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Effects of isoproterenol on the fine structure of the hamster parathyroid gland

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Summary. Ultrastructural changes of the parathyroid glands of isoproterenol-treated golden hamsters were investigated.

Many chief cells in the parathyroid glands after 5 and 10 minutes of administration of isoproterenol contain well-developed Golgi complexes and granular endoplasmic reticulum, numerous prosecretory granules, and many secretory granules in the peripheral cytoplasm as compared with the control animals.

Many chief cells in the parathyroid glands after 1, 3, 6 and 12 hours of administration have poorly-developed Golgi complexes, granular endoplasmic reticulum, many secretory granules and numerous lipid droplets as compared with the control animals.

The morphology of the parathyroid gland after 30 minutes and 24 hours of administration resembles that of the control animals.

It is considered that isoproterenol affects the secretory activity of the parathyroid gland.

Key words: Parathyroid gland, Isoproterenol, Electron microscopy, Hamster, Morphometry

Introduction

Not only the serum calcium concentration, but also the autonomic nervous system have been physiologically known to play an important role in the regulation of parathyroid hormone secretion (Morii et al., 1963; Fischer et al., 1973; Kukreja et al., 1976; Chu et al., 1983; MacGregor et al., 1983; Cardinali and Ladizesky, 1985; Hanley and Wellings, 1985; Williams et al., 1985).

Recent physiological and biochemical studies have suggested that ß-adrenergic agents stimulate the release of parathyroid hormone (Kukreja et al., 1976; 1980; Brown et al., 1977; Morrissey and Cohn, 1979; Blum and Fischer, 1982; MacGregor et al., 1983). However, there have been few morphological reports concerning the effects of autonomic nervous system on function of the parathyroid gland (Isono et al., 1976, 1982; Isono and Shoumura, 1980; Setoguti et al., 1984). In addition, Shoumura et al. (1983) have reported the origin of the autonomic nerve fibers innervating the parathyroid gland using the HRP method.

We investigated morphological changes of the parathyroid gland of the golden hamsters after administration of ß-adrenergic stimulator, isoproterenol.

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Materials and methods

Four- to 6-month-old golden hamsters of both sexes with an average body weight of 180 g were divided into 9 groups of 5 animals each. One group served as controls. The remaining eight groups were given intravenously 3% isoproterenol solution at a dose of 50 mg/kg body weight and were sacrificed at 5, 10 and 30 minutes and 1, 3, 6, 12 and 24 hours after injection. The parathyroid glands of the isoproterenol-treated golden hamsters and the control animals were removed under sodium pentobarbital anesthesia. The glands were immersed in a mixture of 2.5% glutaraldehyde and 2% OsO_4 in Millonig's buffer at pH 7.4 for 1 hour, dehydrated through ascending concentrations of acetone, and embedded in Epon 812. Thin sections were cut with glass knives using a Porter-Blum Mt-1 ultramicrotome and stained with uranyl acetate and lead salts. Electron micrographs were taken with a JEM 100U or Hitachi H-700H electron microscope.

In each golden hamster from the 9 groups, 20 micrographs were taken from different regions of the parathyroid glands at a primary magnification of 7,000×, and photographically enlarged resulting in a final magnification of 14,000×. The area of cytoplasm, nuclei, Golgi complexes, vacuolar bodies, heterogeneously dense bodies, lipid droplets and glycogen areas, and the number of secretory granules were estimated with the aid

of an image analyser (Digigrammer Model-G, Mutoh Ltd.) connected to a microcomputer.

The serum calcium levels of all golden hamsters were measured using a Corning Calcium Analyser 940.

Statistical analysis of data was performed by Student's t-test.

Results

Serum calcium levels

The mean serum calcium concentrations (mg/100ml) of the control and isoproterenol-treated golden hamster are shown in Fig. 1. The serum calcium concentration of 1-hour-treated golden hamsters is significantly high as compared with that of the control animals ($p<0.05$). However, there are no significant differences between the control group and the remaining groups with regard to the serum calcium concentration.

