 (0.17)	440 (8)

[a] Values are means (±SEM) for the number (n) of rats per treatment regimen.

17–20). The solutions administered[3] and the number of rats injected are given in Table I.

Biochemistry and histochemistry. Blood glucose was measured prior to the first injection, and at 5-, 15-, 20-, 25-, and 35-min intervals thereafter. The 5-min reading was made just prior to the second injection. Because multiple samples were taken from each rat for glucose determinations, dextrostrips (Ames Co., Elkhart, Ind.) and an Ames eyetone reflectance meter were used, for they require only a single drop of blood (<0.1 ml) for analysis (14). To ensure accurate sampling, blood (0.5 ml) within the arterial cannula was removed prior to, and reinfused following, the sampling procedure. Glycogen was measured in samples of liver taken at 35 min using a phenol–sulfuric acid method (14). To determine the number of serotonin-containing (Falck–Hillarp positive) mast cells in portal areas, sections of hepatic tissue were prepared and analyzed according to procedures described by Dimlich and co-workers (14, 21).

Analysis of data. Differences among glucose values (mg/dl) and the number of hepatic mast cells were determined using a one-way analysis

[3] Compound 48/80 was purchased from Sigma Chemical Company, St. Louis, Missouri. Lodoxamide tromethamine was generously donated by The Upjohn Company, Kalamazoo, Michigan.

of variance (ANOVA) at no less than the 95% level of confidence. For results that were significant, Duncan's multiple range test was used to indicate which values were statistically different among control and experimental groups (22). Since hepatic glycogen values are represented as percentage wet weight, hepatic glycogen data also were analyzed by ANOVA following an arcsine transformation and application of Anscombe's correction (23).

Results. Circulating blood glucose increased and hepatic glycogen content decreased significantly in rats treated with compound 48/80 when compared to control (Table I, Figs. 1, 2). All doses of lodoxamide, except 0.001 mg/kg, also caused an increase in blood glucose without a concomitant decrease in stored hepatic glycogen (Table I, Figs. 1, 2). Furthermore, glycogen was not significantly affected by treatment with 0.001 mg/kg lodoxamide (Table I, Fig. 2). Pretreatment with the nonglycemic and nonglycogenic dose of lodoxamide (0.001 mg/kg) did not modify compound 48/80-induced systemic hyperglycemia and glycogenolysis (Table I, Figs. 2, 3).

The mean number of serotonin-containing fluorescent cells in rats treated with compound 48/80 was significantly less than control (Table I, Fig. 3). In rats injected with 0.01, 1.0, or 10.0 mg/kg lodoxamide, the mean number of fluorescent cells was significantly greater than control (Table I). However, the number of cells in rats receiving compound 48/80 plus lodoxamide at all doses except 1.0 mg/kg was not significantly different from control (Table I, Fig. 3).

Discussion. A number of drugs, including antihistamines and agents that prevent the release of histamine from mast cells, have been used to treat allergic diseases (19, 20, 24, 25). One of the most promising of these drugs, sodium cromoglycate, has some disadvantages; it does not show oral activity (13) and some asthmatics fail to benefit from aerosol treatments with this agent (26).

A newer drug, lodoxamide tromethamine (U-42,585E) [*N,N*-(2-chloro-5-cyano-*m*-phenylene) dioxamic acid, dithan salt] (26), has oral activity and is 2500 times more effective than disodium cromoglycate as an inhibitor of mast cell-mediated passive cutaneous anaphylaxis (13). Lodoxamide has been studied extensively with respect to its effect on histamine release from *in vitro* preparations of peritoneal mast cells in rats (13) and on lung function in IgE-mediated diseases in primates and humans (18, 26). These studies indicate that the major disadvantage encountered using lodoxamide is its nonlinear dose–response relationship.

