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Baroreceptor function changed by breathing

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Summary. The efferent sympathetic activity (ESA) of the carotid nerve is related to breathing, and can be driven by stimulation of the latter, e.g. by airway occlusion. The ESA controls both carotid wall stiffness and the excitability of nervous receptor elements. Therefore, breathing is capable of changing the carotid baroreceptor function.

Events of efferent control alter the receptor function as was shown for different sense organs[2]. In contrast, receptors involved in visceral systems have not often been investigated to date. Receptors important for blood pressure regulation are generally formed as mechanoreceptors[3], i.e. the intravasal pressure as the adequate stimulus does not affect the nervous receptor elements directly, since the vessel wall is interposed as a stimulus transformer. Above all the blood pressure rise stretches the vessel wall and this in turn alters the geometrical arrangement of nervous receptor elements located in the outer part of vessel wall. The receptor elements respond in terms of a change in their membrane potential and, provided their critical threshold is exceeded, action potentials will be generated.

Therefore, baroreceptor function could be influenced by efferent control in 2 different ways:

a) By changing the vessel wall stiffness; in this case the transformation of the blood pressure into the utilized stimulus affecting the nervous receptor elements is shifted.

b) By changing the excitability of nervous receptor elements. In the latter case, the formation of receptor potential and/or action potentials is altered.

The efferent control of baroreceptors could be mediated by efferent sympathetic activity (ESA) that influences both the vessel wall stiffness[4] and the excitability of nervous receptor elements[5-7].

On the other hand, the ESA is altered by breathing, this fact being well-known and generally accepted. Consequently, it can be supposed that breathing is capable of changing the sensitivity of baroreceptors. In order to test this assumption, experiments were done using the carotid baroreceptors in dogs because this region is easily accessible. The carotid bifurcation is innervated by the efferent fibres of the carotid nerve (CN) sometimes called ganglioglomerular branch. These fibres are routed separately from the carotid sinus nerve (CSN) that leads the baroreceptor afferents to the brain stem. The CN originates in the sympathetic superior cervical ganglia and terminates with a larger part of its fibres directly in the carotid wall[8] forming a terminal network[9].

The quantity of ESA led by the CN is related to the respiration cycle[10]. The influence of breathing upon this quantity can be demonstrated distinctly by mechanical occlusion of the airway. During occlusion, the efferent activity increases simultaneously in both the phrenic nerve and the CN (figure 1).

The influence of the increased ESA induced by airway occlusion upon the wall stiffness in the carotid bifurcation

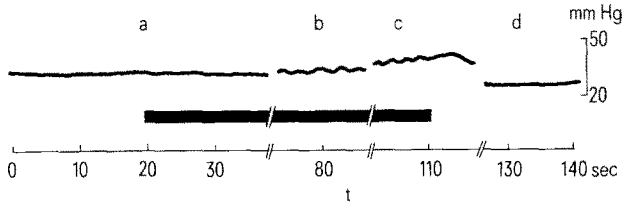

Fig. 2. Rise of perfusion pressure in an isolated carotid bifurcation caused by airway occlusion (line indicates occlusion period).

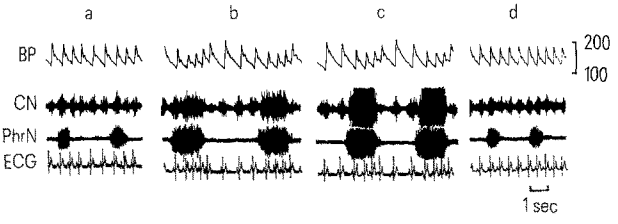

Fig. 1. Increasing efferent activity in both carotid nerve (CN) and phrenic nerve (PhrN) induced by airway occlusion. a and d: control before and after occlusion; b and c: 20 and 60 sec after starting occlusion, respectively; blood pressure (BP) was measured in a lingual artery.

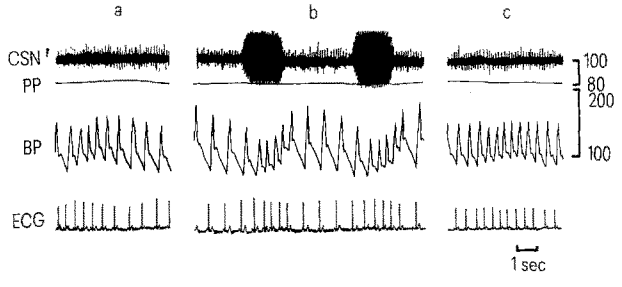

Fig. 3. Spontaneous burst of mass discharges in the neurogram of afferent carotid sinus nerve (CSN) during airway occlusion. The isolated carotid bifurcation was perfused constantly in order to keep the perfusion pressure (PP) at the same level. a and c: control before and after occlusion; c: 20 sec after starting occlusion; blood pressure (BP) was measured in the opposite lingual artery.

was tested in 6 animals. The carotid bifurcation concerned had been previously isolated and was perfused with arterial blood (45 ml/min) by means of a perfusion pump interposed in the common carotid artery. During airway occlusion for a 90-sec period, the perfusion pressure increased from 35±5 mm mercury to 42±5 mm mercury (mean±SE) significantly ($p < 0.01$). Figure 2 shows a typical example obtained in a single experiment. After a latency of about 15 or 20 sec, the pressure rise started and continued throughout the occlusion period.