Fine structure of the parathyroid gland:

Control golden hamster

The parenchyma of the parathyroid gland of the golden hamster consists of only one type of epithelial cell, chief cell. The chief cells are oval or polygonal in shape. The plasma membranes of adjacent chief cells pursue a tortuous course with occasional interdigitations (Fig. 2). The intercellular spaces are generally narrow and occasional enlargements contain floccular or finely particulate material. Mitochondria are round or oval in profile and are dispersed throughout the cytoplasm. Many chief cells are rich in free ribosomes. Cisternae of the granular endoplasmic reticulum are randomly distributed or sometimes arranged in parallel arrays in the cytoplasm (Fig. 2). Most Golgi complexes are relatively well developed and contain some prosecretory granules (Figs. 2, 4). Secretory granules of 150-300 nm in diameter are round or oval bodies filled with a finely particulate material (Fig. 3). Some granules are located in a peripheral cytoplasm. Large secretory granules of 350-600 nm in diameter, large vacuolar bodies of 350-750 nm in diameter and heterogeneously dense bodies are sometimes observed in the cytoplasm (Figs. 4, 5). Large secretory granules are round or oval, homogeneously dense bodies and filled with a finely particulate material (Fig. 4). Large vacuolar bodies contain floccular material and/or vesicles (Fig. 4). Occasional transitional forms between large secretory granules and large vacuolar bodies are present. Numerous vesicles of 40-70 nm in diameter are found juxtaposed to some of large secretory granules and large vacuolar bodies (Fig. 4). Small aggregations of glycogen particles (glycogen areas) and lipid droplets are occasionally found in the cytoplasm (Fig. 2).

Isoproterenol-treated golden hamster

In the parathyroid glands of the golden hamsters 5 and 10 minutes after administration of isoproterenol, most chief cells have rich free ribosomes, abundant mitochondria and well-developed Golgi complexes containing numerous prosecretory granules (Fig. 6). Cisternae of the granular endoplasmic reticulum are frequently arranged in parallel arrays (Fig. 7). Many secretory granules are located in the peripheral cytoplasm adjacent to the plasma membrane, and some granules are situated close to the interdigitated plasma membrane. The enlarged intercellular spaces containing a finely particulate material are sometimes encountered (Fig. 8). Large secretory granules, large vacuolar bodies and heterogeneously dense bodies are sometimes observed, and glycogen areas and lipid droplets are occasionally found in the cytoplasm. Numerous vesicles surround some of large secretory granules and large vacuolar bodies.

The morphology of the parathyroid gland of the golden hamsters 30 minutes after administration of isoproterenol, resembles that of the control animals.

In the parathyroid glands of the golden hamsters 1, 3, 6 and 12 hours after administration of isoproterenol, many chief cells have rich free ribosomes, abundant mitochondria, poorly-developed Golgi complexes containing a few prosecretory granules (Fig. 9), many secretory granules and numerous lipid droplets (Fig. 10). Occasional secretory granules are observed in the peripheral cytoplasm close to the plasma membrane. Glycogen areas are scarcely observed 6 and 12 hours after administration. Cisternae of the granular endoplasmic reticulum are occasionally arranged in

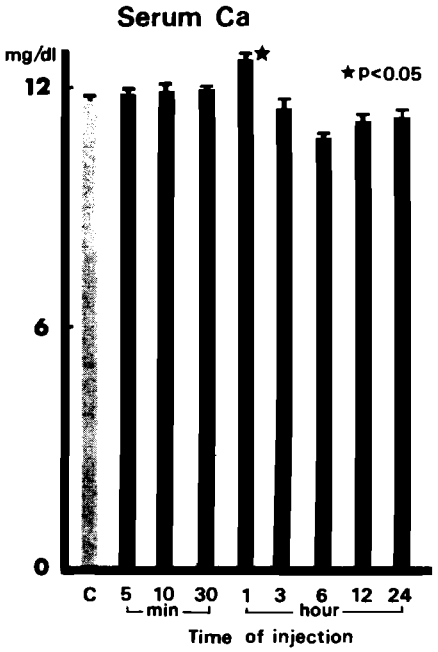

Fig. 1. The mean serum calcium levels from the control (C) and isoproterenol-treated hamsters. *$p<0.05$ (significantly different from control values)

