

Reflex chemoceptive excitation of diencephalic sham rage behavior¹

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BIZZI, E., A. LIBRETTI, A. MALLIANI, AND A. ZANCHETTI. *Reflex chemoceptive excitation of diencephalic sham rage behavior.* Am. J. Physiol. 200(5): 923-926. 1961.—In acute thalamic cats, excitation of the carotid body chemoceptors was induced by intranasal injection of lobeline (10 µg) or by administering low oxygen mixtures (5-12% O₂ in N₂). Bilateral section of the cervical vago-aortic trunks, preliminary to the experiment, permitted the exclusion of the aortic chemoceptive areas from our study. Stimulation of the carotid body chemoceptors was constantly capable of evoking sham rage outbursts identical in pattern and intensity to those induced by tactile or noxious stimulation or occurring spontaneously. When low-intensity stimulation was used (10-12% O₂) the rage fits were preceded in time by signs of excitation of the medullary respiratory and vasomotor centers. Since lobeline and hypoxia became unable to evoke sham rage outbursts following selective inactivation of the carotid body chemoceptors it is concluded that the diencephalic mechanisms for rage behavior are within the sphere of influence of chemoceptive reflexes.

METHODS

The experiments were carried out in 15 acute thalamic cats. Under ether anesthesia a blunt spatula was introduced through an adequate hole in the left aspect of the skull and a transection was performed, reaching the ventral surface of the brain at the prechiasmatic region (prechiasmatic decerebration). The brain frontal to the transection was subsequently removed by suction. Carotid sinus blind sacs were prepared on one or both sides, by carefully tying the external carotid, internal carotid, occipital and ascending pharyngeal arteries. The external carotid was tied distally to the origin of the lingual artery to permit cannulation of the proximal end of this vessel and introduction of lobeline or lycopodium into the blind sac. Whenever one blind sac only was prepared, the contralateral carotid sinus was denervated. Carotid body stimulation was effected by either of the following techniques: *a*) intranasal injection of minute amounts of lobeline (10 µg), or *b*) systemic hypoxia. The latter was obtained by connecting the tracheal cannula of the preparation to a large Douglas bag containing a low oxygen mixture (5-12% O₂ in N₂). Hypercapnia was avoided by placing a small soda lime container between cannula and bag. When selective inactivation of the chemoceptive sensitivity was required this was effected by injecting intranasally a minute amount of a lycopodium suspension through the central stump of the lingual artery (2). Bilateral section of the cervical vago-aortic nerves, performed at the beginning of the experiment, limited our study to the carotid body chemoceptors only.

The behavior of the acute thalamic animal during chemoceptive stimulation was carefully observed, and some of the autonomic and somatic phenomena characterizing sham rage were selected to be photographically recorded on a suitable multichannel apparatus (Battaglia-Rangoni, Multistylus Special). Arterial pressure was measured from a cannulated femoral artery by means of a Sanborn capacitance manometer, and respiration was transduced by a crystal capsule connected to the side arm of the tracheal cannula. Graphic evidence of the somatic discharges paralleling autonomic activity in sham rage outbursts was obtained by leading the

WE HAVE RECENTLY DEMONSTRATED that the diencephalic mechanisms responsible for the sham rage behavior of the decorticate animal are under a tonic inhibitory influence exerted by the pressoreceptive afferents from the carotid sinus and the aortic arch (1). Indeed, in the thalamic cat a transitory decrease in intranasal pressure is regularly followed by patterned outbursts of rage activity, while pressure increase within a carotid blind sac is capable of blocking, or at least reducing, frequency and intensity of the spontaneously occurring fits of sham rage. In the present paper evidence is given that a chemoceptive influence from the carotid body also plays on the diencephalic mechanisms for sham rage behavior. As for the medullary respiratory and vasomotor centers, this chemoceptive influence is opposite in sign to that exerted by the sinoaortic pressoreceptors, being excitatory in nature.

