ACTION OF DRUGS ON CAROTID BODY AND SINUS

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The carotid bifurcation is provided with two sets of receptors, the pressoreceptors, or baroreceptors, and the chemoreceptors. The pressoreceptors are located in the wall of the arteries, mainly the internal carotid artery, at the bifurcation of the common carotid artery or carotid sinus. The chemoreceptors are situated in the carotid body. The anatomical structure of the carotid sinus and body has been investigated by numerous authors (1–5, 12, 13, 21, 30, 37, 43–47, 53, 57, 70, 93–95, 147, 149, 160, 161, 178, 180, 188, 189, 193–195, 199, 200, 202, 204, 208, 214, 218, 220, 229, 233, 235, 246–250, 256).

The pressoreceptive nerve endings are located in the adventitia and media of the arterial wall of the carotid sinus. The pressoreceptors are connected with nerve fibers joining mainly the intercarotid branch of the glossopharyngeal nerve. Fibers have also been traced from the superior cervical ganglion and the nodose ganglion to the carotid sinus and body. Embryologically, the carotid body has a dual origin from the mesoderm of the third branchial arch artery and the ectoderm of the glossopharyngeal nerve.

The carotid body contains epitheloid or glomus cells which are directly in contact with the blood capillaries. According to de Castro (47), an end-plate is present in each glomus cell and is connected with a myelinated nerve fiber. The trophic center of these fibers is located in the ganglion petrosum of the glossopharyngeal nerve. The blood supply of the carotid body is by way of arterial branches which arise from the occipital and external carotid arteries. These branches open directly into sinusoidal spaces lined with endothelium and glomus cells. Arterio-venous anastomoses are located at the origin of the arterial blood supply to the carotid body. The afferent arteries to the arterio-venous anastomoses are provided with smooth muscles and a pressoreceptive innervation regulating the blood supply to the carotid body (30, 37, 43–47, 53, 93, 94, 195, 199).

The histology of the carotid body in the cat, sheep and rat has been reinvestigated recently by de Kock (158, 158a). Besides ordinary glomus cells a second type has been found typically in closer association with the vascular supply than the ordinary type. Stellate and non-stellate interstitial cells occur. The intra-glomular nervous supply has been traced. Fibers of the glossopharyngeal nerve expand into an intra-glomular network in which interstitial cells are enmeshed, thence passing to glomus cells, where they end in an intracellular reticulum. de Castro's finding of direct innervation of glomus cells, and the occurrence in the latter of solid end structures was not confirmed. The nervous relation of interstitial and glomus cells described by de Kock (158) are in substantial agreement with the findings of Meyling (188, 189). Investigators generally agree that the carotid bodies are not "chromaffine" in the usual sense (37, 43, 44, 199), providing further evidence against their being intimately related to the sympathetic nervous system as has been suggested.

The nerve fibers from the carotid bodies enter the central nervous system with the carotid sinus nerve (intercarotid branch of the glossopharyngeal nerve).

I. CAROTID BODY CHEMORECEPTORS

A. Physiological Properties of the Carotid Body Chemoreceptors

Experiments of J. F. and C. Heymans (146), C. Heymans *et al.* (110, 111, 113, 116, 118–123, 127, 128, 138), Bouckaert et al. (31, 35), and Verdonk (240, 241) showed the existence of a "peripheral chemoreflex mechanism" of regulation of the activity of the respiratory and cardio-vascular centers. These researches demonstrated the existence in the aortic and carotid sinus areas of chemoreceptors which are sensitive to increased CO_2 or decreased oxygen tension in the arterial blood. Stimulation of these chemoreceptors by increased CO_2 or hypoxia induces a reflex stimulation of the respiratory center, while decreased arterial CO_2 or increased oxygen tension provokes reflexly an inhibition of the respiratory center. Hyperpnea provoked by acute oxygen deficiency, which had been considered as centrogenic, is brought about by the chemoreceptor reflex mechanism. These experimental observations have been confirmed and extended by a number of investigators (23, 27, 58, 72, 73, 75–77, 83, 86, 91, 103, 104, 106 207, 221–228, 251, 252, 254, 255).

Recordings of the action potentials of the carotid body chemoreceptive fibers (38, 75, 76, 86) showed increasing impulses with increasing hypoxemia. The great sensitivity of the chemoreceptors to changes in oxygen tension is attested, furthermore, by the fact that such chemoreceptor impulses could be recorded as soon as the oxygen saturation of the blood fell below 96 per cent. Increasing the oxygen saturation of the blood above 96 per cent decreases the chemoreceptor nerve impulses. Gemill and Reeves (85), Bouckaert and Pannier (36), and Marshall and Rosenfeld (181) showed that hypoxic hyperpnea is suppressed by vagotomy and exclusion of carotid sinus chemoreceptors. Selladurai and Wright (228), Mertens (187), Benzinger *et al.* (22), and Watt *et al.* (245) also stated that hypoxemia stimulates respiration reflexly by means of the aortic and carotid chemoreceptors. Beyne *et al.* (25) and Jongbloed (154) observed that, in dogs deprived of their chemoreceptors, low atmospheric pressure induces respiratory inhibition rather than hyperpnea. Experiments of Heymans and Jacob (138) showed that suppression of the aortic and carotid body chemoreceptors markedly prolongs acapnic apnea.

Hesser (106) pointed out that "the dominating role of the 'chemoreflex drive' in the respiratory defense against acute oxygen deficiency is now firmly established and that the chemoreflexes are entirely responsible for the hypoxic hyperventilation, at least in the initial stages of oxygen deficiency that are associated with blood alkalosis." Consequently, those opinions must be refuted according to which the hyperventilation during acute oxygen deficiency results from direct stimulant effect of hypoxemia upon the respiratory center, or from increased arterial or intracentral cH.