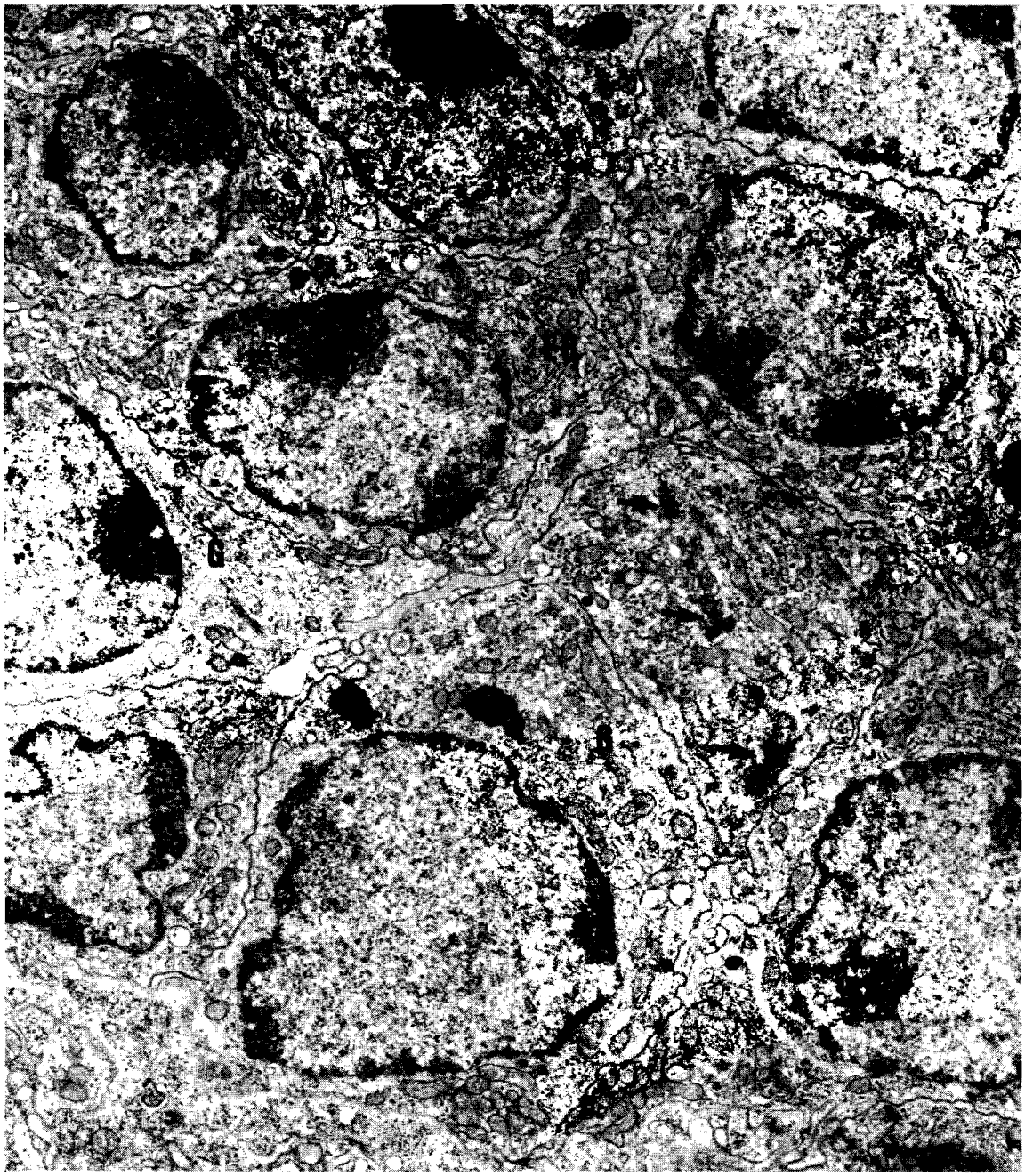

Fig. 2. Parathyroid chief cells of a control golden hamster. Small aggregations of glycogen particles form glycogen areas (arrows). Golgi complexes are relatively well developed (G) and cisternae of the granular endoplasmic reticulum are randomly distributed or arranged in parallel arrays (ER). × 9,000

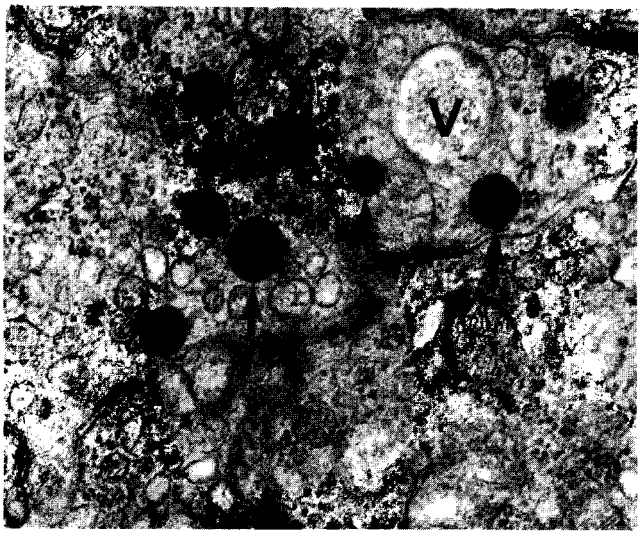

Fig. 3. Secretory granules (arrows) and the large vacuolar body (V) in the chief cell of the control golden hamster. × 31,000