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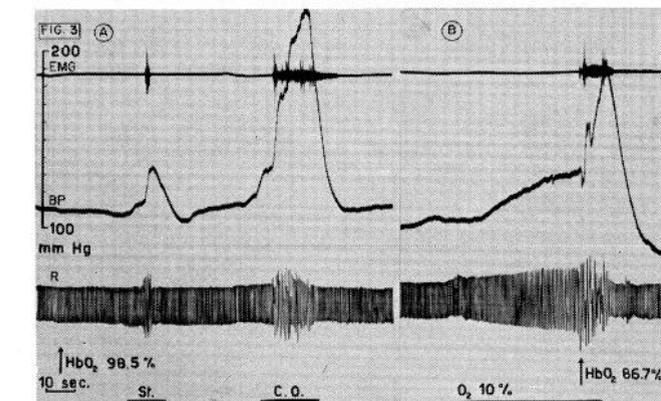
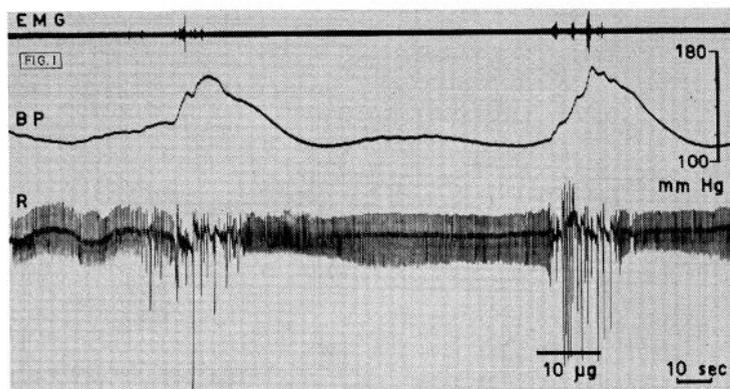


FIG. 1. Identity of sham rage patterns induced upon intrasinal lobeline injection and of those occurring spontaneously in the acute thalamic cat. Bilaterally vagotomized preparation. In this and in the following figures: EMG, electromyogram of triceps muscle of a forelimb; BP, blood pressure as recorded from a femoral

artery; R, respiration. Black bar indicates time of injection of $10 \mu\text{g}$ of lobeline into left carotid sinus blind sac.

When necessary, a blood sample was drawn anaerobically by means of an arterial puncture and was analyzed in a Van Slyke manometric apparatus. O_2 content and capacity were measured according to the techniques of Van Slyke and Neill (3) and of Sendroy (4).

RESULTS

Effects of intrasinal introduction of lobeline. When a minute amount of lobeline ($10 \mu\text{g}$ in 0.3 ml) was introduced into a carotid sinus blind sac during a period of quiet in the preparation, arterial pressure began to increase, breathing augmented in amplitude, pupils dilated, nictitating membranes became retracted, and soon, phasic struggling and clawing movements, lashing of the tail, and the facial expression of rage became apparent. Intrasinal lobeline injection evoked outbursts of activity which were by no means distinguishable from those either induced in the same preparation by any kind of somatic peripheral stimulation, or occurring spontaneously (Fig. 1). No such effect was ever obtained when a comparable amount of warm saline was introduced intrasinally through the same approach.

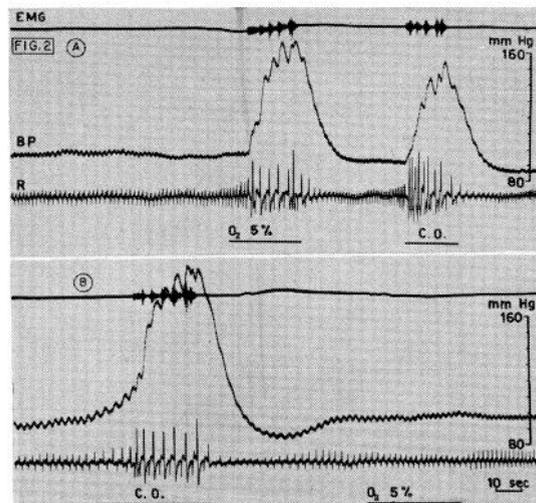


FIG. 2. Effects of systemic hypoxia in the acute thalamic cat. A: before and B: after selective chemoceptive inactivation. Bilaterally vagotomized preparation. Between A and B selective inactivation of the carotid body chemoceptors was performed by introducing a minute amount of a lycopodium suspension into both carotid sinus blind sacs. Note disappearance of rage fits induced by hypoxia (O_2 5%), but persistence of those induced by carotid occlusion (C.O.).

artery; R, respiration. Black bar indicates time of injection of $10 \mu\text{g}$ of lobeline into left carotid sinus blind sac.