The present study produced similar results. The numbers of mast cells counted in the livers of rats treated with lodoxamide (0.01, 1.0, or 10.0 mg/kg) were significantly greater than in those of nonpretreated (control) rats. Furthermore, all but the 1.0 mg/kg dose of lodox-

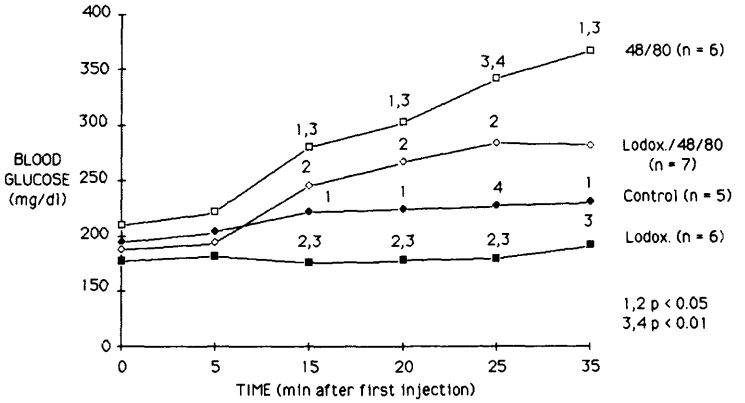

FIG. 1. Mean blood glucose concentrations (mg/dl) following treatment (iv) with (a) Ringer's solution, (b) lodoxamide (0.001 mg/kg), and/or (c) compound 48/80 (0.125 mg/kg). Note that lodoxamide alone does not affect blood glucose levels and that pretreatment with lodoxamide does not prevent compound 48/80-induced increase in blood glucose. Range SEM, ±4–32; range coefficient of variation, 6–36.

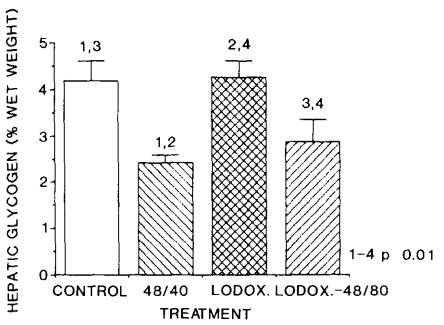

FIG. 2. Mean hepatic glycogen (% wet wt) in rats 35 min after injection (iv) of (a) Ringer's solution (control), (b) lodoxamide (0.001 mg/kg), and/or (c) compound 48/80 (0.125 mg/kg). Note the significant difference ($P < 0.01$) in glycogen content between rats treated with compound 48/80 alone when compared to rats treated with Ringer's or lodoxamide alone. Also note that glycogen in rats stimulated by compound 48/80 were not different from those in rats treated with lodoxamide and compound 48/80. Range SEM, ±0.18–0.54; range coefficient of variation, 10–50.

amide prevented compound 48/80-induced loss of fluorescence. Lodoxamide at every dose except 0.001 mg/kg produced an increase in blood glucose in a nonlinear manner. Since lodoxamide at 0.001 mg/kg inhibited mast cell degranulation and was not glycemic, it was used to evaluate the relationship among hepatic mast cell degranulation, hyperglycemia, and hepatic glycogenolysis. The ability of this dose to prevent dissipation of fluorescence (i.e., mast cell degranulation) without suppressing the glucotropic effect of compound 48/80 suggests that (a) release of mast cell constituents does not mediate compound 48/80-induced hyperglycemia and hepatic glycogenolysis, and (b) provocation of a glycemic response to stress is not a function of the mast cell.

Care was taken to prevent the production of artifacts when using histochemical methods to quantify serotonin-containing cells within sections of liver. Although older rats have more mast cells than younger ones (27, 28), rats in this experiment were paired with controls of similar size and weight, and therefore age. As a result, differences in number of cells counted should not be due to variations in this parameter. Shrinkage due to freeze-drying that as in fixation might affect cell counts (29) was controlled for by comparing sections of control with experimental tissue. Shrinkage of cells that might occur due to compound 48/80 was not evident when rats were treated with as much as 0.5 mg/kg iv compound 48/80 (30). Therefore, compound 48/80 at half that dosage should not affect cell size. Another safeguard limiting erroneous cellular counts was restricting quantification to portal areas of standardized cross-sectional area in liver sections of fixed thickness (10 μm) (21). However, since quantitation is dependent on the concentration of mediator, it is conceivable that the apparent increase in the number of cells may be due to a lodoxamide-induced uptake, synthesis, and/or storage of mediators in cells that ordinarily would not be visualized and counted in nonpretreated sections. Since quantitation also depends on the total number of cells found in the microscopic field of evaluation and since mononuclear leukocytes have been seen adhering to endothelium in association with hepatocytes in lodoxamide-pretreated rats (31), apparent increases in fluorescent cells might be attributed to an influx of circulating precursors destined to become connective tissue mast cells (32).

