Absorption and metabolism of steroids administered intratracheally to rat isolated lungs

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A number of endogenous and exogenous substances are metabolized on passage through the pulmonary circulation (for refs. see Bakhle & Vane, 1974). Steroids are metabolized by homogenates of lung from several species (Sowell, Hagen & Troop, 1971; Hartiala, Nienstedt & Hartiala, 1973; Hartiala, 1974) and recently the metabolism of two steroids on transit through the pulmonary circulation of isolated lungs has been demonstrated. [^{3}H]-Cortisol was detected in the venous effluent of rat lungs perfused with Krebs solution containing [^{3}H]-cortisone (Nicholas & Kim, 1975). In the same tissue [^{14}C]-testosterone was taken up and metabolized avidly when the perfusate was protein-free (45% of the radioactivity in the lung was metabolite) but less (29%) when diluted rat blood was used as perfusate (Hartiala, Uotila & Nienstedt, 1976). With the introduction of steroids in aerosol form into clinical practice we decided to study the uptake and metabolism of two steroids, testosterone and beclomethasone diproprionate, administered intratracheally to rat isolated lungs.

Male rat lungs were perfused via the pulmonary artery with fresh rat blood diluted with Tyrode solution (haematocrit 0.28) at a flow rate of 10 ml/min and ventilated with room air. In 'single pass' experiments the perfusate was not recirculated and the effluent was collected in two portions, 0–2 min and 2–5.5 minutes. Analysis of effluent and lung samples was carried out as described previously (Nienstedt, 1967; Nienstedt & Hartiala, 1969). The steroid (4-[^{14}C]-testosterone, 57.7 nCi/nmol, New England Nuclear; 16,16α-[^{3}H]-beclomethasone diproprionate, 55 nCi/nmol) was instilled into the airways and the perfusion started. With testosterone (0.4 nmol in 0.1 ml of isotonic saline), 2 min after instillation, 40% of the radioactivity had appeared in the perfusate, the majority (89%) as unchanged testosterone. For comparison, cortisol and dexamethasone similarly applied to rat lungs are absorbed with half-lives of 1.0 and 1.7 min respectively (Burton & Schanker, 1974). In our experiments, analysis of the radioactivity left in the lung at 2 min showed only 33% to be unchanged testosterone. No conjugated metabolites of testosterone were found in either effluent or lung.

With beclomethasone dipropionate (10–16 nmol in 0.1 ml isotonic saline), the initial rate of absorption of radioactivity from the lungs to the perfusion medium proceeded with a half-life of 15–20 minutes. These results are comparable with those of Martin, Harrison & Tanner (1975). Analysis of the radioactivity remaining in the lung at 2 min showed that about half of the original amount was present as unchanged steroid. The major metabolite (about 30%) had the same mobility as beclomethasone monopropionate on thin layer chromatography. Five min after instillation, the proportion of unchanged steroid had dropped to one third with a considerable increase in polar metabolites other than the monopropionate. Further identification of the polar metabolites of beclomethasone was made difficult by the lack of reference compounds.

From these results we conclude that the slow absorption rate from the trachea and the extensive intra-pulmonary metabolism of beclomethasone may account for the low adrenal suppression observed with beclomethasone aerosol.

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