FIG. 3. Threshold responsiveness of sham rage mechanisms to chemoceptive stimulation. Acute thalamic cat, bilaterally vagotomized. A: sham rage outbursts induced by twisting the pinna (St.) and by carotid occlusion (C.O.). B: ventilation with a 10% O_2 mixture (O_2 10%); respiration and blood pressure increase soon after beginning of hypoxic stimulation, while a sham rage outburst supervenes only when oxyhemoglobin saturation (HbO_2) falls from 98.5% to 86.7%.

Effects of systemic hypoxia: role of chemoceptive stimulation. When a decorticate animal, during a period of spontaneous quiescence, was made to breathe a low oxygen mixture, patterned outbursts of sham rage soon became evident (Fig. 2A). The latency between beginning of hypoxic ventilation and occurrence of rage fits was clearly dependent on oxygen concentration in the inspired gas (vide infra).

Fig. 2B demonstrates that the rage outbursts following hypoxic ventilation are evoked by stimulation of the carotid body chemoceptors (the aortic bodies being denervated in our preparations) rather than by cerebral hypoxia. Selective inactivation of chemoceptive sensitivity was obtained by embolization of the carotid bodies with a minute amount of a lycopodium suspension introduced into both carotid sinus blind sacs (2). Following this procedure, low oxygen breathing was unable to evoke any signs of somatic or autonomic discharge. On the contrary, a slight but definite decrease in respiration amplitude was observed; this was the only evidence of the direct depressing action of hypoxia on the brain (5). However, following selective inactivation of the carotid body chemoceptors, carotid occlusion, i.e., a transient interruption of the pressoreceptive inflow, could still evoke dramatic fits of sham rage (Fig. 2B). This confirms

our previous conclusion (1) that rage outbursts following decreased intrasinus pressure result from interruption of pressoreceptive discharges, independently of anoxic excitation of the chemoceptors.

Finally, it has been observed in a few control animals that the facial component of rage behavior could still be evoked by the hypoxic stimulus after a high spinal transection (C_1 , C_2), designed to prevent any sympathetic regulation of blood vessels and of adrenal secretion, and to require artificial ventilation of the lungs. This rules out the possibility that sham rage outbursts might be induced indirectly through the reflex hyperventilation or the changes in systemic circulation, rather than through a neural chemoceptive excitation of the diencephalic mechanisms of rage.

Threshold responsiveness of rage mechanisms to chemoceptive discharges. When very low oxygen mixtures (5–7% O_2 in N_2) were administered, the onset of the induced sham rage fit had a short latency, and all the autonomic and somatic phenomena making up the patterned response were seen almost simultaneously (Fig. 2A). However, this was not the case when a lesser degree of hypoxia was induced. Fig. 3B shows that when a 10% O_2 mixture was used the sham rage outburst had a more delayed onset, and was regularly preceded by a slowly progressive increase in blood pressure and amplitude of respiration, the response which is classically described in anesthetized or decerebrated preparations (5). In four animals, oxyhemoglobin saturation in arterial blood was measured immediately before administration of the hypoxic stimulus (10–12% O_2 in N_2), and again at the very moment when sham rage appeared. In the experiment reproduced in Fig. 3 arterial oxyhemoglobin saturation was found to have fallen from 98.5% (A) to 86.7% (B) at the beginning of the chemoceptively evoked fit of sham rage. In the remaining animals, the first appearance of rage outbursts following hypoxic stimulation occurred at saturation values ranging between 80% and 85%. As pointed out above, the respiratory response started soon after the administration of the stimulus, several seconds (20–60 sec) in advance of the patterned diencephalic reaction, showing that it had a lower threshold to chemoceptive firing.

