ELECTRON MICROSCOPIC RADIOAUTOGRAPHIC STUDIES OF THE CAROTID BODY FOLLOWING INJECTIONS OF LABELED BIOGENIC AMINE PRECURSORS

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ABSTRACT

Adult Syrian hamsters were given a subcutaneous injection of reserpine 3 days before an intraperitoneal injection of ^{3}H-3,4 dihydroxyphenylalanine or ^{3}H-5, hydroxytryptophan and the carotid bodies were subsequently prepared for electron microscopic radioautography. Other Syrian hamsters were given a subcutaneous injection of reserpine and the carotid bodies were subjected to a sensitive cytochemical test for the detection of unsubstituted amines. These studies were made to determine whether the labeled amine precursors were incorporated into the cells and to see whether the parenchymal cells were affected by reserpine treatment. Material from hamsters treated first with reserpine and subsequently injected with ^{3}H-3,4 dihydroxyphenylalanine or ^{3}H-5, hydroxytryptophan exhibited reduced grains of silver over the cells which were associated mainly with the dense cores of the cytoplasmic granules. These studies offer evidence that the granules of the carotid body incorporate catecholamine and indolamine precursors. Material from hamsters incubated for the presence of unsubstituted amines gave a positive reaction (opaque cytoplasmic granules) for catecholamines but not for indolamines. The latter substances may not be present in quantities sufficient to register a positive reaction in the cytochemical test. The opaque granules, indicative of the presence of catecholamines, decreased in density after reserpine treatment. 5 days after one reserpine injection the granules had regained opacity and were comparable to those seen in the control cells.

INTRODUCTION

The carotid body is thought to be a chemoreceptor the cells of which respond to certain physiological or chemical stimuli by releasing a transmitter substance. This substance, in turn, excites afferent nerve terminals. In spite of this general agreement there has been controversy about the particular transmitter substance or substances which the cells release. Several chemical agents have been suggested: acetylcholine (Eyzaquirre et al., 1965), catecholamines (Lever et al., 1959), carotidin (Christie, 1933), serotonin (Douglas and Toh, 1952) and histamine (Fabinyi and Szebehelyi, 1948).

Electron microscope studies of the glomus or chief cells show many membrane-bounded, electron-opaque granules (Lever and Boyd, 1957; Lever

et al., 1959; Ross, 1959; de Kock and Dunn, 1964; Biscoe and Stehbens, 1966; Duncan and Yates, 1967; Blümcke et al., 1967; Hoglund, 1967; and Kobayashi, 1968) similar in appearance to those in the cells of the adrenal medulla which are known to contain catecholamines (Hillarp et al., 1953; Hagen and Barrnett, 1960; Yates, 1963, 1964; and Wood and Barrnett, 1964). It has been suggested that the amine-depleting agent reserpine (Lever et al., 1959) and hypoxia (Blümcke, et al., 1967) result in a disappearance of the granules from the glomus cells. These data offer evidence that the granules contain biogenic amines which may be responsible for the transmission mechanism. However, other studies (Duncan and Yates, 1967; Heymans et al., 1968; and Hess, 1968) have been inconclusive with regard to the effects of reserpine on the granules. More sensitive and accurate methods for the detection of amines were necessary prior to undertaking experimental procedures to elucidate the functional mechanisms of the carotid body. Recently, tritium-labeled norepinephrine, dihydroxyphenylalanine (dopa) and 5-hydroxytryptophan (5-HTP) have been used to localize biogenic amines in the hypothalamus (Aghajanian and Bloom, 1966a, b), nerve terminals (Wolfe et al., 1962), and in the adrenal medulla (Elfvin et al., 1966). In the current study, the presence of catecholamines and indolamines has been demonstrated at the fine structural level in the glomus cells of the carotid body by means of radioautographic techniques and cytochemical methods for the detection of unsubstituted amines.

MATERIALS AND METHODS

22 Syrian hamsters weighing 35–70 g were used in these studies.

Radioautography

Five hamsters were injected intraperitoneally with 29 μc/gm body weight of tritiated DL 3,4-dihydroxyphenylalanine (specific activity, 0.690 c/mmole). Two of these animals had been injected with a single dose of reserpine (2 mg/kg) 3 days prior to the administration of the radioisotope. Another hamster was injected intraperitoneally with tritiated DL 5-hydroxytryptophan (29 μc/gm, specific activity, 1 c/mmole) 3 days after a single dose of reserpine (2 mg/kg). All animals were sacrificed 4 hr after the injection of the isotope by perfusion through the left ventricle with a cold 3% glutaraldehyde solution in 0.1 M phosphate buffer (pH 7.4). The carotid bodies were excised bilaterally and placed (for 2 additional hr at 4°C) in vials containing the fixative. The tissues were then washed in 0.1 M phosphate buffer (pH 7.4) containing 10% sucrose for 2–4 hr at 4°C and post-fixed in 1% osmium tetroxide in phosphate buffer for 1 hr. Following fixation the tissues were rinsed briefly in normal saline, rapidly dehydrated through a graded series of ethanols and embedded in Epon 812 (Luft, 1961).