As to the role of the chemoreceptor reflex mechanism in the hyperventilation induced by prolonged and chronic oxygen want, experiments of Bjurstedt (27)

indicated that the initial effect of oxygen lack on respiration is due exclusively to chemoreceptive reflex drive, while the effect of prolonged hypoxemia is due mainly to direct central impulses. In hypoxemia of long duration, the alkalinity of the blood, due to the hyperpnea, progressively disappears. At the same time the chemoreflex drive becomes less active, and the central drive becomes more and more important and finally controls respiration almost entirely. Winterstein (257), however, pointed out that in spite of the reduction of the O_2-saturation of the blood during oxygen lack, the increase in arterial cH has induced an increase in O_2-tension of the blood, which might well be sufficient to explain the decrease in chemoreflex drive during prolonged hypoxemia. Experiments of Schmidt and Comroe (223) showed, indeed, that the oxygen tension in the arterial blood, rather than the oxygen saturation, is the main factor affecting the chemoreceptors. Rudberg (217) observed that oxygen inhalation decreases the hyperpnea induced by occlusion of the carotid arteries.

Furthermore, Åstrand (14) found evidence of marked chemoreceptor activity in cats which had been subjected to sustained hypoxia (4000 m simulated altitude, tracheal pO_2 87 mm Hg) for periods up to 64 hours. Such animals also showed a reduction of this chemoreceptor activity when the inspired oxygen tension was increased.

Rahn and Otis (212) and Riley and Houston (215) have reinvestigated Bjurstedt's (27) claim that the centrogenic "drive" is largely responsible for the pulmonary ventilation in man acclimatized to altitude. Experiments of Åstrand (15) in man showed, however, that the hypoxic "drive" from the chemoreceptors occurring during acclimatization to altitude remains constant and of the same value as that seen during acute hypoxia.

As to the role of the chemoreceptors in the regulation of respiration by arterial CO_2, experiments indicated that the chemoreceptors are stimulated by a slight increase in arterial CO_2 (122). Recordings of action potentials of chemoreceptive fibers (76) further showed that these fibers began to discharge as soon as the alveolar pCO_2 exceeded about 30 mm Hg, and that the discharge increased in approximatively linear relation to the alveolar pCO_2. Experiments of Heymans *et al.* (120, 122, 128) demonstrated that the respiratory center, deprived of its chemoreflex innervation, still responds to increased CO_2 in the inhaled air and in the arterial blood. The respiratory center thus also reacts directly to the arterial pCO_2.

The relative importance of chemoreflexes and of the respiratory center itself in the regulation of breathing by CO_2 has been much discussed. According to one viewpoint, the chemoreflex mechanism plays a significant part in the control of breathing by CO_2, under all circumstances (29, 73, 76, 79, 83, 86–90, 106, 128, 226, 227, 228, 251, 252). The second viewpoint (52) implies that the chemoreceptors are not active under normal conditions and become so only in unusual (emergency) circumstances typified by hypoxemia, the marked hypercarbia associated with severe respiratory depression, and the action of certain drugs.

The importance of the aortic and carotid chemoreflex component, as compared with that of the direct central drive, in the regulation of breathing by

CO_2 in different physiological and pathological conditions, is still open for discussion. Under some conditions the chemoreflex component may, indeed, be the most important, while in other conditions the centrogenic drive may be predominant. The regulation of respiration by CO_2, therefore, must be considered in the light of the "multiple theory" of respiratory regulation as emphasized by Gray (96, 97). The interaction between the different factors regulating respiration controls the pulmonary ventilation under different physiological or physiopathological conditions. The physical reflexes of respiratory regulation may also interfere with the chemical centrogenic, and chemoreceptive reflex regulatory mechanisms of breathing. Thus, the importance of any factor regulating respiration may vary according to the interference of other factors acting directly or reflexly on the respiratory center. As stated a long time ago by Haldane and Priestley (100), "the evaluation of each factor in the regulation of breathing depends on its varying relation to the others".

The question arises as to the extent to which the "chemoreflex mechanism" of regulation of respiration brings about a modification of the "reaction theory" of the regulation of breathing. This problem has been examined recently principally by Hesser (106) and Winterstein (257).

Heymans *et al.* (122) showed that acidity stimulates the chemoreceptors, while alkalinity acts in the opposite way. Euler *et al.* (76) presented evidence that the factor exciting the chemoreceptors during oxygen want and CO_2 excess is the cH within the chemoreceptive cells themselves. Winterstein (257), after summarizing the results of the investigations performed by different authors, proposes the following picture of the chemical regulation of respiration: the activity of the respiratory center goes entirely parallel with the reaction of the blood, and, as far as hematogenic regulation of breathing is concerned, agrees completely with the "reaction theory". The effect of lack of oxygen is entirely reflex by way of the chemoreceptors, whose activity—again in complete agreement with the "reaction theory"—depends on the intracellular hydrogen-ion concentration in the glomi (chemoreceptive cells). The chemoreceptive regulation of respiration in hypoxia leads to an increase in the alkalinity of the blood because of the induced hyperpnea. This increase in alkalinity reduces the oxygen tension of the blood for the same oxygen saturation, and thus increases again the intracellular cH in the glomi (chemoreceptive cells) and consequently reinforces the hyperpnea by chemoreflex drive. The sensitivity of the respiratory center and of the chemoreceptors to any variation in cH may therefore explain the changes in respiration induced by CO_2 and by hypoxemia.

In the opinion of Hesser (106), the experimental evidence speaks in favor of the "intracentral acidity theory" for the chemical stimulation of the center itself. The peripheral chemoreceptors probably respond more rapidly than do the central chemosensitive cells (respiratory center) to changes in arterial cH. Experiments of Åstrom (16) and Åstrand (14, 15) showed that the stimulation of respiration by CO_2 is dependent upon the degree of O_2 saturation. The stimulating effect of O_2 deficiency, elicited entirely via the chemoreceptors, is dependent upon the prevailing arterial cH. The possibility of a specific action of CO_2

on the chemoreceptors and on the respiratory center, apart from the action by the cH, is, however, still open for discussion (197).

