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EFFECT OF HISTAMINE ON WOUND HEALING

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Abstract : Using incision, excision and dead space wound models in rats, a study was conducted on the effect of histamine on wound healing. Exogenous histamine given either ip or locally was without any effect. Semicarbazide as (histamine synthesis inhibitor) suppressed healing process (breaking strength of skin incision wound), decreased breaking strength and hydroxyproline content of granulation tissue and delay in period of epithelization. On the other hand compound 48/80 (a promoter of histamine forming capacity) was found to promote wound healing. Exogeneous histamine (topical) reversed the anti-healing effect of semicarbazide on incision and excision wounds.

The findings support to the view that histamine auguments healing process, that both endogenous and exogenous histamine promote healing process, and that exogenous histamine has prohealing action only when endogenous histamine level is suboptimal.

Key words : breaking strength, histamine, epithelization, granulation tissue, semicarbazide, compound 48/80, wound contraction, wound healing

INTRODUCTION

Inflammation is said to be essential prelude for healing (1). A number of autacoids are known to play a role in inflammation and possibly in the healing process. Of these histmine has been implicated as prohealer, though there is controversy. Some workers (2, 3) suggest that endogenous (that too nascent) histamine and not the exogenous histamine promote healing. On the other hand Boyd and Smith (4) found that exogenous histamine is equally effective. We have reinvestigated the role of histamine in wound healing in view of this controversy.

METHODS

Various groups (n = 8-15) of Wister rats of either sex weighing 150-200 g were used. Wounding (incision, excision or dead space wound) was done on overnight fasted animals under pentobarbitone (3 mg/100 g) anaesthesia. Depilation of the back of the rat was done a day earlier to wounding. No local/systemic antimicrobials were used. Animals showing infection were excluded from the study.

Incision wounds were made by the method of Ehrlich and Hunt (5). Sutures were removed on day-7. Animals were sacrificed on day-10 and breaking strength was measured by continuous waterflow technique (6).

To cause excision wound, a circular piece of full thickness skin (500 mm^2) was excised from the dorsal intercapular region (1). Wound contraction was monitored by alternate day measurement of wound area planimetrically till the wounds were completly

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healed. The extent of wound contraction was expressed as % original wound size. Wound half closure time (Wc_{50}) was calculated by Litchfield-Wilcoxon method (8) to monitor equieffective time in different groups. Time taken for epithelization was measured in days as indicated by falling of scab leaving no raw-wound behind.

Dead space wounds were created by implantation of a polypropylene tube (2.5 × 0.5 cm) beneath the dorsal paravertical lumbar skin. On day-10 the harvested granulation tissue was subjected to physical as well as biochemical evaluation. Hydroxyproline (measure of collagan) was estimated colorimetrically (9) and breaking strength of the granulation tissue was measured by continuous waterflow technique (6).

Animals bearing a similar wound were randomly allotted to various groups - saline (control), histamine acid phosphate (5 mg/kg, ip), histamine acid phosphate topically (0.5% in saline), compund 48/80 (1 mgkg, ip) and semicarbazide (70 mg/kg, ip).

Except compound 48/80 all drugs were given for 10 days from day of wounding while compound 48/80 was given for 3 days prior to wounding.

Results were analysed by Student's 't' test.

RESULTS

Exogenous histamine (ip or local) did not materially alter the breaking strength of 10 day old incision or of granulation tissue in normal rats. On other hand, semicarbazide (a histamine synthesis inhibitor) significantly decreased the skin breaking strength while compound 48/80 (which increases histamine forming capacity) increased the breaking strength. The antihealing effect of semicarbazide was significantly prevented by local histamine but not by histamine (ip) (Table I).

Semicarbazide significantly decreased the breaking strength of granulation tissue, while compound 48/80 significantly increased granulation tissue breaking strength and histamine (ip) itself did not affect the breaking strength significantly. Hydroxyproline content of the granulation tissue was significantly increased by compound 48/80, decreased

TABLE II : Showing the period of epithelization and wound contraction in excision wound.

Drug	*n*	*Epithelization period (days) mean*±SEM	*Wound contraction as* Wc_{50} (days)$
Control	8	19.4±0.4	7.8±0.1
Histamine, ip	8	19.9±0.8	7.5±0.09
Histamine, local	8	20.4±0.09	7.6±0.11
Semicarbazide	9	22.9±0.81*	8.1±0.09
Semicarbazide +Histamine, ip	8	22.0±0.8	7.0±0.12*
Semicarbazide +Histamine, local	8	18.8±0.9+	6.8±0.15++
Compound 48/80	12	19.8±0.7	7.7±0.15

$ no. of days required for 50% closure of wounds.
P Value vs control * < 0.001
P Value vs semicarbazide + < 0.01; ++ < 0.001.

TABLE I : Breaking strength in (g) of 10-day old skin wound (SBS) and granulation tissue (GBS) and hydroxyproline (OHP mg/g) content of the latter. All value are mean ± SEM.

	Control n=15	*Histamine n=8*	*Histamine local n=8*	*Semicarbazide n=10*	*Semicarbazide + Histamine, ip n=8*	*Semicarbazide + Histamine local n=8*	*Compound 48/80 n=10*
SBS	269 ±15	266 ±12	261±21	205±19**	197 ±12*	288±22@	322 ±11*
GBS	258 ±20	240 ±17	—	207±13**	193 ±23***	—	325 ±27***
OPH	17.7±0.3	18.0± 2.0	—	15± 0.8**	15.5±0.5	—	34 ± 2****

P Value vs control *<0.01; **<0.02; ***<0.05; ****<0.001.
P Value vs semicarbazide @ <0.01

by semicarbazide and was not affected by histamine (Table I).

Histamine (ip or local) did not affect period of epithelization or wound contraction while semicarbazide significantly delayed the period of epithelization but not the wound contraction. The antihealing effect of semicarbazide was significantly reversed by local histamine but not by histamine (ip). Compound 48/80 did not modify period of epithelizaion or wound contraction (Table II).

DISCUSSION

Earlier reports (2, 3; 4) implicate histamine being a promotor of wound healing. However, they differed in as much as the type of histamine (endogenous/exogenous) used. The findings of the present study support that histamine promotes healing because semicarbazide (a histamine synthesis inhibitor) suppressed healing while compound 48/80 (which increase histamine forming capacity) promoted healing, and topical application of histmine reversed the healing-suppressant effect of semicarbazide.

Histamine administered ip or topically did not modify healing of incision, deadspace and excision wounds in normal rats. These findings agree with those in earlier reports (2, 3), and suggest that exogenous histamine has no influence on healing process. However, we found that in incision and excision wounds, topically administered histamine reversed the anti-healing effect of semicarbazide. This suggests that even exogenous histamine did not enhance healing in rats not receiving semicarbazide. Possibly, in the healing wound tissue there is normally increased histamine formation (10) and additional, exogenous histamine is superfluous. From our data it appear that histamine, endogenous or exogenous, has a prohealing effect which is seen only when endogenous histamine is suboptimal. Exogenous histamine given ip has failed to promote healing in normal and semicarbazide treated animals, probably due to pharmacokinetic reasons: 80% or more of drug given ip reaches liver (11) via portal system, and hence may fail to reach wound site in enough concentration. This eventuality is bypassed by topical application of histamine.

If the suggestion that the healing wound has optimal histamine and hence additional histamine is superfluous is reasonable it become unclear why compound 48/80, which stimulates histamine formation, promotes healing. It is possible that difference in the animal status (normal animals acquire increased histamine forming capacity after wounding while compound 48/80 pretreated animal has increased histamine forming capacity before wounding) may explain this finding.

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