For light microscopic radioautography 0.5–1 μ sections were cut on a Porter-Blum ultramicrotome and mounted on glass slides. The emulsion used was Ilford L-4, Ilford Limited, Ilford, Essex, England, diluted 1:1 with distilled water. The sections were exposed for 2–5 wk at 4°C, after which they were developed in Microdol X for 5 min and fixed in hypo for 3 min. The sections were then stained with 1% toluidine blue and examined with a Spencer binocular microscope.

For electron microscopic radioautography, sections showing gold interference colors were placed on Parlodion-coated glass slides and stained for 1 min with lead citrate (Reynolds, 1963). The slides and sections were coated with a carbon film in a vacuum evaporator, immersed in a 1:4 dilution of Ilford L-4 Nuclear Research Emulsion, allowed to dry, and stored at 4°C in dry, light-tight boxes for 2–5 wk. The slides were developed in Microdol X for 3–5 min and fixed in hypo for 3 min. The Parlodion film and the sections were detached from the glass slides picked up on copper grids and examined with an RCA EMU 3G microscope.

GLUTARALDEHYDE-DICHROMATE METHOD: Hamsters were treated with one injection of reserpine and sacrificed after 1, 2, or 24 hr and after 3 or 5 days. The carotid bodies from untreated hamsters were processed with material from the treated animals. Other hamsters were given one injection of reserpine (2 mg/kg) and one carotid body was removed after 1 or 2 days. The carotid body from the opposite side of these animals was subsequently removed 3 or 5 days after treatment. All tissues were fixed with 3% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) for 2–4 hr, washed in 0.1 M phosphate buffer with 10% sucrose for 2 hr and subsequently incubated in a solution of 2.5% potassium dichromate and 1% sodium sulfate in 0.2 M acetate buffer, pH 4.1 (Wood and Barrnett, 1964). The tissues were dehydrated in ethanol and embedded in Epon 812. Unstained gold sections were examined in the electron microscope.

FORMALDEHYDE-GLUTARALDEHYDE-DICHROMATE METHOD: The carotid bodies of untreated and DL, 5-hydroxytryptophan (1 mg)-injected hamsters were processed for electron microscopy according to the method of Wood (1967). The formaldehyde pretreatment blocks the active sites of catecholamines but does not prevent the indolamines from reacting with glutaraldehyde to form a Schiff mono-