Experiments of Heymans *et al.* (125), and Bjurstedt and Euler (26) showed that stimulation of the carotid body chemoreceptors by CO_2, or oxygen want, also induces a reflex tachycardia and rise of blood pressure. Schmidt and Comroe (223), in experiments in dogs, noted that bradycardia may ensue upon powerful stimulation of the carotid body chemoreceptors. Landgren and Neil (170) observed in cats that local carotid chemoreceptor stimulation causes reflex tachycardia and hypertension. Comroe (51) compared the circulatory responses to anoxia in cats and dogs before and after exclusion of the chemoreceptors of the carotid and aortic bodies. In the dog, most of the rise of arterial blood pressure caused by anoxia seemed to be due to stimulation of the aortic chemoreceptors. In the cat, the carotid body appeared to contribute a more equal share to the chemoreflex vasomotor responses. Bernthal *et al.* have made a series of carefully controlled experiments on the chemoreflex vasomotor response (23, 24, 253). The carotid body was separately perfused and the animals were maintained under constant artificial respiration. The experiments showed that the substitution, in the carotid body perfusion, of blood equilibrated with 15 per cent O_2 in N_2 for blood equilibrated with room air, caused definite vasomotor responses. Bernthal's experiments also demonstrated clearly that efferent vasomotor activity is increased by reflex chemoreceptor stimulation. The effect of carotid occlusion is reinforced by hypoxia (74). Experiments of Mertens (187), Gellhorn and Lambert (84), and Bouckaert *et al.* (32, 33, 34) showed that, after exclusion of aortic and carotid body chemoreceptors, anoxia no longer induces hyperpnea and hypertension, but inhibits respiration and causes a fall in blood pressure. Andersson *et al.* (8), and Kenney and Neil (156) found that the Mayer blood pressure waves are related to periodic activity of the chemoreceptors.

B. Pharmacological Actions on Carotid Body Chemoreceptors

Experiments of J. F. and C. Heymans (146) showed that nicotine stimulates receptors located in the aortic arch area and thereby causes reflex excitation of the respiratory center. These observations made it highly desirable to investigate whether or not the carotid sinus area could also be influenced by the chemical composition of the blood and by drugs. Experiments carried out by Heymans *et al.* (122, 123, 124) proved this to be the case. They showed that cyanides, sulfides, lobeline, and nicotine stimulate respiration by way of carotid sinus reflexes. They localized this chemical stimulation to receptors in the carotid body. The same conclusion was reached by Heymans *et al.* (123) with regard to the action of nitrites and by Zunz and Tremonti (263, 264) with regard to sparteine, coramine (nikethamide) and metrazol (pentylenetetrazol).

These observations have been confirmed (7, 76, 87) for cyanide, lobeline and nicotine. Acetylcholine was found to be an effective chemoreceptor stimulant by Heymans *et al.* (126) and this has been confirmed by others (19, 71, 209, 223, 227). A large number of other substances have since been reported to be capable of stimulating the chemoreceptors, such as ammonium chloride (258), tri-

methylamine, potassium chloride (71) α- and β-nicotine (121), isolobinine (205), anabasine, coniine, cytisine (9), and other nicotinic drugs (9, 186, 223), acetaldehyde, and a series of compounds related to choline (59, 209, 223, 226).

De Wispelaere (259, 260) reported stimulation of the chemoreceptors by the acetyl ester and the ethyl ether of β-methylcholine, which Philippot (209), and Schmidt and Comroe (223) found to be ineffective. Succinylcholine is a very potent stimulant of carotid body chemoreceptors, although it blocks skeletal neuromuscular transmission (67). Gernandt (86) reported stimulation of chemoreceptors by piperidine, Philippot and Dallemagne (210, 211) by monophenol ether of homo-iso-muscarine and acetylsalicylamides.

Stimulation of the carotid body chemoreceptors by the alkaloids of veratrum has been reported by a number of authors (20, 48, 143, 150, 151, 152, 163, 185, 216, 261).

Jarisch *et al.* (150) found that sodium citrate, adenosinetriphosphate and dinitrophenol increase the carotid body chemoreceptor discharge. Landgren *et al.* (169) observed that caffeine, theobromine and theophylline produced a moderate increase in the activity of the chemoreceptors; histamine did not influence them. Ethyl alcohol, ether and chloroform also increase the action potentials of the carotid body chemoreceptors. Dawes *et al.* (61) reported that phenyldiguanide stimulates carotid body chemoreceptors in dogs. Heymans *et al.* (137) did not confirm this observation.

Verbeke and de Vleeschhouwer (238) showed that iodomethylate of dimethylaminomethylenedioxypropane stimulates the carotid body chemoreceptors and thus causes a reflex rise of blood pressure. Ethyltrimethylammoniumpropane (206) and trimethylammonium (64) induce respiratory stimulation by way of the chemoreceptors.

According to Douglas and Toh (69), hydroxytryptamine induces hyperpnea by stimulation of carotid body chemoreceptors. Heymans and van den Heuvel-Heymans (135) could not confirm this observation.

Dallemagne and Philippot (54, 55) observed chemoreceptive stimulation by several new choline and alkyltrimethylammonium derivates. Van Damme (56) found stimulation of chemoreceptors in sheep by several drugs. Experiments of Nims *et al.* (198) showed that papaverine stimulates respiration in cats and dogs through carotid and aortic chemoreceptors, rather than by a direct action on the respiratory center.

A large number of experiments have been performed in an effort to elucidate the mechanism of action of various agents on the chemoreceptors. The problem of transmission at the chemoreceptors has been reviewed recently by Liljestrand (177), de Burgh Daly (39), and Douglas (68).