DISCUSSION

A few conclusions can be drawn from the experiments reported above. It seems worth pointing out that impulses from visceral receptors have been found to rank among the multifarious sensory influences of different modality, viz. tactile, muscular, nociceptive, etc., coming from every part of the body periphery and known to drive the diencephalic structures regulating rage behavior. It is not without significance that the effect of visceral impulses can be strong enough to call these mechanisms into action, inducing rage outbursts that cannot be distinguished either in pattern or intensity from those evoked, for example, by tactile or noxious stimulation.

Some further implications of our results should be

emphasized. Evidence has recently accumulated suggesting that the sphere of influence of the chemoceptive afferents is not limited to the bulbopontine respiratory and circulatory centers, being spread to brain-stem mechanisms involved in the regulation of muscular tone and electrocortical activity (6, pp. 341, 342; 7–9). The results of our experiments fully agree with this opinion, and suggest that the sphere of action of the chemoceptive reflexes covers the diencephalic mechanisms for emotional behavior as well. If it is considered that sino-aortic pressoreceptors have been shown to exert an inhibitory influence, on descending and ascending reticular systems (6, pp. 285, 341), and, as we have recently demonstrated (1), on the diencephalic rage mechanisms as well, the findings here reported contribute to build up a broader pattern of opposing pressoreceptive and chemoceptive reflexes. The former appear to be inhibitory and the latter excitatory for a number of different neural mechanisms: the medullary respiratory and vasomotor centers, the descending reticular system facilitating postural tone and movement, the ascending reticular system for EEG arousal, and finally the diencephalic structures controlling sham rage behavior.

The question now arises as to whether the classical medullary effects of pressoreceptive or chemoceptive stimulation, such as are shown in decerebrate or anesthetized preparations, can still be considered as the main result of the homeostatic function of these reflexes; or if they represent only a component, and a rather peripheral one, of an over-all inhibitory or excitatory action exerted by these visceral receptors on behavioral performance.

Within this frame of thought, it seems important to evaluate the degree of responsiveness of higher nervous mechanisms to chemoceptive firing. It has been found in our experiments that following administration of a mild hypoxic stimulus the appearance of the patterned activity of rage is heralded by the progressive development of a respiratory and circulatory response, such as is observed in decerebrate or anesthetized preparations (Fig. 3B). It seems likely, therefore, that the bulbopontine respiratory and circulatory centers have a lower threshold to chemoceptive firing than the diencephalic mechanisms for rage. This same conclusion seems to hold for the pressoreceptive influence as well. Indeed, experiments published elsewhere (1) have shown that sometimes pressoreceptive stimuli can act on the pressor and respiratory components of a sham rage outburst though the patterned response is not appreciably modified.

The peculiar responsiveness of the medullary respiratory and circulatory centers to the afferent signals coming from both pressoreceptive and chemoceptors in the carotid sinuses and bodies is well consistent with the classical conception of regional homeostasis. Nevertheless, although their threshold may be higher, other neural mechanisms, endowed with more integrative functions and controlling definite behavioral patterns, are also within the sphere of influence of such reflexes. This does not seem meaningless for the body homeostasis. Indeed, in the intact animal, visceral and somatic changes occur only as integral parts of complex per-

formances and it might be significant that also those higher nervous mechanisms which are responsible for composite behavioral patterns be subjected to reflex control from visceral and somatic receptors.

A final comment seems in point here. It has recently been shown by Bonvallet, Audisio and Hugelin (10) that the electrocortical arousal following chemoceptive stimulation is accompanied by a short-lived increase followed by a lasting decrease in motor responsiveness, as already observed by Hugelin and Bonvallet (11) during arousal elicited by other kinds of stimuli. However, a lasting increase of the motor responses were observed after chemoceptive stimuli in animals with a diencephalic

transection. Our results in decorticate preparations are in full agreement with the findings of Bonvallet et al. (10), thus adding further support to the hypothesis (12) that decreased motor performance during electrocortical arousal would depend on mechanisms involving the cerebral cortex, or structures rostral to the diencephalon. It is suggestive to reason that those upper brain structures that have to be removed to release the hypothalamic sham rage mechanisms from the tonic descending inhibition may be identical with, or at least related to, those responsible for the restraining "corticifugal" influence on motor activity reported by Hugelin and Bonvallet (12).

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