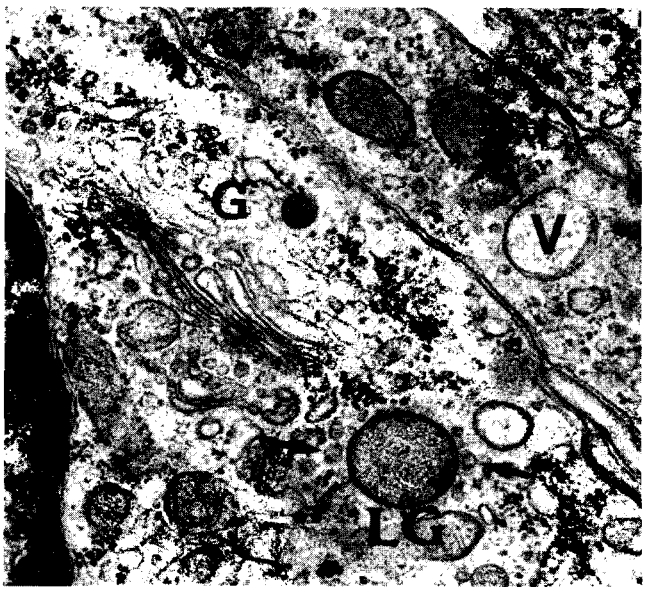

Fig. 4. Parathyroid chief cell of the control golden hamster. Well developed Golgi complex (G) contains prosecretory granules (double arrows). Large secretory granule (LG) near the Golgi complex (G) is surrounded by vesicles (arrows). Large vacuolar body (V) has a dense plaque (arrow head) along the outer surface of its limiting membrane. × 30,000

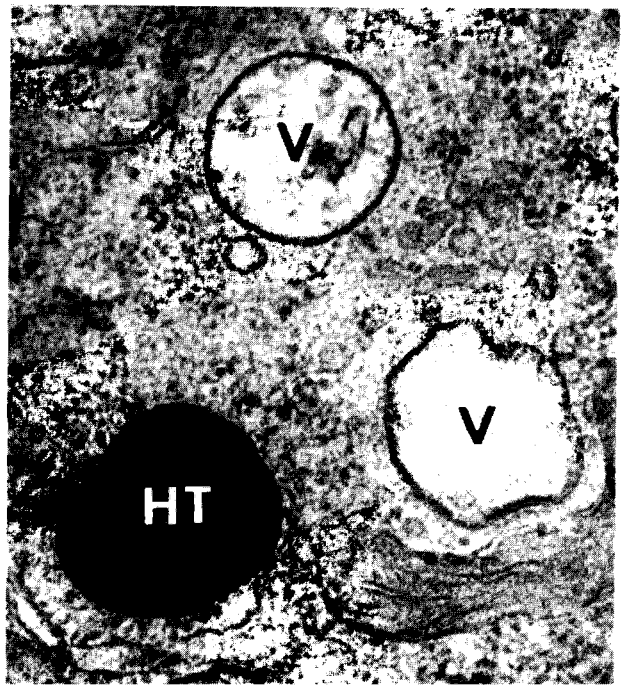

Fig. 5. Large vacuolar bodies (V) and the heterogeneously dense body (HT) thought to be lysosome in nature in the chief cell of the control golden hamster. × 45,000

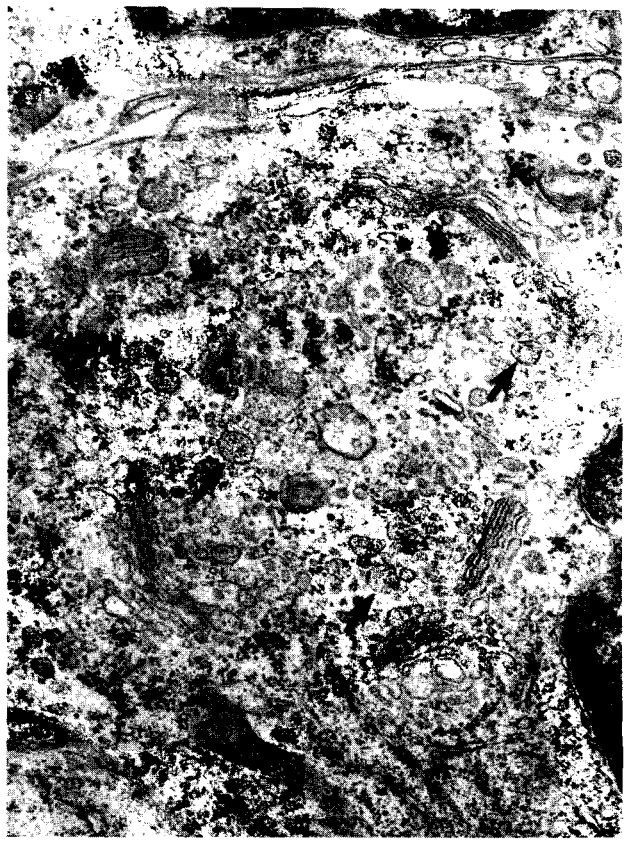

Fig. 6. Well-developed Golgi complexes contain many prosecretory granules (arrows) in the chief cell of 10-min-isoproterenol-treated golden hamster. × 20,000