Experiments of Heymans *et al.* (122) showed that acidity stimulates, while alkalinity inhibits, carotid body chemoreceptor activity. Intravenous injection of a small dose of ammonia or sodium bicarbonate led to a sudden temporary disappearance of the action potentials of the carotid body chemoreceptor fibers set up by oxygen want or carbon dioxide (76). These observations suggest that both kinds of stimuli act by increasing the cH in the chemoreceptors.

Since stimulation of the chemoreceptors by anoxia was abolished by monoiodo- and monobromoacetic acid, Winder (251) and Anitschkov (10, 11) concluded that the metabolic products of the glycolytic process, and, in particular, lactic acid, play a prominent role in the physiological mechanism regulating the activity of the chemoreceptors.

Anitschkov (10, 11) found that the chemoreceptors of the carotid body did not react to cyanide, or to acetylcholine, after local application of monoiodoacetic acid. Adenosinetriphosphate applied to the chemoreceptors increased their sensitivity. A marked increase of chemoreceptor activity after this drug was observed also by Jarisch *et al.* (150).

Landgren *et al.* (169) showed that the intracarotid injection of 2 mg sodium iodoacetate in cats was followed by greatly increased activity of the chemoreceptors of the carotid body, whereas injection of 10 mg quickly resulted in paralysis. Anitschkov (11) observed that perfusion of the carotid body with iodoacetate, fluoride, arsenite, malonate, or with a solution poor in glucose, lowered the excitability of the carotid body chemoreceptors. Excitability also fell after prolonged perfusion with adenosinetriphosphate. Prolonged perfusion with KCN made the chemoreceptors insensitive to CN or to acetylcholine. When adenosinetriphosphate was added, the excitability was reestablished. The hypothesis was therefore developed that excitation of the carotid body chemoreceptors depends on normal carbohydrate metabolism.

Bernthal and Weeks (24) showed chemoreceptor stimulation to be dependent on the rate of metabolism of the chemoreceptor cells by varying the temperature of the blood perfusing the carotid body. Shen and Hauss (230, 231) demonstrated that the increase of local metabolism of carotid body tissues produced by dinitrophenol and dinitrocresol caused marked excitation of the chemoreceptor cells. Gernandt (86) and Euler *et al.* (76) found that increased blood flow through the chemoreceptor tissues led to a disappearance of chemoreceptor discharge. Conversely, Euler and Liljestrand (72) and Winder *et al.* (253) showed that ischemia of the carotid body caused progressive excitation of the chemoreceptors. Neil (196) therefore proposed the following picture of chemoreceptor activity: the carotid body cells may be considered to produce some anaerobic metabolites even when supplied with blood of normal oxygen tension. The majority of such metabolites are removed by the blood flowing through the glomus tissue, leaving only a low concentration which causes the mild chemoreceptor firing clearly demonstrated by Euler *et al.* (76) in animals slightly overventilated with room air. Increased chemoreceptor discharge in hypoxic conditions may be elicited in two ways, by reduction of the blood flow through the glomus tissue (*e.g.*, hemorrhage), and by reduction of the oxygen tension of the arterial blood supplying the glomus cells (anoxic anoxia).

Though there can be no doubt about the importance of intracellular acidity of the carotid body for the response of chemoreceptors to physiological stimuli, other observations clearly demonstrate that this cannot be the only determining factor.

Cyanide induces a marked increase of the action potentials of the carotid

body nerve (76, 219). In this case pure oxygen inhalation or injection of ammonia could counteract the cyanide, supporting the view that cyanides interfere with oxidation processes in the carotid body. The action potentials of the chemoreceptor nerves elicited by lobeline or nicotine, on the other hand, were not abolished by moderate doses of ammonia. It was therefore concluded that these drugs act on the carotid body receptors centrally to the point of stimulation by oxygen lack, carbon dioxide excess, or cyanide.

The possibility that drugs, or changes in the blood which stimulate the chemoreceptors, produce their effects by liberation of acetylcholine as the chemical transmitter was first emphasized by Schweitzer and Wright (227), after it had been observed (126) that acetylcholine is able to stimulate the chemoreceptors. Meyling (189), Goormaghtigh and Pannier (94) and Christie (49) pointed out that the carotid body contains glandular structures which might liberate acetylcholine. de Castro (47), however, presented evidence that the sensitive nerve endings in the carotid body terminate in the cytoplasm of the epitheloid cells. These cells are believed to be sensitive to chemical changes occurring in the irrigating blood and to stimulate the intracellular nerve endings by modifying the metabolic activity of their cytoplasm.

From the pharmacological point of view, there is the striking fact that substances like acetylcholine, nicotine, and lobeline strongly stimulate both the ganglionic cells of the autonomic ganglia and the chemoreceptors of the carotid body. This fact suggested that the glomus cells and the nerve endings of the carotid body are reacting as functional synapses (77, 162).

Schweitzer and Wright (227) showed that prostigmine has an initial stimulatory action on breathing, mainly produced reflexly from the chemoreceptors, and that chemoreceptor stimulation by acetylcholine is intensified by previous injection of anticholinesterases such as eserine or prostigmine. If these actions on the chemoreceptors are due to the anticholinesterase properties of the drugs, it would suggest that acetylcholine may normally be formed at these nerve endings and possibly serve as a normal stimulant.

Heymans *et al.* (127) and Heymans and Pannier (140) also showed that close intra-arterial injection of eserine to the carotid body enhances the sensitivity of the chemoreceptors to acetylcholine but not to lobeline.

