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EFFECT OF S-CARBOXYMETHYLCYSTEINE, N-ACETYLCYSTEINE AND BROMHEXINE HYDROCHLORIDE ON MUCUS SECRETION IN RAT ISOLATED TRACHEA

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The therapeutic activity of bromhexine hydrochloride (BHC) and S-carboxymethyl-cysteine (SCMC) is claimed to be associated, at least in part, with a decrease in synthesis of mucus glycoproteins. However the wet weights of secretions into the tracheal pouch of the mini pig appeared to be increased by SCMC and decreased by BHC (Marriott et al 1983; Martin 1986) and studies in these laboratories have shown that SCMC increased fucose (glycoprotein) secretion in rat tracheas. In contrast N-acetylcysteine (NAC) is believed to exert its therapeutic action by direct disruption of S-S bonding in the mucus glycoproteins, increasing the fluidity and ease of clearance of the mucus, although an action on mucus synthesis may also occur. In an effort to clarify the mode of action of these compounds their effect on glycoprotein synthesis by tracheal explants has been studied.

Tracheas were removed from male Wistar rats and washed for 1 hour in incubation medium (Medium 199 [Sigma] with tricine:sodium bicarbonate buffer, 25 mM:15 mM, pH 7.4, gentamycin, 0.5 mg ml^{-1} and amphotericin, 1 $\mu g\ ml^{-1}$) in an atmosphere of O_2/CO_2 95%/5% at 37°C. Tracheas were then placed in fresh culture medium containing ^{3}H-glucosamine ([Amersham] specific activity 151 mCi mg^{-1}, 1 $\mu Ci\ ml^{-1}$), using two tracheas in each tube containing 5 ml of medium. The incubation was continued, the medium being replaced at 3, 6, 9, 12, 24 and 27 hours. Where appropriate SCMC, NAC or BHC (5 mM) were present in the medium throughout the 27 hour period. Labelled glycoprotein was precipitated with trichloroacetic acid (TCA), final concentration 5%, and prepared for liquid scintillation counting.

Data were fitted to a regression equation and compared using a modified T test. The table shows the cumulative TCA precipitable dpm released by the extracts over the 27 hour period. NAC had no significant effect on the release of labelled glycoprotein whereas SCMC and BHC decreased the release of labelled glycoprotein ($p = 0.005$ and 0.001 respectively).

Table The effect of NAC, SCMC and BHC on the release of ^{3}H-glucosamine labelled protein from rat tracheal explants. Results are cumulative mean dpm ± S.E., n=5.

	time/hours					
	3	6	9	12	24	27
control	1759±174	6772±715	14572±1773	24111±2409	60526±8845	67258±9228
NAC	1848±377	6322±823	13418±1913	22238±2927	50005±2711	62667±4036
SCMC	1508±199	5396±623	10736±1466	17662±2266	42600±4473	53014±6235
BHC	1195±131	4375±534	9745±1291	16130±1895	41758±6824	49012±9265

Under the conditions used the amount of radioactive protein released depends on a balance between the uptake of precursor, the synthesis of the glycoprotein and glycoprotein release. Previous studies have shown that SCMC, NAC and BHC do not effect the release of radiolabelled protein from tracheal explants (Chakrin et al 1973) and thus it appears that SCMC and BHC decrease either the uptake of glycoprotein precursors or the extent of glycoprotein synthesis while NAC, at the dosage used, does not affect these processes. Thus SCMC and BHC, two chemically unrelated compounds, may act in chronic obstructive airway disease by decreasing mucus output whereas NAC, although chemically related to SCMC, does not appear to exert this effect.

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