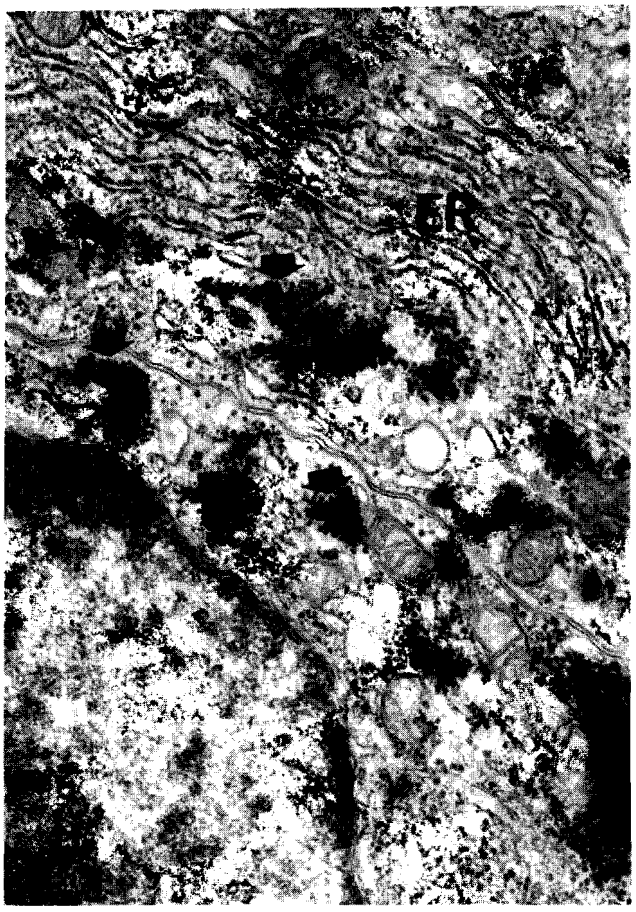

Fig. 7. Well-developed granular endoplasmic reticulum (ER) and many glycogen areas (arrows) in the chief cells of the 5-min-isoproterenol-treated golden hamster. × 25,000

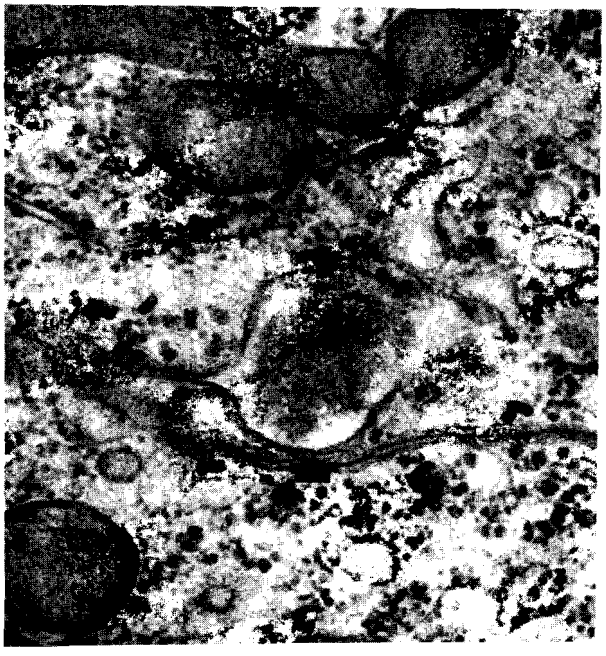

Fig. 8. Enlarged intercellular space containing finely particulate substance (arrow) in the chief cell of the 10-min-isoproterenol-treated golden hamster. × 46,000