Verbeke (236, 237) observed that diisopropylfluorophosphate and tetraethylpyrophosphate sensitize the carotid body chemoreceptors to acetylcholine but not to potassium cyanide. Heymans *et al.* (141), Verbeke (237), Verbeke and Votava (239) observed a marked increase of respiratory stimulation by acetylcholine after administration of hexaethylpyrophosphate, tetraethylpyrophosphate and dimethylcarbamate of hydroxyphenyltrimethylammonium (Nu-683). Lauryldimethylaminoethanol suppresses the effects of diisopropylfluorophosphate and nicotine (107). Atanackovic (17, 18) showed that tetramethoquinemethiodide, an anticholinesterase drug, markedly sensitizes the carotid body chemoreceptors to acetylcholine but not to nicotine, lobeline, sodium sulfide or potassium cyanide. Casier and de Vleeschhouwer (42) stated that chlorophenylmethylcarbamate of hydroxyphenyltrimethylammonium inhibits

selectively, and completely, the pseudo-cholinesterase of blood serum of dogs but has no influence upon the true-cholinesterase. This drug induces, however, marked cholinergic symptoms and sensitization of chemoreceptors to acetylcholine.

It was shown by Kaindl and Werner (155), and Landgren *et al.* (167) that in cats both local application and intravenous injection of eserine, neostigmine, diisopropylfluorophosphate and tetraethylpyrophosphate lead to increased action potentials in the carotid body chemoreceptive fibers. Liljestrand (174, 175, 177) found that local application of eserine salicylate to the carotid bodies led to an increased respiratory response to oxygen deficiency and carbon dioxide accumulation.

According to Landgren *et al.* (167), the chemoreceptor nerve impulse activity during breathing of oxygen or air may be enhanced by close intra-arterial injection of different drugs that inhibit cholinesterases, and the effect of oxygen want on the chemoreceptive nerve potentials may also be greatly increased. Substances like atropine, curarine, tetramethylammonium, and decamethonium which antagonize acetylcholine were found to decrease, or to abolish, the response of chemoreceptors elicited by oxygen want. These results also suggested that acetylcholine plays a role as a transmitter of impulses in the carotid body.

Douglas (68) observed that tetraethylpyrophosphate (TEPP) injected or perfused in the carotid body region failed to produce any definite effect on the normal physiologic response to oxygen lack, although the response to injected acetylcholine was greatly intensified.

According to Caldeyro and Garcia Austt (41), Mazzella and Migliaro (183), Fernandez (81) and Atanackovic and Dalgaard-Mikkelsen (19), dimethylcarbamate of hydroxyphenyltrimethylammonium, a potent anticholinesterase, sensitizes the chemoreceptors to acetylcholine, but does not increase the respiratory response of the chemoreceptors to sodium sulfide.

Experiments of Heymans *et al.* (132) showed that local application of eserine on the carotid bodies increases markedly the sensitivity of the chemoreceptors towards acetylcholine, but does not induce respiratory stimulation. The sensitivity of the chemoreceptors to lobeline and to potassium cyanide may be slightly increased by eserine. Local application of neostigmine to the carotid bodies induces a moderate respiratory stimulation, increases markedly the sensitivity of the chemoreceptors to acetylcholine and may increase slightly the sensitivity of the chemoreceptors to lobeline.

Schweitzer and Wright (227), Euler *et al.* (76, 77), Schmidt and Comroe (223) and Heymans *et al.* (132) did not observe a significant difference in the respiratory response to acetylcholine after massive intravenous doses of atropine. Liljestrand (177) showed that local application of a one per cent solution of atropine sulphate to the carotid sinus and bodies, but not the intravenous administration of this drug, leads to a pronounced decrease of the chemoreceptor sensitivity towards oxygen lack, carbon dioxide excess, lobeline, and acetylcholine. Anitschkov (10, 11) obtained a similar change in the response to acetylcholine. Experiments of Heymans *et al.* (132) showed that local carotid sinus

and carotid body application of large doses of atropine induces marked arterial hypertension. During this hypertensive phase, the usual respiratory responses to lobeline and acetylcholine are absent. These results may, however, be fully explained by the local anesthetic action of atropine. If acetylcholine or lobeline is administered following the local application of small amounts of atropine to the carotid bodies, normal respiratory responses are obtained.

Floyd and Neil (82) showed that increased sympathetic activity led to an increase in the chemoreceptor discharge of the carotid body. By making direct measurements of carotid body blood flow, de Burgh Daly *et al.* (40) found that stimulation of the cervical sympathetic nerve caused, by local vasoconstriction, a reduction in the carotid body flow of sufficient magnitude as to possibly lead to local anoxemia. de Burgh Daly (39) raised the question of whether or not drugs, injected into the common carotid artery and reaching the superior cervical ganglion, may not induce the increased chemoreceptor discharge by a potentiation of the sympathetic nervous effects through an action on the ganglion rather than by a direct action on the carotid body. This potential mechanism has thus far not been ruled out.

According to Hollinshead and Sawyer (148), the carotid body contains nonspecific, as well as specific, cholinesterase, the former being present in larger amounts than the latter. Using histochemical methods, Koelle (159) arrived at the same conclusion, and pointed out that the presence not only of the specific but also of the nonspecific cholinesterase indicates some important function. It must be admitted that, as yet, a release of acetylcholine from the active carotid body has not been definitely proved, and the possibility cannot be excluded that the transmitter substance consists of some unknown choline ester with a general behavior and action similar to those of acetylcholine. This would harmonize well with the relatively large amounts of nonspecific cholinesterase in the carotid body.

We fully agree with Daly's (39) statement and conclusion that the evidence, at present available, favoring the view that acetylcholine plays a role in the transmission of nervous effects in chemoreceptors of the carotid body is still equivocal.

Experimental observations with ganglionic blocking drugs also suggested that the glomus cells of the chemoreceptors and their nerve endings might correspond to functional synapses. Moe *et al.* (189a) stated, indeed, that continuous intravenous infusion of tetraethylammonium in dogs inhibits the respiratory chemoreceptor stimulation induced by acetylcholine, nicotine, and lobeline, but not that caused by anoxia, or by potassium cyanide. However, Boelaert (28) obtained negative results with intravenous injections of large amounts of tetraethylammonium.