In some animals, the neurogram of peripheral CSN was recorded under identical conditions. In these cases, the carotid bifurcation was perfused with a larger volume (90 ml/min) in order to make the intravasal pressure exceed the threshold as well as to keep the pressure consistent. Before and after airway occlusion, the afferent discharges of the CSN occurred spontaneously but less frequently (figure 3). In contrast, a few seconds after airway occlusion had started, bursts of mass discharges appeared with a tendency to become larger over the entire occlusion period. These bursts coincided with the periods of efferent activity in the neurogram of both the phrenic nerve and the CN. This fact can be seen by comparing figure 3 with figure 1, especially by comparison of the time related arrangement of these bursts with the simultaneous change in blood pressure and heart rate.

Consequently, breathing seems to be capable of influencing the baroreceptor function by

a) modulating the phasic quantity of ESA that is led to the carotid bifurcation and may make the nervous receptor elements subthreshold for each of these small time periods, and

b) modulating the tonic quantity of ESA that alters the vessel wall stiffness.

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Brominated benzene induction of hepatic porphyria[1]

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Summary. Unlike the highly porphyrinogenic fungicide hexachlorobenzene, hexabromobenzene was a poor inducer of porphyria. Similarly, 1,2-dibromobenzene and 1,2,4-tribromobenzene, while causing small increases in hepatic porphyrins, did not increase ALA synthetase or the urinary excretion of porphobilinogen (PBG), aminolevulinic acid (ALA) or porphyrins.

The porphyrinogenic effects of the fungicide hexachlorobenzene have been observed in a number of laboratory species[2-5] and in humans[6,7]. The less chlorinated benzenes cause much less porphyria[8,9]. Since brominated compounds are often times more active than the chlorinated analogs, it was important to investigate the effects of the fire retardant hexabromobenzene (HBB) on porphyrin synthesis. Mendoza et al.[10] found that in the male rat feeding of HBB at levels up to 160 ppm for 12 weeks did not result in porphyria although there was a non-significant tendency toward increased liver porphyrins. It was also of interest to examine the effects of 2 less halogenated benzenes, 1,4-dibromobenzene and 1,2,4-tribromobenzene. In the induction of xenobiotic metabolism these 2 compounds were more potent than the chlorinated analogs[11]. Dibromobenzene has been identified in drinking water in the United States[12].

Materials and methods. Groups of 5 female (known to be more susceptible than males to the porphyrinogenic effects of hexachlorobenzene[2,13]) Sprague-Dawley derived rats (Laboratory Supply, Indianapolis, IN) were administered 50, 100 or 200 mg/kg of 1,4-dibromobenzene, 1,2,4-tribromobenzene or hexabromobenzene in corn oil daily p.o. for 30, 60, 90 or 120 days. Controls received corn oil (1% v/w). Immediately after the last dose, the rats were placed in metabolism cages for the collection of 24 h urine samples. The animals were sacrificed, livers removed and portions prepared as 33⅓% homogenates in 0.9% NaCl containing 0.5 mM EDTA and 10 mM tris buffer pH 7.2. Samples were precipitated with 0.3 M trichloroacetic acid and centrifuged. Urine samples or liver supernatants were passed through 'piggy-back' ion exchange columns[14] and separations carried out[15] by washing with water and eluting the anionic column once with 2 ml of 1.0 N acetic acid and 2.0 ml of 0.2 N acetic acid for porphobilinogen (PBG) measurement[16]. The column was then washed with 8 ml of 1.5 N HCl and porphyrins measured fluorometrically (excitation at 400 nm and emission at 600 nm) with coproporphyrin as the standard. The cationic column was eluted with 7 ml of 1 M sodium acetate and delta-aminolevulinic acid (ALA) determined[14]. For the livers, only porphyrin content was measured. Portions of the liver homogenate were also used to measure ALA synthetase activity using the procedure of Marver et al.[17] as modified by Goldstein et al.[18] Comparisons among the dose levels were made using Duncan's new multiple range test[19].

Results and discussion. Despite the ability of hexachlorobenzene to increase the production and excretion of porphyrins many-fold[3-5,9], hexabromobenzene had very little effect (table 1). Even at a dose of 200 mg/kg daily for 120 days there was only a 42% increase in porphyrin content of the liver and no increased excretion in the urine. No increases were observed in ALA synthetase or the excretion of ALA or PBG in the urine.

1,4-Dibromobenzene also was not very porphyrinogenic (table 2). The highest increase in liver porphyrin content was approximately 2-fold. In this regard it was slightly more potent than the chlorine derivative[9]. If one considers the enlargement of the liver, the increase is amplified. There was no increase in the urinary excretion of porphyrins, PBG or ALA or in the hepatic synthesis of ALA.

The administration of 1,2,4-tribromobenzene caused a sig-