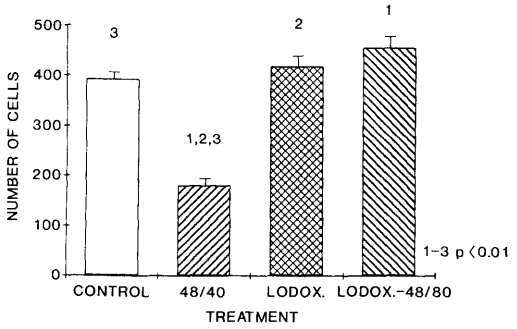

FIG. 3. The number of hepatic mast cells as determined by the Falck–Hillarp histochemical technique in 150 portal areas of rats treated with (a) Ringer's solution (control), (b) lodoxamide (0.001 mg/kg), and/or (c) compound 48/80 (0.125 mg/kg). Note the significant difference ($P < 0.01$) in the number of cells in rats treated with compound 48/80 alone when compared to all other groups. There was no significant difference among rats treated with Ringer's solution, lodoxamide, or compound 48/80 plus lodoxamide. Range SEM, ±7.2–14.0; range coefficient of variation, 3–9.

Compound 48/80 mimicked numerous features of histamine-induced and anaphylactic shock, e.g., edema formation and hypotension (33). Systemic hypotension has been implicated as the effector of numerous compound 48/80-mediated responses, e.g., the increased release of renin from juxtaglomerular cells of the kidney (34). Hypotension and reduced perfusion also have been postulated to provoke anoxia in the liver which in turn might trigger hyperglycemia and glycogenolysis (35). However, data reported in other manuscripts suggested that glycogenolysis and hyperglycemia are independent of changes in systemic blood pressure and hepatic blood flow (14, 16). Subsequent studies showed that pretreatment with lodoxamide at 0.001 mg/kg antagonized systemic hypotension and low flow elicited in the liver by either compound 48/80 or a nonhypotensive dose of endotoxin (10, 11).

Since the activation of α-l-adrenergic receptors in the rat produce hepatic glycogenolysis and hyperglycemia (36–38), studies are in progress to evaluate the role of these receptors in lodoxamide or compound 48/80-induced glucogenesis. However, a variety of factors other than hepatic glycogen metabolism regulate circulating levels of blood glucose in the intact animal, e.g., glucagon and insulin release from the pancreas as well as the rate of peripheral uptake of glucose (36). Therefore, the glycemic effect of lodoxamide or compound 48/80 also may relate to the effects of these agents on these other organs.

Most pathophysiological responses to compound 48/80, including an increase in uterine glycogen 6 hr after the intraluminal administration of compound 48/80 (39), have been attributed to the activities of mast cell mediators, e.g., histamine and heparin, as well as serotonin in the rat (e.g., 40–42). However more recent evidence has suggested that compound 48/80 has activities that are unrelated to its function as a mast cell degranulator. Compound 48/80 is a highly specific inhibitor of calmodulin-mediated Ca^{2+}-dependent cell functions and enzyme systems (43, 44). For example, it inhibits calmodulin-dependent platelet aggregation (45) and reacts with substance P receptors, producing a noncytotoxic noncalmodulin-related inhibition of the release of phosphatidyl choline from respiratory Type II epithelial cells (46). In addition, compound 48/80 may affect cells indirectly by way of its metabolites, especially the aldehydes that can interfere with collagen maturation (47) and that have been reported to be toxic to the liver (48). Although compound 48/80 does not produce pathologic changes in hepatocyte morphology such as edema (30), decreases in the uptake of fluorescent latex particles by Kupffer cells and corroborative changes in Kupffer cell morphology have been reported which are suggestive of inactivation (49). Therefore, compound 48/80 either directly or indirectly may produce a wide range of effects when given *in vivo,* and the activities previously attributed to mast cell mediators may result from other properties of compound 48/80.