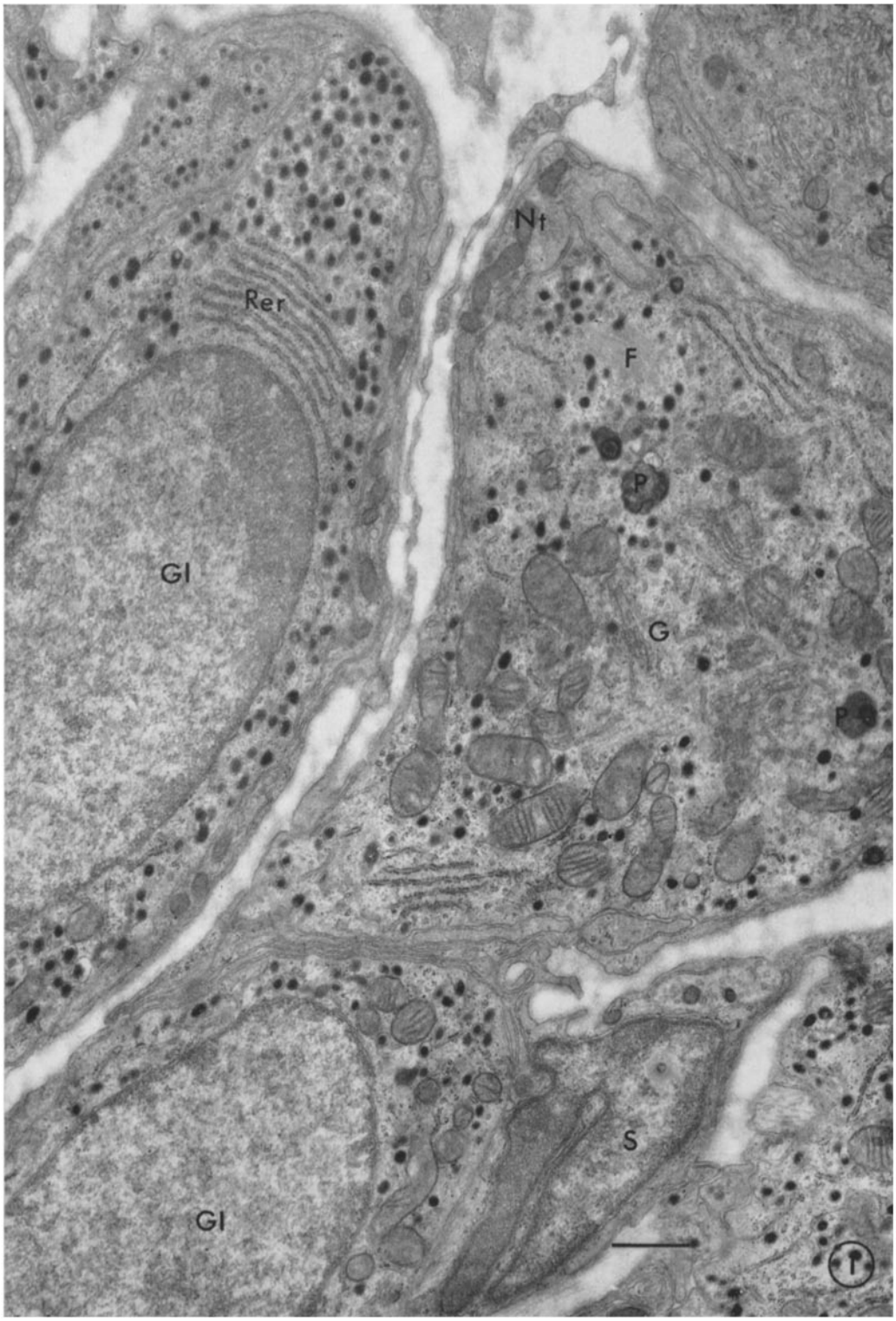


FIGURE 1 An electron micrograph showing two types of parenchymal cells of the hamster carotid body: glomus (*Gl*) (Type I) and supporting (*S*) (Type II). The glomus cells are characterized by the presence of numerous membrane-bounded electron-opaque granules and parallel arrays of granular endoplasmic reticulum (*Rer*). An aggregation of fine filaments (*F*), pigment granules (*P*), and mitochondria are illustrated in the vicinity of the Golgi complex (*G*). Note that the nerve terminal (*Nt*) shows a close relationship with one of the glomus cells. × 16,600.