On the other hand, Douglas (67), experimenting in cats, described varying degrees of inhibition of the chemoreceptor stimulation, induced by acetylcholine, lobeline, and nicotine, after intravenous administration of high doses of hexamethonium. No inhibition of the respiratory chemoreceptive stimulation induced

by oxygen lack or potassium cyanide was seen. Douglas concludes that his observations do not fit the hypothesis that acetylcholine stimulates chemoreceptors by acting at some synaptic site of the afferent pathway from the oxygen-sensitive elements.

Landgren *et al.* (167) reported that very high doses of tetraethylammonium or decamethonium, injected locally into the carotid body region, decrease or abolish the chemosensory response to lobeline and acetylcholine, as well as to oxygen want, the effect being considerably less pronounced against the latter.

Experiments of Heymans *et al.* (132) in dogs showed that intravenous injections of large doses of tetraethylammonium, hexamethonium, methantheline (banthine), or pendiomid[1] do not affect significantly the respiratory responses induced by stimulation of chemoreceptors by acetylcholine, lobeline or potassium cyanide. Local application of these ganglionic blocking drugs on the carotid bodies also does not affect significantly the sensitivity of the chemoreceptors towards acetylcholine, lobeline or potassium cyanide.

According to Dontas and Nickerson (66), tetraethylammonium, hexamethonium and pendiomide depress spontaneous chemoreceptor action potentials. Responses to acetylcholine or lobeline were delayed in onset, and were smaller and shorter, or completely abolished, following administration of the blocking agent through the carotid artery, while chemoreceptor responses to anoxia or to potassium chloride were unaffected, except by very large doses of the blocking agents. In appropriate doses, quaternary, and, to a lesser degree, tertiary ganglionic blocking agents increase chemoreceptor activity.

The effect of deca-, hexa- and pentamethonium on the carotid chemoreceptors was also investigated in cats by Gollwitzer-Meier and Witzleb (92). The drugs were injected directly into the carotid artery. Decamethonium in small doses had no effect on the chemoreceptor potentials. In large doses there was a secondary effect from respiratory paralysis. Pentamethonium inhibited the action potentials even during anoxia or after a preliminary injection of lobeline or acetylcholine.

The question arises whether or not these drugs, apart from their ganglion-blocking effect, have other pharmacological properties and act on nerve endings, or nerve fibers, when injected locally in large doses. Could not the reaction of the solutions and the bromide or iodide ion of the salts used in the experiments also play a role in the pharmacological actions of these drugs? These possibilities would have to be ruled out.

Landgren *et al.* (167) have likened the carotid body mechanism to the autonomic ganglion, largely on the grounds that acetylcholine and other related carotid body stimulants are ganglion excitants and that, according to their observations, chemoreceptor stimulation may be suppressed by ganglionic blocking drugs. However, as stated by Douglas (68), evidence has been presented that acetylcholine and similar substances may stimulate afferent nerve endings

[1] N,N,N′,N′-3-Pentamethyl-N,N′-diethyl-3-azopentane-1,5-diammonium dibromide.

where there is no question of there being ganglia or synapses, and that ganglionic blocking agents at least do not suppress the chemoreceptor stimulation induced by all physiological and pharmacological excitants. In answer to the question of whether or not there is chemical transmission at chemoreceptors, Douglas (68) states: "It seems rather, that a better hypothesis to explain the actions of acetylcholine and hexamethonium and related drugs is this: that the carotid body afferents, in addition to being responsive to oxygen lack, possess a sensitivity to acetylcholine and similar drugs which is altogether independent of normal transmission mechanisms. The argument that acetylcholine is involved in chemosensory transmission appears to stand but poorly at present. . . ." The hypothesis that the glomus cells and the nerve endings of the carotid body are reacting as functional synapses thus lacks a secure foundation and requires more convincing evidence.

Acetylcholine is not the only substance that has been considered as a chemical transmitter in the carotid body. According to Fabinyi and Szebehelyi (80), increase of respiration after inhalation of 10 per cent oxygen may be prevented by cholesterol, by antistine (antazoline)[2] or by desensitization to histamine. These observations suggested that histamine might be concerned with the stimulation of the chemoreceptors by oxygen want. This could not be confirmed by Å. Liljestrand (173). Intravenous injection of lergitine,[3] an antihistaminic drug, in doses that suppressed the blood pressure action of moderate doses of histamine in the cat, did indeed not diminish the respiratory response to oxygen lack. Landgren *et al.* (169) observed that histamine given by intracarotid injection in small doses did not influence the chemoreceptor activity and that antihistamines did not abolish the chemoreceptive potentials elicited by oxygen lack. Large amounts of lergitine suppressed the chemoreceptive potentials, probably as the result of a local anesthetic effect of the drug injected into the carotid artery.

Potassium ion in small doses stimulates the chemoreceptors but, if the small doses are repeated frequently, or if large doses are administered, depression or paralysis of the chemoreceptors occurs (71). Hauss and Shen (102) also observed chemoreceptive stimulation with potassium ion. It seems probable that we are dealing here with a non-selective action of potassium ion, rather than with a specific stimulation.

II. ACTION OF DRUGS ON CAROTID SINUS PRESSORECEPTORS

It is well known that the aortic and carotid sinus nerves are not only the means of the reflex blood pressure regulation, but are also the reflex buffer or moderator nerves of the systemic arterial pressure. This reflex regulation of blood pressure occurs by the action of arterial pressure itself on receptors located in the vascular wall of the sino-aortic areas (78, 79, 105, 108, 109, 112, 128, 157).