1. Kaliner MA. The mast cell—A fascinating riddle. N Engl J Med **301**:498–499, 1979.
2. Benditt EP. Mast cell function: Chemical and structural aspects. In: Austen, KF, Becker, EL, eds. Biochemistry of the Acute Allergic Reactions. Philadelphia, Davis, pp119–130, 1968.
3. Riley JF. The Mast Cells. Edinburgh, Livingston, 1959.
4. Riley JF, West GB. Histamine in tissue mast cells. J Physiol (London) **117**:72p–73p, 1952.
5. Benditt EP, Wong RL, Arase M, Roeper E. 5-Hydroxytryptamine in mast cells. Proc Soc Exp Biol Med **90**:303–304, 1955.
6. Fernex M. The Mast-Cell System. Baltimore, Williams & Wilkins, 1968.
7. Padawer J. The ins and outs of mast cell function. Amer J Anat **141**:299–302, 1974.
8. Sagher F, Even-Paz Z. Mastocytosis and the Mast Cell. Basel, Karger, 1967.
9. Selye H. The Mast Cells. Washington, Butterworths, 1965.
10. Reilly FD, Dimlich RVW. Hepatic microvascular regulatory mechanisms. IV. Effect of lodoxamide tromethamine and arterenol-HCl on vascular responses evoked by compound 48/80. Microcirc Endothel Lymph **1**:87–106, 1984.
11. Reilly FD, Dimlich RVW. Hepatic microvascular regulatory mechanisms. VI. Effects of lodoxamide tromethamine or phentolamine-HCl on early hemodynamic and glycotropic alterations by endotoxin. Microcirc Endothel Lymph **2**:271–292, 1985.
12. Reilly FD, Dimlich RVW, Cilento EV, McCuskey RS. Hepatic microvascular regulatory mechanisms. III. Aminergic mechanisms as related to mast cells. Int J Microcirc Clin Exp **2**:61–73, 1983.