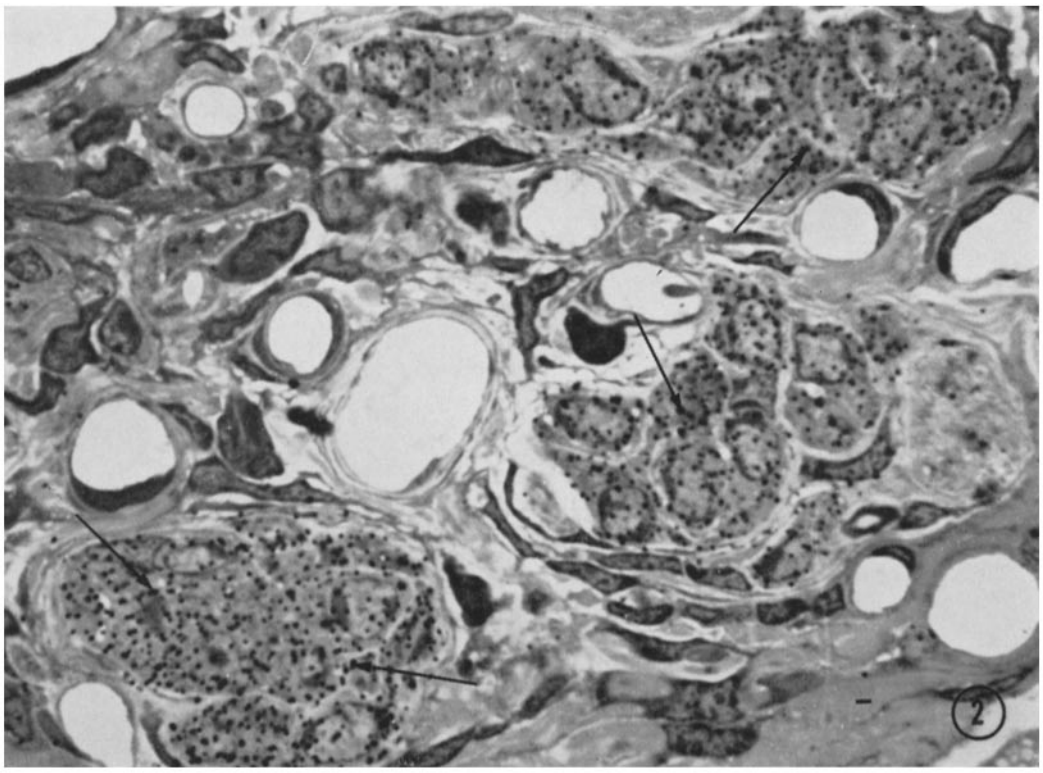


FIGURE 2 Light microscopic radioautograph taken from a 0.5–1 μ thick Epon section of the carotid body of an animal which had been injected with ^{3}H-DOPA 3 days after a single dose of reserpine. Positive grains of silver are specifically concentrated over the clusters of glomus cells (arrows). × 1450.

base. The monobase is necessary for the subsequent reaction with potassium dichromate to form electron-opaque deposits. This technique differentiates catecholamines from indolamines (Wood, 1967).

RESULTS

Histological Organization and Fine Structure of Hamster Carotid Bodies

The hamster carotid body consists of groups of epithelioid cells, among which are numerous blood vessels and nerve fibers (Fig. 2), as well as connective tissue cells and their attenuated processes. The parenchymal cells are of two types, glomus (Type I) and supporting (Type II) (Fig. 1). Each glomus cell is provided with several cytoplasmic processes, some of which extend into the interstitial spaces. The glomus cells and their processes are partially surrounded by the cytoplasm of supporting cells.

The fine structural features of the glomus cells of the hamster carotid body are similar to those in other animal types (Lever et al., 1959; Ross, 1959; Biscoe and Stehbens, 1966; Duncan and Yates, 1967; Blümcke et al., 1967; Hoglund, 1967). The spherical or oval nucleus is usually eccentrically located and well developed Golgi complexes are located in the juxtanuclear cytoplasm (Fig. 1). The granular endoplasmic reticulum is usually arranged in discrete systems of parallel cisternae (Fig. 1). The most striking feature of the glomus cell is the presence of numerous electron-opaque, membrane-bounded granules (granulated vesicles) ranging from 500 to 2000 A in diameter and seen primarily at the periphery and in the processes of the cells (Fig. 1).

Radioautography

Table I shows the distribution of the silver grains over the carotid bodies. The grain counts were tabulated from eight electron micrographs of each animal; the micrographs were taken ran-

domly at original magnifications of 4200 diameters. Nearly all of the silver grains were concentrated over the glomus cells (Fig. 2). In ^{3}H-dopa-injected animals the grains over the carotid bodies of the untreated animals (Nos. 1 to 3) were less numerous than those in animals treated with reserpine 3 days prior to the injection of the isotope (Nos. 4 and 5; Table I). In the ^{3}H-5HTP-injected animal (No. 6; Table I) the silver grains were less numerous than in the corresponding ^{3}H-dopa-injected hamsters (Nos. 4 and 5; Table I). It should be noted again that only one animal was injected with ^{3}H-5HTP. Nevertheless, in the 5-HTP-injected hamster, grains were also specifically localized over the glomus cells.

The distribution of the silver grains over the cytoplasmic structures in the glomus cells is shown in Table II. The silver grains which were associated with more than two structures were not counted. All of the glomus cells were labeled both in the control animals and in the animals injected with reserpine 3 days before isotope administration. The silver grains were not distributed at random over the glomus cells; instead, more than 50% of the grains were localized over the sites where the granules were concentrated (Figs. 3, 4, and 5; Table II).

Cytochemistry

GLUTARALDEHYDE-DICHROMATE METHOD: Most of the granules in the glomus cells of the untreated animals reacted intensely in this technique (Fig. 6). 2 hr after a single injection of reserpine some glomus cells exhibited granules which were normal in appearance, whereas other granules displayed a marked decrease in density. 24 hr following a reserpine injection the density of the

TABLE I

Distribution of Silver Grains Over the Carotid Bodies

Isotope	Total grains counted	Glomus cells	Supporting and Schwann cells	Fibroblasts and interstitial cells	Nerves	Extracellular space*	Endothelial cells
	#1 395‡	88.77	3.02	3.24	1.73	2.59	0.65
	#2 389‡	87.92	4.11	2.31	2.06	3.60	0.00
	#3 263‡	90.11	3.42	1.52	2.66	2.28	0.00
^{3}H-dopa	#4 481§	93.76	1.04	0.21	2.29	2.49	0.21
	#5 473§	93.45	2.75	0.85	0.63	2.33	0.00
^{3}H-5HTP	#6 202	91.09	0.99	1.49	2.48	3.96	

* Includes the vascular lumen.
‡ Untreated Controls.
§ Reserpine Treated, Three Days.

