The effect of intraarticular hydrocortisone injection on the articular cartilage of rabbits

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We investigated the effect of hydrocortisone on the articular cartilage of the knee in rabbits. 27 New Zealand white rabbits were injected intraarticularly with 25, 50 or 100 mg betamethasone acetate in 2 or 4 weakly intervals. Control animals were injected with normal saline and demonstrated no histological changes in the articular cartilage. Hydrocortisone administration was associated with increased cell size, as well as an increased stain density in the cytoplasm surrounding vacuoles. In addition, loss of cell organelles was also observed. High dose of hydrocortisone was associated with an obvious loss of cell shape and distortion of the cell membrane and nucleus. The magnitude of histological changes, found under light and electron microscopy, were proportional to the amount of hydrocortisone injected. Our findings strongly indicate that intraarticular injection of hydrocortisone alters the shape of articular cartilage chondrocytes, producing abnormal changes in the cytoplasm and nucleus and leading to cell degeneration.

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In orthopedics, corticosteroids are administered both systemically and locally (intraarticular) for the treatment of a number of arthritic lesions. Chandler et al. (1958a, 1958b) studied the effects of intraarticular injections of corticosteroids on articular cartilage and observed that in a number of cases, the functional improvement was accompanied by excessive and accelerated destruction of the joints. It is now generally accepted that local and systemic administration of corticosteroids affect the structure and function of the articular cartilage (Behrens 1975 and 1976, Higuchi et al. 1980, Mankin and Conger 1966, Shaw and Lacey 1973). In addition, local administration of hydrocortisone was also found to produce destructive changes in the meniscus.

We characterized the morphological changes produce in chondrocytes following therapeutic doses of hydrocortisone administered intraarticularly in normal knee joints of rabbits.

Materials and methods

27 New Zealand white rabbits, 4–6 months old, were used. Animals were divided into 2 groups with 3 subgroups in each. The first group of 13 animals were treated as follows: 3 control animals received 0.1 mL of 0.9% sodium chloride intraarticularly. 5 animals received 0.1 mL of 0.9% sodium chloride in the left knee, and 0.1 mL of 25 mg betamethasone acetate once a week for 2 weeks in the right knee. The third subgroup of 5 animals received 0.1 mL of sodium chloride in the left knee, and 0.1 mL of 25 mg betamethasone acetate once a week for 4 weeks in the right knee.

The second group of 14 animals were treated as follows: 4 control animals received double the amount of sodium chloride solution that was injected in the first control group (e.g. 0.2 mL). 5 animals were injected intraarticularly with 50 mg of betamethasone acetate once a week for 2 weeks in the left knee, and with 100 mg once a week for 2 weeks in the right knee. The third subgroup of 5 animals received 100 mg of betamethasone acetate once a week for 4 weeks in the left knee and 50 mg of betamethasone acetate once a week for 4 weeks in the right knee.

All animals of the 2 groups were killed on the fourth and sixth week, respectively, after the initiation of treatment. The articular cartilage of the femoral condyles was examined under light and electron microscopy.

Results

Light microscopy demonstrated no changes in the control group. Animals who received a total of 0.2 mL of hydrocortisone had an increased cell size of about

5% in the articular cartilage chondrocytes, while those treated with 0.4 mL showed an increased stain density in the cytoplasm in addition to the increased cell size. Only about 20% of the cells remained normal. Animals who received 0.8 mL of hydrocortisone had a loss of normal structure, including increased cell size, an increased number of vacuoles, with or without membrane, within the cytoplasm, as well as an increased number of lysosomes. In addition, the cytoplasm demonstrated an increased stain density and the cell nucleus was not well defined.

Similar to the histological findings under light microscopy, electron microscopy did not show changes in the articular cartilage of control animals. Furthermore, the nuclei appeared normal in the chondrocytes of rabbits who received 0.2 mL of hydrocortisone. Up to 8 vacuoles were observed in the cytoplasm and a more dense area near the cell membrane (Figure 1). Rabbits who received 0.4 mL of hydrocortisone demonstrated changes in the shape of the cell nucleus, several intracellular vacuoles, the largest of which usually had a membrane, and an area more dense than the cytoplasm (Figure 2). Animals who received a total of 0.8 mL of hydrocortisone had a loss of normal cell shape in about 10–15% of the cells (Figure 3). In addition, a total loss of cell organelles was observed, as well as distortion of the cell nuclei in a bout 10 to 15% of the cells. The dense area of the cytoplasm observed around the vacuoles at lower doses was larger. Finally, most of the cells examined also had degenerative changes.