Experiments of Koch (157), Heymans *et al.* (128) and Hauss *et al.* (101) showed that arterial pressure does not act directly on the sino-aortic receptors,

[2] 2-(N-Benzylanilinomethyl)-2-imidazoline.

[3] N-Benzyl-N,N′-dimethyl-N-phenylethylene diamine.

but indirectly by stretching the wall of the arteries where the sino-aortic receptors are located. These experimental observations suggested that the state of contraction, tension and distensibility of the arterial wall of the sino-aortic areas could play a role in the mechanisms of reflex regulation and homeostasis of arterial pressure. For this purpose, drugs known, or supposed, to contract or relax the arterial wall were applied locally to the carotid sinus and aortic pressoreceptive areas.

Heymans *et al.* (128) and others (190, 191) showed that adrenaline lowers the threshold of the carotid sinus pressoreceptors; and Palme (201, 203) observed that local application of adrenaline to the carotid sinus areas of the rabbit, hare, and dog provokes a reflex fall of the systemic blood pressure. The latter attributed this action of adrenaline to a direct stimulation of the pressoreceptors by the drug. Meurer (187a) also observed that local application of adrenaline on the carotid sinus of man induces a reflex fall of the systemic arterial pressure. He attributed this action of adrenaline to a stimulation of the chemoreceptors.

Adrenaline, noradrenaline, diacetyladrenaline thiosulfonic acid, synephrine, ephedrine, hydroxyphenylaminopropanol, hydroxytryptamine, or vasopressin, applied locally to the carotid sinus, provoke a marked reflex fall of the systemic arterial pressure and a reduction, or suppression, of the hypertensive reflexes, normally provoked by decrease of intracarotid sinus pressure (114, 115, 117, 129–131, 133–136, 139, 142, 144, 184). These phenomena, induced by local application of the drugs on the arterial walls of the carotid sinus, are due to stimulation of the carotid sinus pressoreceptors. Indeed, section of the carotid sinus nerves, when the systemic arterial pressure has been lowered by local carotid sinus application of the drugs, provokes an immediate and marked rise of the systemic arterial pressure.

The local carotid sinus action of adrenaline and noradrenaline may be suppressed, or reversed, by the local application of an adrenolytic drug such as N-(2-bromoethyl)-N-ethyl-1-naphtalenemethylamine hydrobromide, dibenamine, dihydroergotamine, hydergin,[4] or regitine (phentolamine)[5] (62, 115, 131, 133, 145, 182). de Vleeschhouwer *et al.* (242) showed that local application of adrenaline, or noradrenaline, to the aortic pressoreceptive area also provokes a reflex fall of the systemic arterial pressure.

Drugs such as papaverine and priscoline,[6] known to relax smooth muscles, applied locally to the wall of the arteries of the carotid sinus, induce a reflex rise of the systemic arterial pressure (133, 134).

Experiments of Heymans and Delaunois (129, 130) demonstrated that adrenaline and noradrenaline, acting on the isolated carotid sinus preparation of dogs, induce a contraction of the carotid sinus arterial wall, an increase of the response to a rise in pressure and a decrease in distensibility, while priscoline has the opposite effects. From these experimental observations, it has been concluded

[4] Mixture of equal parts of methane sulfonate derivatives of dihydroergocornine, dihydroergocristine and dihydroergocryptine.

[5] 2-{[-(m-Hydroxyphenyl)p-toluidino]methyl}-2-imidazoline.

[6] 2-Benzyl-4,5-imidazoline hydrochloride.

by Heymans and his coworkers that drugs contracting the arterial wall of the carotid sinus, increasing its intrinsic tension, and decreasing its distensibility, cause a stimulation of the pressoreceptors. This stimulation induces reflexly a fall in the systemic arterial pressure and decreases, or suppresses, the hypertensive reflexes normally provoked by decreasing the pressure in the carotid sinus. Drugs relaxing the arterial wall of the carotid sinus and increasing its distensibility, decrease the stimulation of the pressoreceptors and thus induce a reflex rise of the systemic arterial pressure. These findings demonstrated the fundamental role of the biologic condition and, particularly, of the distensibility and resistance to stretch of the sino-aortic wall in the reflex regulation and homeostasis of arterial pressure.

Landgren *et al.* (171) confirmed these observations in cats with adrenaline, noradrenaline, and vasopressin, and, in addition, showed that local carotid sinus application of these drugs elicits a very marked increase of the impulse traffic of the pressoreceptor nerve. Sodium nitrite, applied locally to the carotid sinus areas, causes, on the contrary, a marked reduction of the pressoreceptor fiber activity. The local carotid sinus action of papaverine and priscoline was attributed to their local anesthetic action.

Landgren (165, 166) concluded from his experiments on the isolated carotid sinus preparation of cats, that local application of adrenaline causes a contraction and a decrease of distensibility of the carotid sinus wall at low intrasinusal pressures, but an increase of distensibility in the range of physiologic intrasinusal pressures. Experiments of Heymans *et al.* (131) in dogs showed, however, that the same reactions induced by local carotid sinus application of noradrenaline occur *in vivo* at different physiologic, or nonphysiologic, intrasinusal pressure ranges. It was also demonstrated that adrenaline, or noradrenaline, applied locally to the isolated carotid sinus preparation of dogs, induces a contraction, an increase in the response to pressure and a decrease in the distensibility of the arterial wall of the carotid sinus at low, normal, or high internal pressure ranges. Priscoline has the opposite effects.

Experiments of Witzleb (262) further showed that local application of adrenaline, or noradrenaline, to the carotid sinus induces a prolonged increase of the action potentials of the pressoreceptor nerves, while the chemoreceptors are unaffected.

According to Palme (201) and Kezdi (156a) electrical stimulation of the sympathetic branch supplying the carotid sinus causes a fall of systemic arterial pressure. Floyd and Neil (82) obtained, however, little evidence that the activity in the sympathetic innervation influences the responsiveness of the carotid sinus pressoreceptive nerve endings.