TABLE II

Distribution of Silver Grains Over the Organelles in the Glomus Cells

Isotope	Animal number and treatment	Total grains counted	Percentage of grains over glomus cell structures: Granules	Mitochondria	Nucleus	Cytoplasmic matrix	Others*
	#1 Control	351	54.99	14.11	10.95	18.25	1.70
	#2 Control	342	63.74	10.82	10.23	14.04	1.17
	#3 Control	237	51.90	15.19	13.92	16.46	2.53
	#4 Reserpine 3 days	451	56.76	11.53	19.73	10.42	1.55
	#5 Reserpine 3 days	442	55.43	5.88	21.95	13.80	2.95
^{3}H-5HTP	#6 Reserpine 3 days	184	66.85	10.33	5.98	13.04	3.81

* Golgi complex, granular endoplasmic reticulum and lipofuscin pigment granules

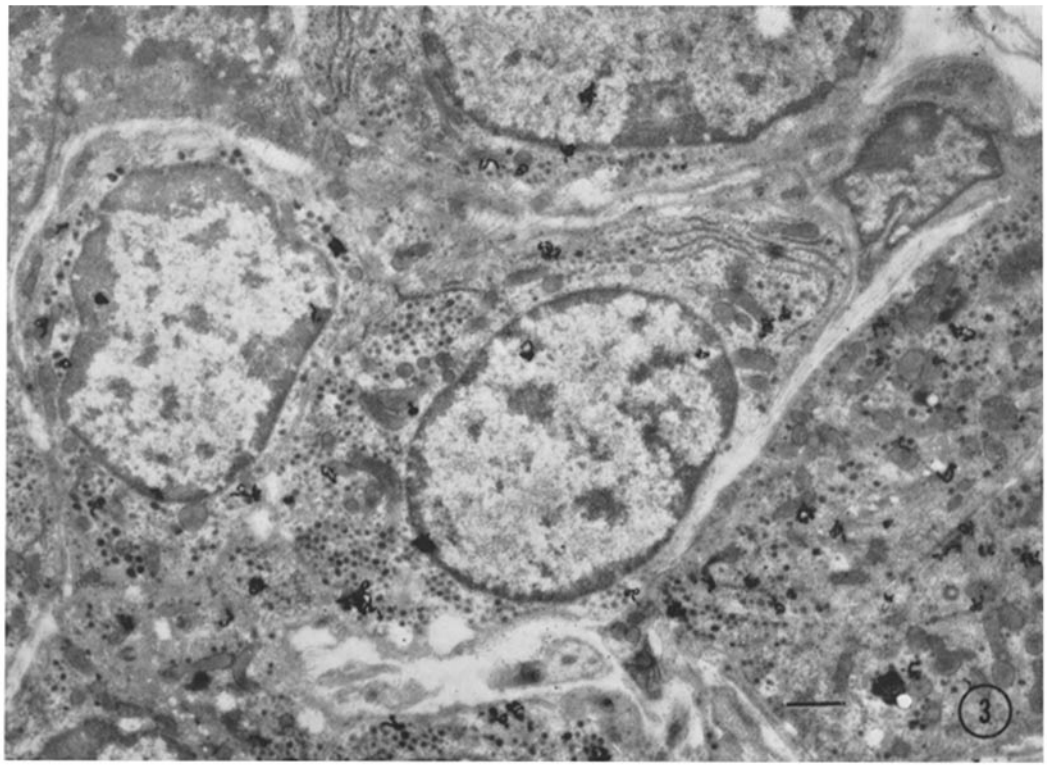


FIGURE 3 Low power electron microscopic radioautograph taken from the carotid body of an animal which had been treated as described in Fig. 2. All the glomus cells are labeled. × 7700.