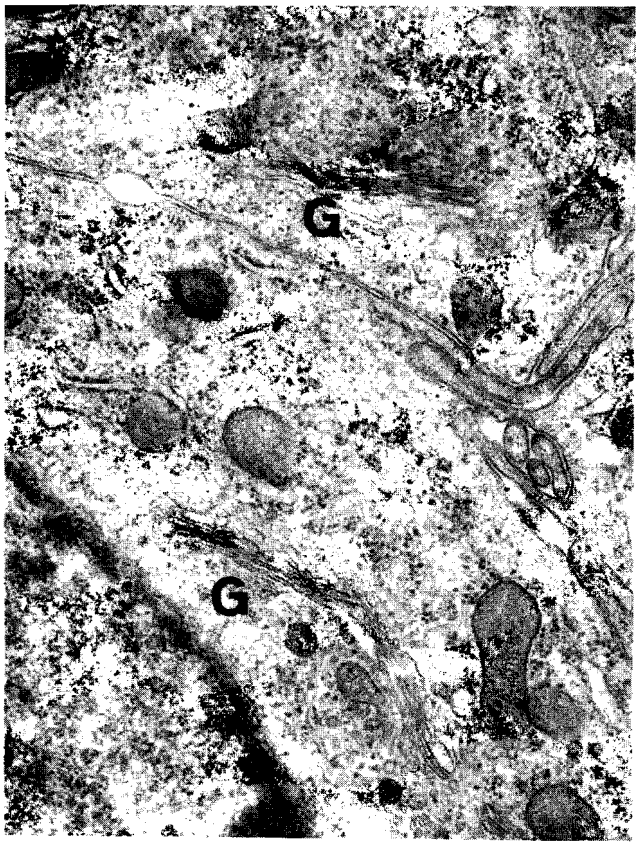

Fig. 9. Poorly-developed Golgi complexes (G) in the chief cells of the 12-h-isoproterenol-treated golden hamster. × 22,000

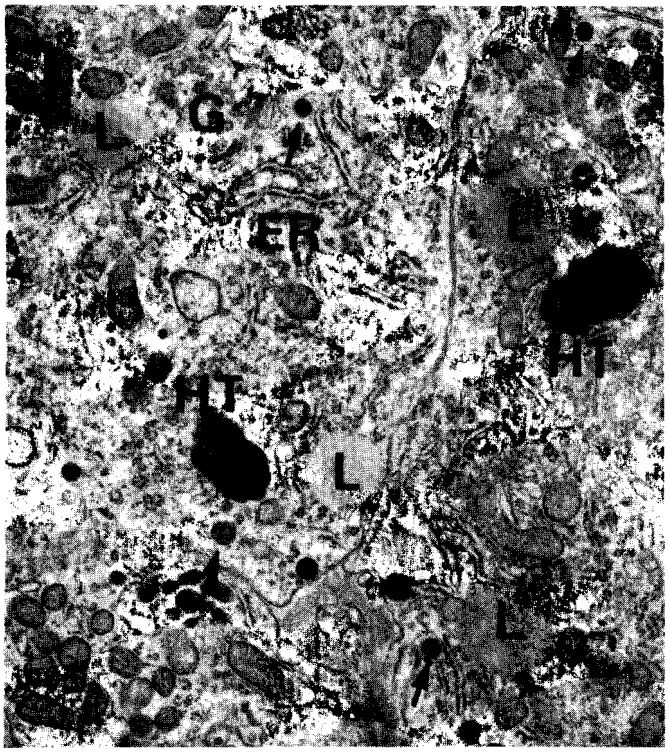

Fig. 10. Parathyroid chief cells of the 3-h-isoproterenol-treated golden hamster. Many lipid droplets (L) and secretory granules (arrows) are observed. G: Golgi complex, Ht: heterogeneously dense body, ER: cisternae of granular endoplasmic reticulum. × 13,000