Jewell (153), Wang *et al.* (243), and Chungeharoen *et al.* (50) emphasized the influence of the vascular communications between the blood vessels of the carotid sinus on the intrasinusal pressure and the pressoreceptors.

A strong increase of pressoreceptor nerve activity after adenosinetriphosphate was observed by Jarisch *et al.* (150).

Jarisch and Richter (151, 152), Aviado *et al.* (20), Alexander *et al.* (6), and

Richardson *et al.* (213) demonstrated the action of veratrum alkaloids on the reflexogenic area of the carotid bifurcation. According to Stutzman *et al.* (232), the carotid sinus and body mechanisms are not required for either the corporeal or the cephalic action of veratrum derivatives. Aviado *et al.* (20) stated that veratridine has effects upon the chemoreceptors but not upon the pressoreceptors of the carotid sinus region. Heymans and de Vleeschhouwer (143) showed that, in dogs, veratridine may induce a reflex stimulation of the cardioinhibitory and respiratory centers by way of the carotid body chemoreceptors. Swiss and Maison (234), however, could not demonstrate a participation of the carotid sinus receptor area in the mediation of the responses to veriloid (alkavervir)[7]. Gruhzit *et al.* (98) showed that the vasodepressive action of veriloid in dogs was abolished by section of the vagi and of the carotid sinus nerves, but not by either procedure alone. The investigators concluded that the drug sensitizes the carotid sinus and aortic pressoreceptors. Witzleb (261) showed that veratrine stimulates the carotid sinus pressoreceptors. High doses of veratrine, however, paralyze the pressoreceptors.

According to Jarisch *et al.* (150), intracarotid injection of veratrine is followed by increased activity of carotid sinus pressoreceptor nerve activity. Intravenous injection of even large doses of veratrine caused, however, no effect on pressoreceptor fiber activity. Kreuziger *et al.* (164) stated that anesthesia of the carotid sinus area with procaine prevents the fall of blood pressure normally induced by protoveratrine.

According to Wang *et al.* (244), veratrum alkaloids applied locally to the carotid bifurcation produce neither a systemic hypotension nor a marked reduction of the sinus pressure response. The hypotensive action of veriloid, protoveratrine, germitrine, neogermitrine and germerine in vagotomized animals is due largely to the stimulation of the carotid sinus receptors, while that of veratridine and veratramine is due largely to a reflex depression of the central vasomotor mechanism.

Maison *et al.* (179) and Dawes *et al.* (60, 61) also studied the relative hypotensive activity of certain veratrum alkaloids. According to Rothlin and Cerletti (216), protoveratrine stimulates the pressoreceptors and chemoreceptors of the carotid sinus area.

Moran *et al.* (192) showed that doses of andromedotoxin, an active principle from *Rhododendron maximum*, which produce a significant circulatory depressant effect in vagotomized dogs, exerted no depressor action after carotid sinus denervation. These experiments suggest that the extravagal hypotensive action of andromedotoxin is due to stimulation of the carotid sinuses and/or the carotid bodies, resulting in a reflex vasodilatation.

According to Landgren *et al.* (167), the large pressoreceptor spikes are not influenced by eserine, prostigmine, diisopropylfluorophosphate, tetraethylpyrophosphate, ergotamine, morphine and sodium fluoride in the concentrations used in their experiments. Liljestrand (176), and Landgren *et al.* (168) showed that

[7] Mixture of ester alkaloids from *Veratrum viride*.

intracarotid injection of ethyl alcohol, certain higher alcohols, ether, or chloroform causes a temporary paralysis of pressoreceptors and a stimulation of chemoreceptors of the carotid sinus area.

Guruswami and Chenoweth (99) stated that local application to the carotid sinus area of sodium fluoroacetate induced first an apparent increase of the pressor response provoked by clamping the carotid arteries, but later the pressor response was gradually depressed, then abolished, and finally reversed. Glyceryl monoacetate, given intramuscularly, or applied locally to the carotid sinus, before or after sodium fluoroacetate, antagonized the effects of sodium fluoroacetate.

Experiments of Landgren *et al.* (172) showed that the pressoreceptors of the carotid sinus of the cat are sensitized to their adequate stimulus by low concentrations of acetylcholine, while larger amounts exert an inhibiting effect. Menthol exerts an inhibiting effect upon the pressoreceptors, occasionally followed by an increased sensitivity to the stimulus. Succinylcholine strongly stimulates the pressoreceptors (167).

Dontas (65) also investigated the effect of ganglionic blocking agents, potassium chloride, and sodium cyanide on carotid sinus pressoreceptor fiber activity and observed that tetraethylammonium increases the sensitivity of pressoreceptors innervated by both large and medium fibers. Hexamethonium has a similar, but much weaker, effect. Pentamethonium and pendiomid do not produce sensitization. Sodium cyanide, in small doses, and potassium chloride exert a stimulant action resulting in repetitive firing of large and medium fibers. Higher doses of sodium cyanide may depress pressoreceptor discharge.

Diamond (63) studied the effects of drugs on isolated perfused carotid sinus preparations of the cat and observed that acetylcholine, or nicotine, produced an increased firing of active pressoreceptors and a discharge of some whose threshold was above the perfusion pressure used. This activity was not affected by the presence of atropine in the perfusing fluid. Hexamethonium, or *d*-tubocurarine, prevented the response to acetylcholine or nicotine, but not that to potassium ion which still produced a discharge. The doses of hexamethonium and *d*-tubocurarine used had no effect on the discharge of pressoreceptors caused by pressure change.

Acetylcholine does not appear to be involved in the physiological stimulation of the carotid sinus pressoreceptors; rather, the experimental evidence suggests a pharmacological action.

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