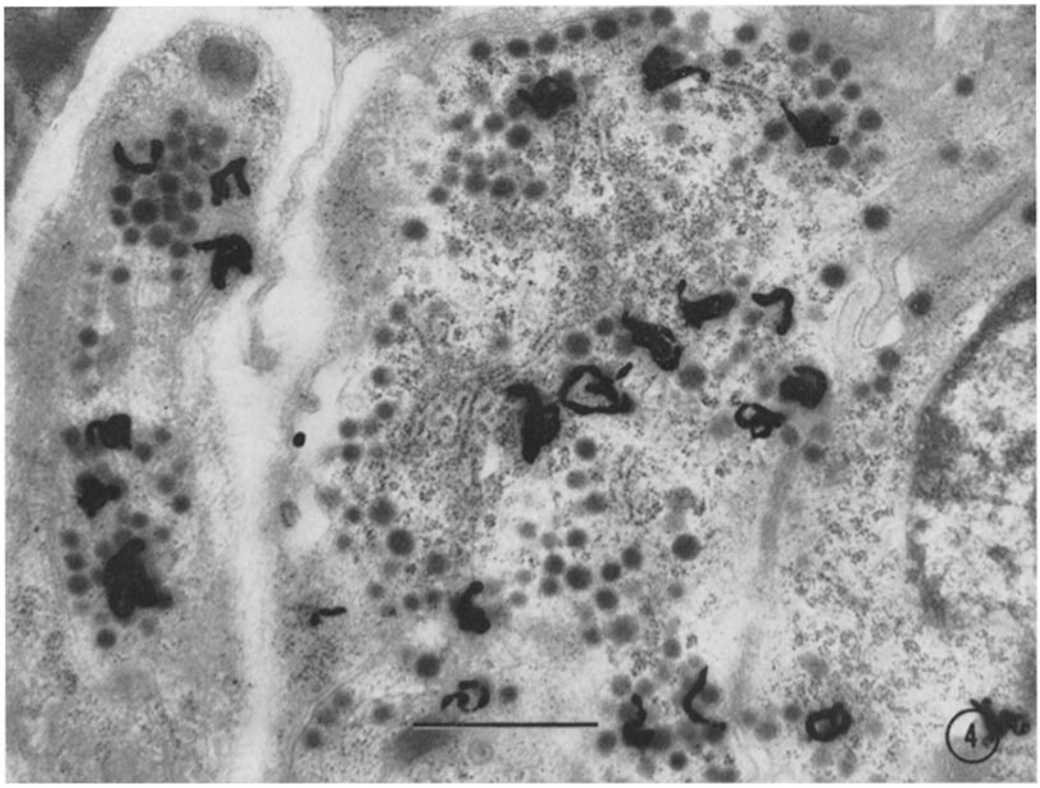


FIGURE 4 Electron microscopic radioautograph showing a close association of silver grains with membrane-bounded granules in the glomus cells. The animal had been treated as described in Fig. 2. × 24,500.