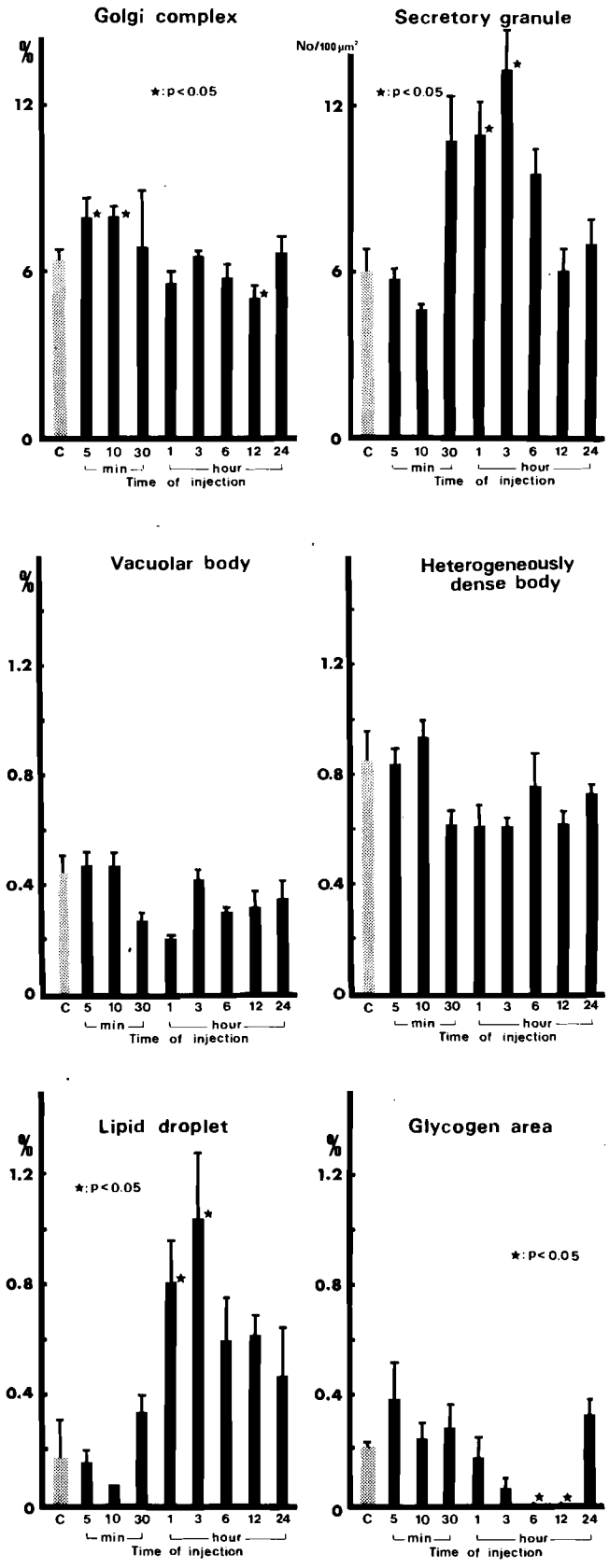

Fig. 11. The cytoplasmic volume densities of the Golgi complex, vacuolar body, heterogeneously dense body, lipid droplet and glycogen area, and the number of the secretory granule per 100 μm^2 of the cytoplasm from the control (C) and isoproterenol-treated golden hamsters.
*$p<0.05$ (significantly different from control values

parallel arrays or randomly distributed in the cytoplasm. Large secretory granules, large vacuolar bodies and heterogeneously dense bodies are sometimes observed in the cytoplasm. Numerous vesicles surround some of the large secretory granules and large vacuolar bodies.

The morphology of the parathyroid glands 24 hours after administration resembles that of the control golden hamsters.

Stereological analysis of the parathyroid gland

The analytical results obtained from the control group and the isoproterenol-treated groups are shown in Fig. 11. All experimental values are compared with those of the control animals.

In the parathyroid glands 5 and 10 minutes after administration of isoproterenol, the volume density occupied by the Golgi complexeses is significantly increased ($p<0.05$). 1 and 3 hours after administration, the volume density occupied by lipid droplets and the number of secretory granules per 100 μm^2 of the cytoplasm are significantly increased ($p<0.05$). 6 hours after administration, the volume density occupied by glycogen areas is significantly decreased ($p<0.05$). 12 hours after administration, volume densities occupied by the Golgi complexes and glycogen areas are significantly decreased ($p<0.05$).

There are no significant differences between the control and isoproterenol-treated animals with regard to large vacuolar bodies and heterogeneously dense bodies.

Discussion

The serum ionized calcium concentration is known to be the regulator of parathyroid hormone secretion. In addition, many authors have suggested that the ß-adrenergic system may also play an important role in the secretion of parathyroid hormone (Fischer et al., 1973; Kukreja et al., 1975, 1976; Brown et al., 1976; 1977; Blum et al., 1978; Mayer et al., 1979; Metz et al., 1978; Morrissey and Cohn, 1979; Schneider and Sherwood, 1980; Blum and Fischer, 1982; MacGregor et al., 1983). Several authors have reported that the serum calcium level in isoproterenol-treated animals is not changed (Kukreja et al., 1975; Blum et al., 1978 ; Mayer et al., 1979; Blum and Fischer, 1982) and that it is changed after administration of isoproterenol (Fischer et al., 1973; McCarron et al., 1982). In the present study, the serum calcium level is significantly increased after 1 hour of administration of isoproterenol.