13. Johnson HG, Van Hout CA, Wright JB. Inhibition of allergic reactions by cromoglycate and by a new anti-allergy drug U-42,585E. I. Activity in rats. Int Arch Allergy Appl Immunol **56**:416–423, 1978.
14. Dimlich RVW, Townsend SF, Reilly FD. Mast cell degranulation, hepatic glycogen depletion, and hyperglycemia in Compound 48/80 or pilocarpine-treated rats. Hepatology **2**:372–378, 1982.
15. Levine RA, Pesch LA, Klatskin G, Giarman NJ. Effect of serotonin on glycogen metabolism in isolated rat liver. J Clin Invest **43**:797–809, 1964.
16. Dimlich RVW. Histamine antagonists in the treatment of shock hyperglycemia in the rat. Ann Emerg Med **4**:91–96, 1985.
17. Dimlich RVW, Townsend SF, Reilly FD, Cardell RR. Mast cell degranulation, glycogen depletion, and hyperglycemia in rats treated with Compound 48/80 and pilocarpine. Anat Rec **199**:70A, 1981.
18. Johnson HG, Van Hout CA, Wright JB. Inhibition of allergic reactions by cromoglycate and by a new antiallergy drug U-42,585E. II. Activity in primates against aerosolized *Ascaris suum* antigen. Int Arch Allergy Appl Immunol **56**:481–487, 1978.
19. Niemegeers CJE, Awouters F, Van Neuten JM, DeNollin S, Janssen PAJ. Protection of rats from Compound 48/80-induced lethality: A simple test for inhibitors of mast cell-mediated shock. Arch Int Pharmacodyn Ther **234**:164–176, 1978.
20. Dews PB, Wnuck AL, Fanelli RV, Light AE, Tornaben JA, Norton S, Ellis CH, deBeer EJ. The pharmacology of No. 48-80, a long-acting vasodepressor drug. J Pharmacol **107**:1–11, 1953.
21. Dimlich RVW, Reilly FD, Meineke HA, McCuskey RS. Characterization of intensely fluorescent cells in the liver of the rat. I. Histochemistry and 48/80-induced degranulation. Anat Rec **198**:475–484, 1980.
22. Duncan DB. Multiple range and multiple F tests. Biometrics **11**:1–42, 1955.
23. Anscombe FJ. The transformation of Poisson, binomial, and negative binomial data. Biometrika **35**:246–254, 1948.
24. Alvarez RG, Kazimierczak W. New light on the mechanism of action of disodium cromoglycate. Agents Actions **11**:94–96, 1981.
25. Papacostas CA, Loew ER, West GB. Studies on the toxicology of a histamine liberator, compound 48-80. Arch Int Pharmacodyn **120**:353–362, 1959.
26. Watt GD, Bui TC, Bewtra AK, Townley RG. Protective effect of lodoxamide tromethamine on allergen inhalation challenge. J Allergy Clin Immunol **66**:286–294, 1980.
27. Padawer J, Gordon AS. Peritoneal fluid mast cells: Their numbers and morphology in rats of various body weights (ages). J Gerontol **11**:268–272, 1956.
28. Berlin G, Enerback L. Changes in numbers and heparin content of peritoneal fluid mast cells of growing rats measured by flow cytofluorometry. J Histochem Cytochem **26**:14–21, 1978.
29. Padawer J. Quantitative studies with mast cells. Ann NY Acad Sci **103**:87–138, 1963.
30. Dimlich RVW, Cardell RR. Morphometric analysis of hepatocytes from rats subjected to compound 48/80-induced anaphylactic shock. Tissue Cell **17**:293–308, 1985.
31. Reilly FD, McCafferty RE, McCuskey PA, Dimlich RVW. Hepatic microvascular regulatory mechanisms. VIII. Glucogenic responses and morphologic changes following serotonin-induced low flow. Microcirc Endothel Lymph, in press.
32. Kitamura Y, Matsuda H, Hatanaka K. Clonal nature of mast-cell clusters formed in W/W^v mice after bone marrow transplantation. Nature (London) **281**:154–155, 1979.
33. Johnson, AR. Liberation of vasoactive materials from mast cells in anaphylactic shock. In: Hinshaw LB, Cox BC, eds. The Fundamental Mechanisms of Shock. New York, Plenum, pp365–379, 1972.
34. Izumi H, Ho S-C, Michelakis AM, Aoki T. Increase of plasma renin activity after subcutaneous application of compound 48/80 in the rat. Eur J Pharmacol **109**: 249–256, 1985.
35. Dimlich RVW, Cardell RR. Effects of compound 48/80 on hepatic glycogen and glucose-6-phosphatase early in the diurnal cycle of the rat. Amer J Anat **169**: 437–449, 1984.
36. Exton JH. Mechanisms involved in effects of catecholamines on liver carbohydrate metabolism. Biochem Pharmacol **28**:2237–2240, 1979.
37. Sherline P, Lynch A, Glinsmann WH. Cyclic AMP and adrenergic receptor control of rat liver glycogen metabolism. Endocrinology (Baltimore) **91**:680–690, 1972.
38. Lautt WW, Cote MG. The effect of 6-hydroxydopamine-induced hepatic sympathectomy on the early hyperglycemic response to surgical trauma under anesthesia. J Trauma **17**:270–274, 1977.
39. Mohla S, Prasad MRN. Effect of clomiphene and compound 48/80 on uterine glycogen in the rat. Fertil Steril **20**:654–660, 1969.
40. Riley JF. The effects of histamine-liberators on the mast cells of the rat. J Pathol Bacteriol **65**:471–479, 1953.
41. Bhattacharya BK, Lewis GP. The release of 5-hydroxytryptamine by histamine liberators. Brit J Pharmacol **11**:202–208, 1956.
42. Paton WKM. Compound 48/80: A potent histamine liberator. Brit J Pharmacol **6**:499–508, 1951.
43. Gietzen K. Comparison of the calmodulin antagonists compound 48/80 and calmidazolium. Biochem J **216**: 611–616, 1983.
44. Gietzen K, Adamczyk-Engelmann P, Wuthrich A, Konstantinova A, Bader H. Compound 48/80 is a selective and powerful inhibitor of calmodulin-regulated functions. Biochim Biophys Acta **736**:109–118, 1983.
45. Heinrich J, Zimmermann RE. Compound 48/80 is a

potent inhibitor of human platelet aggregation antagonizing the calmodulin-dependent platelet reaction in vitro. Thrombosis Res **36**:475–480, 1984.
46. Rice WR, Whitsett JA. Inhibition of surfactant release from isolated Type II cells by compound 48/80. Biochim Biophys Acta **805**:261–267, 1984.
47. Dabrowski R, Szczepanowska A. Histamine and collagen levels in the lathyritic chick embryos after administration of 48/80. Agents Actions **16**:3, 4, 1985.
48. Christoffersen P, Poulsen H, Alcoholic liver disease. In: MacSween RNM, Anthony PP, Scheuer PJ, eds. Pathology of the Liver. Edinburgh, Churchill-Livingstone, p232, 1979.
49. Dimlich RVW, Reilly FD, McCuskey RS. Alterations in Kupffer cells following administration of compound 48/80. In: Knook DL, Wisse E, eds. Sinusoidal Liver Cells. pp463–466, 1982.

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