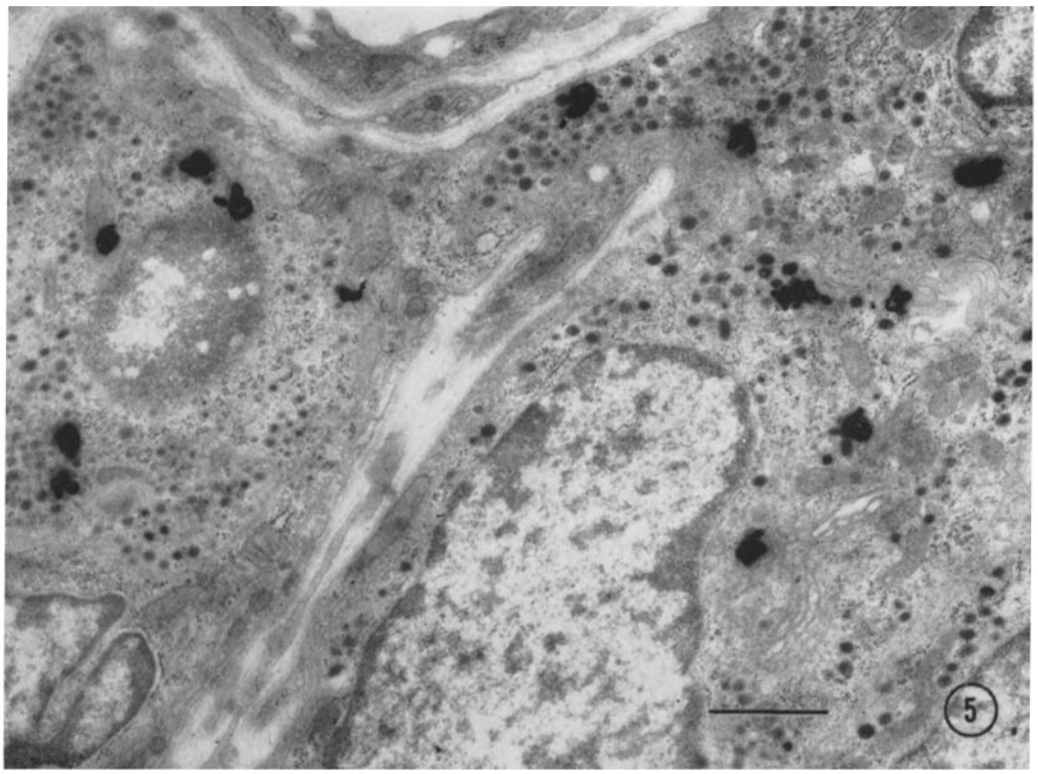


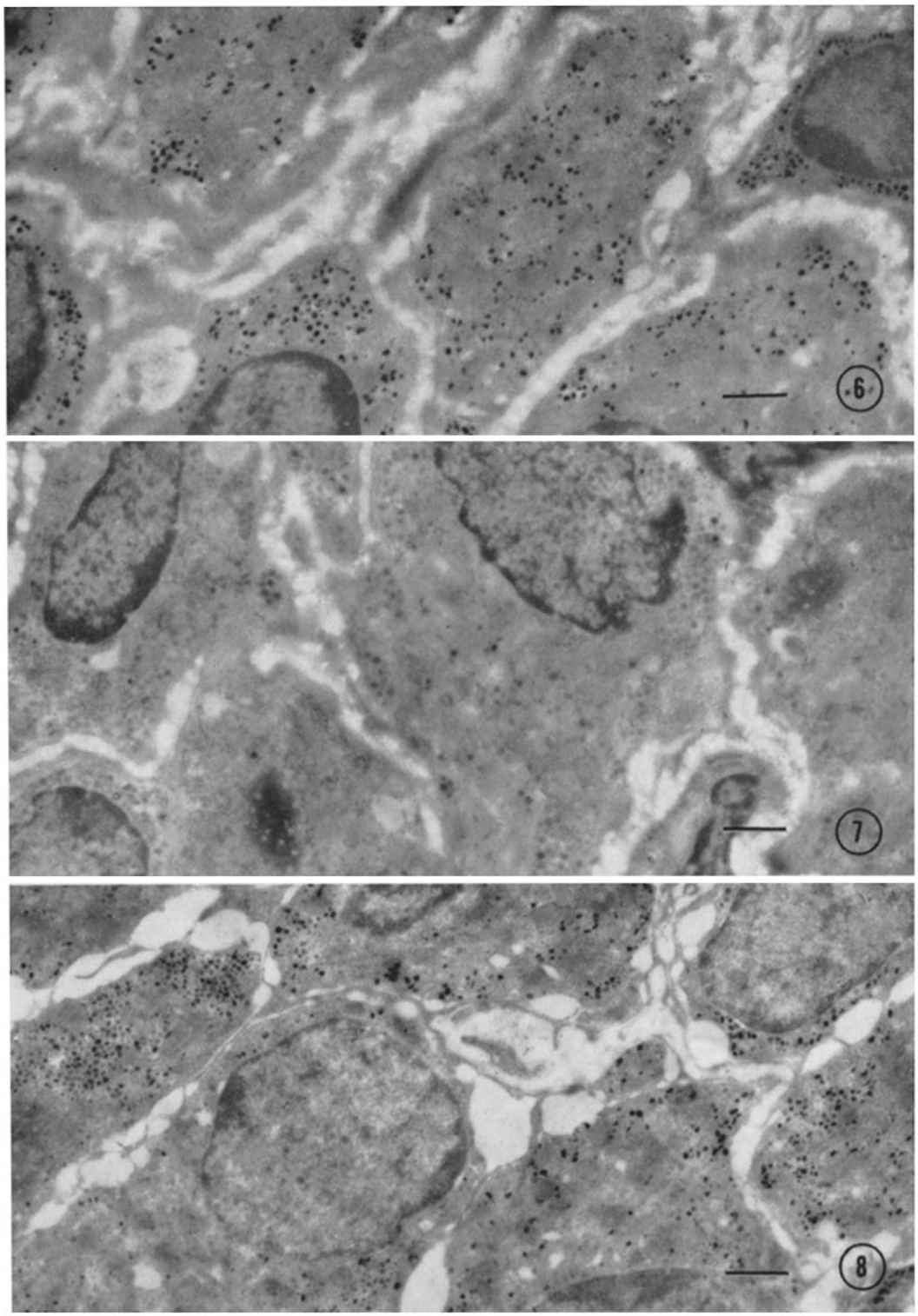
FIGURE 5 Electron microscopic radioautograph taken from a carotid body of an animal which had been injected with ^{3}H-5HTP 3 days after a single dose of reserpine. Silver grains are localized predominantly over the cytoplasmic granules. × 15,400.

granules had practically disappeared in most of the glomus cells (Fig. 7). The restoration of the granules began 2 to 3 days after a single injection of reserpine (Fig. 8), and after 5 days the granules exhibited density comparable to that of granules in the control cells.