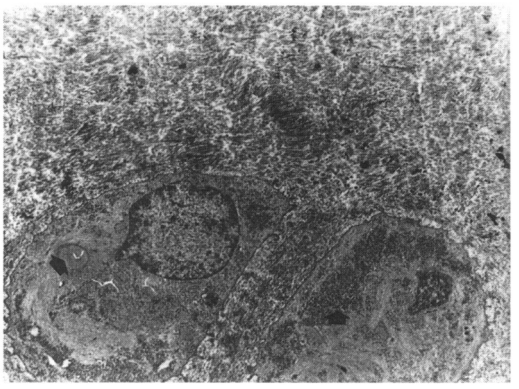

Figure 1. Micrograph showing chondrocytes after 0.2 ml of hydrocortisone administered intraarticularly. Although the nuclei are normal, the cytoplasm shows an increased stain density area (right arrow) and vacuoles (left arrow). (Electron microscopy, x15,000).

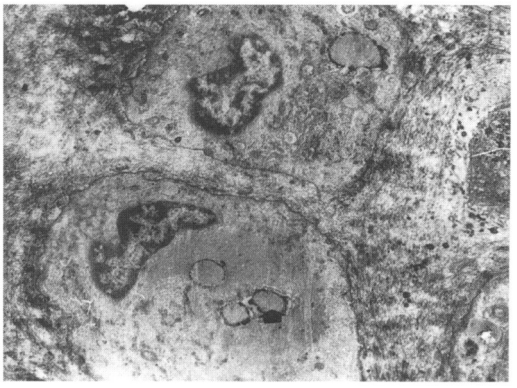

Figure 2. Micrograph showing chondrocytes after 0.4 mL of hydrocortisone administered intraarticularly. Note the change in the shape of the nucleus and the presence of vacuoles (electron microscopy, x10,000).

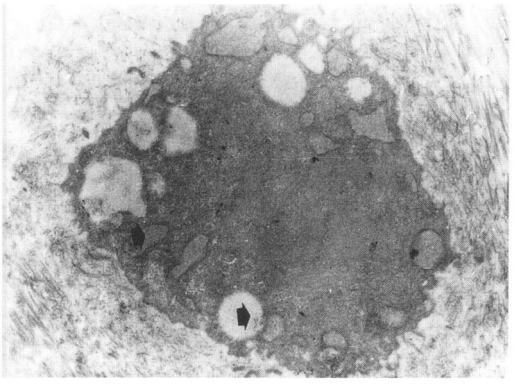

Figure 3. Micrograph showing chondrocytes after 0.8 mL of hydrocortisone administered intraarticularly. Note the distortion of the chondrocyte. There are several vacuoles, some of which possesses membrane and have particles within (left arrow) while others lack a membrane and are empty (electron microscopy, x15,000).

Discussion

We found that intraarticular administration of hydrocortisone affects the shape of chondrocytes. The size of the cells gradually increased in a manner which resembles that observed in arthrosis. The increase in cell size is also believed to be associated with an increase in the level of cell metabolism. Hydrocortisone administration was also associated with an increased presence of vacuoles, the largest of which possessed membranes. Vacuoles were surrounded by cytoplasm which was noted to have an increased stain density under light microscopy or a more dense area under electron microscopy. We hypothesize that this dense area probably reflects an alteration in the metabolic activity of the cytoplasm. Hydrocortisone was also found to change and distort the shape of the cell nuclei. Some nuclei were destroyed at higher doses of the steroid. At high doses of hydrocortisone, the chondrocytes demonstrated a significant distortion or even loss of cell organelles, including the Golgi apparatus,

lysosomes and mitochondria. A complete loss of the cellular membrane was observed in 10–15% of the cells. These findings had a direct relationship with the amount of injected hydrocortisone.

The histological changes noted in the chondrocytes have been associated with abnormal function of the tissue. The magnitude of these changes alter the function of the chondrocytes, which in turn can lead to degenerative changes in the cartilage. The loss of organelles directly affects the production of proteins and proteoglycans and interferes with the extracellular production of collagen fibers which are responsible for articular cartilage strength.

In general, these structural changes are followed by functional ones which negatively affect the synthesis of proteoglycans and collagen. It has been reported that the functional alterations have the potential to return to normal about 6 months after the cessation of steroid injections (Behrens et al. 1976). On the other hand, it is not clear if the structural changes are able to show the same recovery. In addition, the behavior of the matrix around the distorted cells and its influence on the articular cartilage remains obscure.

Our findings suggest that intraarticular injection of hydrocortisone is associated with a high risk of impairing the structure, and in turn the function of the articular cartilage.

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