The present study demonstrates that many chief cells in the parathyroid glands of golden hamsters after 5 and 10 minutes of administration of isoproterenol contain

well-developed Golgi complexes and cisternae of the granular endoplasmic reticulum, numerous prosecretory granules, and many secretory granules in the peripheral cytoplasm as compared with the control animals. These findings are fairly consistent with the observations of an increase in functional activity of the parathyroid gland (Roth and Raisz, 1964; Isono et al., 1971, 1977, 1979a, 1979b, 1986; Fujii and Isono, 1972; Isono and Shoumura, 1973; Nunez et al., 1974; Roth and Capen, 1974; Chertow et al., 1975; Roth and Schiller, 1976; Takai, 1976; Capen, 1980; Hayashi et al., 1980; Wild, 1980; Emura et al., 1982, 1984; Ishizaki et al., 1983; Wild and Manser, 1986). Therefore, it is possible to speculate that the synthesis and release of parathyroid hormone may be stimulated in many chief cells of the parathyroid glands after 5 and 10 minutes of administration of isoproterenol. Physiological and biochemical reports have suggested that isoproterenol stimulates the release of parathyroid hormone (Brown et al., 1977; Morrissey and Cohn, 1979; Blum and Fischer, 1982; Chu et al., 1983; MacGregor et al., 1983).

Our results demonstrate that many chief cells in the parathyroid glands of golden hamsters after 1, 3, 6 and 12 hours of administration of isoproterenol have poorly-developed Golgi complexes and cisternae of the granular endoplasmic reticulum, and many secretory granules and numerous lipid droplets as compared with the control animals. These changes are considered to be induced by suppression of the synthesis and release of parathyroid hormone in many chief cells of the parathyroid glands after 1, 3, 6 and 12 hours of administration of isoproterenol. These results are fairly consistent with the findings which indicate a decrease in function of the parathyroid gland (Stoeckel and Porte, 1966; Isono and Shoumura-Sakurai, 1973; Young et al., 1973; Roth and Schiller, 1976; Isono et al., 1977, 1978, 1980, 1981, 1982, 1983, 1985; Hayashi et al., 1981; Emura et al., 1984a).

In the present study, the morphology of the parathyroid gland after 24 hours of administration of isoproterenol resembles that of the control animals. It is conceivable that the parathyroid gland indicating an increase and decrease in functional activity after administration of isoproterenol returns to the control parathyroid gland after 24 hours.

The number of secretory granules in the chief cells of the parathyroid gland does not appear to correlate with the functional states of the gland (Roth and Raisz, 1966; Altenähr and Seifert, 1971). It has been reported that in active chief cells secretory granules have a tendency to gather beneath the plasma membrane (Fujii and Isono, 1972; Takai, 1976; Isono and Shoumura, 1980; Emura et al., 1982, 1984b; Ishizaki et al., 1983). In the preset study, some secretory granules in the parathyroid glands of the control golden hamsters and many secretory granules in the parathyroid glands after 5 and 10 minutes of administration are present in the peripheral cytoplasm, and some granules are situated close to the plasma membrane. The enlarged intercellular spaces contain a finely particulate material similar to the contents of the secretory granule. These findings suggest the possibility of exocytosis of the secretory granule in the parathyroid gland of the golden hamster. A similar type of secretion has been indicated in many studies of the parathyroid glands.

Many studies have described large secretory granules as being storage granules in the parathyroid gland (Altenähr, 1970; Haase, 1978; Isono et al., 1978, 1980, 1981, 1982, 1983, 1985; Hayashi et al., 1980, 1981; Isono and Shoumura, 1980; Setoguti et al., 1981; Emura et al., 1982, 1984a,b; Ishizaki et al., 1983). In the present study, large secretory granules of 350-600 nm in diameter are also observed in the control and isoproterenol-treated animals. Our interpretation that such large secretory granules are thought to be storage granules which remain undischarged in the cells is supported by the observations that large secretory granules are acid-phosphatase negative (Shannon and Roth, 1974; Hayashi et al., 1980; Setoguti et al., 1980) and show immunoreactivity for the parathyroid hormone (Shoumura et al., in press). In our study, numerous vesicles similar to those inside and outside large vacuolar bodies surround some of the large secretory granules, and large vacuolar bodies contain material similar to the contents of secretory granule. Multivesicular bodies in the parathyroid gland are acid-phosphatase negative (Hayashi et al., 1980; Setoguti et al., 1980) and do not show immunoreactivity for the parathyroid hormone (Shoumura et al., in press). We believe that some of the vesicles lying adjacent to the storage granules are incorporated into the latter to form certain kinds of the large vacuolar bodies. It is thought that such transformation involves lysosomal digestion of the strorage granules. Recently, Setoguti et al. (1981) have mentioned that storage granules are released only as an emergency supply of parathyroid hormone. However, additional investigations are required to clarify the fate of the storage granules.

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