FORMALDEHYDE-GLUTARALDEHYDE-DICHROMATE TECHNIQUE: Though the granules in some adrenal medullary cells and the enterochromaffin cells in the duodenal mucosa gave an intensely positive reaction for serotonin (Wood, 1967), the presence of this compound in the granules of the glomus cells in either untreated or 5-hydroxytryptophan-treated animals could not be identified with this technique. The quantity of serotonin in the glomus cells may be insufficient in amount to register as dense deposits with the dichromate incubation method. However, a small quantity may be detectable radioautographically as stated earlier in the results.

DISCUSSION

The exact chemical nature of the substances which register as positive grains of silver on the sections cannot be given specifically at the present time. It seems improbable that the radioactivity in the carotid body following administration of tritium-labeled 5-HTP or dopa was due merely to the original substance injected since (1) following the injection of radioactive precursors of amines, labeling was found specifically over the glomus cells, and (2) during the recovery period in reserpine-treated animals, glomus cell labelings were found much more abundantly than in the control animals. It has been shown that injected dopa is rapidly taken up by adrenal medullary cells and converted into dopamine and norepinephrine, most of which becomes particle-bound (Bertler et al., 1960). Similar results were obtained in certain tissues of 5-HTP-injected animals (Gershon and



FIGURES 6–8 Electron micrographs of parts of carotid bodies from untreated (Fig. 6), reserpine-treated (24 hr) (Fig. 7) and reserpine-treated (3 days) (Fig. 8) hamsters. The tissues were subjected to the glutaraldehyde-potassium dichromate technique and photographed unstained in the electron microscope. Most of the granules in the control tissue (Fig. 6) appear electron opaque. 24 hr after a single injection of reserpine (Fig. 7) the density of the granules has practically disappeared. 3 days (Fig. 8) after one reserpine injection, many granules have regained density but they still appear less opaque than do those in the cells of control tissues. × 9600.

Ross, 1966a, b). The assumption is that in the carotid body the injected precursors of the amines are concentrated in the glomus cells and converted into the corresponding amines which become particle bound. However, microspectrofluorometric and radiochromatographic techniques would be useful in determining if the precursors are converted to catechol- and indolamines.

The significance of the localization of silver grains over other organelles such as mitochondria and the nucleus is not clear, especially since only the Golgi complex is thought to be involved in the biosynthesis of amines (Ross, 1959). In this study reserpine treatment and the dichromate incubation techniques indicate that the amines in the granules can be released intracellularly, so it is possible that small amounts of the radioactive amines diffuse from the granules and are fixed in the general cytoplasm. The presence of extragranular amines has been described (Van Orden et al., 1967). Such amines may not be detected with the dichromate technique, but may be registered with radioautographic methods. Elfvin et al. (1966) stated that in addition to the firmly bound amines there might be a minor fraction which has a tendency to migrate during the penetration of the fixing fluid.

The carotid bodies were more heavily labeled following ^{3}H-dopa than following ^{3}H-5HTP with the same total radioactivity, but showed higher specific activity with 5-HTP (1 c/mmole) than with dopa (0.690 c/mmole). These observations suggest that the serotonin content in the granules is much less than that of catecholamines. The results do not parallel those obtained in the cat in which the amount of serotonin predominates over catecholamines (Chiocchil et al., 1967). With ammoniacal silver methods the latter workers differentiated norepinephrine-, serotonin- and epinephrine-storing granules in the glomus cells. Hamberger et al. (1966), using microspectrophotometric techniques, reported that some of the cells in the human carotid body contained 5-hydroxytryptamine (5-HT) while others stored catecholamines. In our experiments with the syrian hamster most of the glomus cells contained both catecholamine- and indolamine-storing granules since all the glomus cells were labeled following an injection of either of the tritiated precursors. The enzyme which catalyzes the conversion of dopa to dopamine (dopa decarboxylase) may not exhibit specificity (Westermann et al., 1958). Consequently, when there is an excess of 5-HTP, as in the present experiments, this enzyme may convert 5-HTP to 5-hydroxytryptamine (5-HT) which is stored in the granules.

The present radioautographic studies demonstrate that biogenic amine precursors are incorporated into the granules of the carotid body glomus cells. The cytochemical studies support the concept that the amines are localized in the cytoplasmic granules. The positive reaction of the granules after glutaraldehyde-dichromate incubation and the inhibition of the reaction by formaldehyde pretreatment indicate that the granules contain predominantly unsubstituted catechol- rather than indolamines.

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