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Carotid and cardiopulmonary chemoreceptor activity increases hippocampal theta rhythm in conscious rabbits

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Yu, Ying-Hui, and W. W. Blessing. Carotid and cardiopulmonary chemoreceptor activity increases hippocampal theta rhythm in conscious rabbits. *Am J Physiol Regulatory Integrative Comp Physiol* 278: R973–R979, 2000.—We have examined whether activation of carotid artery chemoreceptors causes alerting in conscious rabbits. Injection of phenylbiguanide (a 5-hydroxytryptamine$_3$-receptor agonist) into the common carotid artery of conscious rabbits increased the proportion of theta rhythm in the hippocampal EEG, commencing in the first 5-s epoch after the injection. Intravenous injection of phenylbiguanide also increased the proportion of theta rhythm in the hippocampal electroencephalogram (EEG), but the onset of the change was not until the second 5-s epoch following injection. Injection of Ringer solution, either into the common carotid artery or into the marginal ear vein, did not affect the hippocampal EEG. Results suggest that phenylbiguanide-mediated activation of carotid and cardiopulmonary chemoreceptor afferents alerts the animal, as assessed by induction of theta rhythm in the hippocampal EEG. This alerting response presumably reflects the action of neural inputs that enter the brain with the carotid sinus nerve at the level of the medulla oblongata.

electroencephalogram; arousal/orientation response; carotid body; carotid sinus nerve; sudden infant death syndrome; 5-hydroxytryptamine$_3$ receptors.

EFFECTS OF CAROTID CHEMORECEPTOR activation on cardiovascular and respiratory parameters are now reasonably understood (22). Less is known regarding the effects of peripheral chemoreceptor activation on arousal responses. An inadequate arousal response to such activation could underlie sudden infant death syndrome (SIDS) (7, 8, 12, 13, 19, 23). However, identification of brain stem pathways mediating the various effects initiated by peripheral chemoreceptors is confounded by direct effects of hypoxia and hypercapnia on the central nervous system. Because the neuroanatomical substrates of the relevant neural circuitry are still obscure, it is difficult to carry out hypothesis-driven postmortem neuropathological studies in SIDS patients (14). Direct stimulation of peripheral chemoreceptor afferents is more likely to prove useful in the identification of central pathways mediating their effects, because the direct links of these receptors with the medulla oblongata are now reasonably understood (5, 6).

Physiological indices of alerting/arousal responses include activation of the neocortical electroencephalogram (EEG) and the appearance of a regular slow activity in the hippocampal EEG (hippocampal theta rhythm). Effects of carotid chemoreceptor activation on alerting-related EEG parameters, including hippocampal theta rhythm, have not been adequately established in conscious animals. We have previously documented the occurrence of hippocampal theta rhythm in conscious rabbits alerted by stimuli in the external environment (29). In the present study, we first measured breathing indices in anesthetized rabbits to confirm that intracarotid administration of phenylbiguanide (PBG), a 5-hydroxytryptamine$_3$ (5HT$_3$)-receptor agonist, activates carotid arterial chemoreceptors, as has been demonstrated directly in rats (10, 26) and indirectly in rabbits (27). We have now determined in conscious rabbits the effects of intracarotid PBG on the hippocampal EEG and compared the results with the effects of intravenous injections.

METHODS

New Zealand White rabbits (2.5–3.5 kg), bred for laboratory use, were cared for in accordance with Flinders University Animal Welfare Committee guidelines.

We first established a model of intracarotid PBG injection in anesthetized rabbits, using respiratory parameters to monitor the effects of chemoreceptor stimulation. For these experiments, rabbits were anesthetized with thiopentone sodium (40 mg/kg iv) and intubated; anesthesia was maintained with 1–2% halothane in O_2 via endotracheal tube. We recorded arterial pressure from one femoral artery and assessed respiratory activity either by recording the phrenic nerve electrical discharge in the conventional manner or by measuring respiratory rate from the end-tidal CO_2 monitor (Datex, Helsinki, Finland) or with a spirometer (MacLab, ADInstruments Sydney). Signals were digitized (40-Hz sampling rate) with MacLab and displayed on an Apple Macintosh G3 computer using MacLab Chart Software.

A catheter was placed in the left common carotid artery with the distal end directed away from the heart and positioned about 1.5 cm proximal to the carotid bifurcation (Fig. 1). We employed either an “open carotid” preparation (*ligatures A* and *B* in Fig. 1 not tied) or a “blind-sac” preparation formed by ligating the external carotid artery just distal to the common carotid bifurcation and the internal carotid artery ~5 mm distal to the carotid sinus region (*ligatures A* and *B* in Fig. 1 tied). PBG (0.1–5 mg/ml in 0.2 ml Ringer) was injected into the common carotid artery in ~2 s. Effects on arterial pressure, heart rate, and respiration rate were

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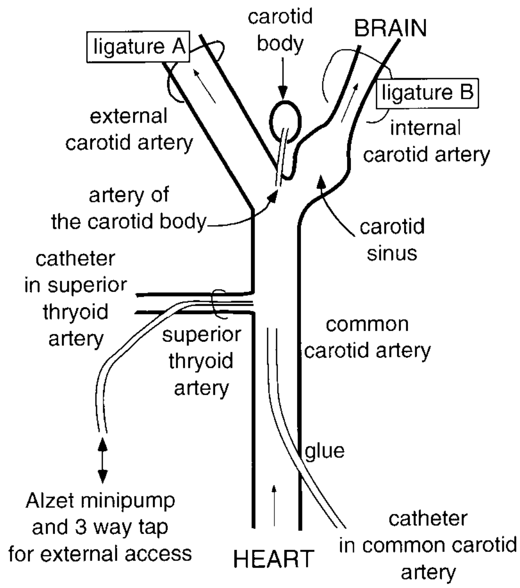

Fig. 1. Diagram explaining different methods of injecting phenylbiguanide (PBG) or Ringer vehicle into carotid chemoreceptor region. In anesthetized rabbits, catheter was introduced into common carotid artery and glued in position, with artery remaining patent. In open carotid situation, neither external carotid ligature (*ligature A* in Fig. 1) nor internal carotid ligature (*ligature B* in Fig. 1) was tightened. In blind-sac preparation, both these ligatures were tightened. In unanesthetized rabbits, PBG or vehicle was introduced via a catheter in superior thyroid artery with both external and internal carotid arteries patent.

determined. When rabbits with a blind-sac preparation recovered from anesthesia, some animals developed a contralateral hemiparesis (presumably from cerebral emboli arising from thrombosis on the brain side of the internal carotid ligation), so the animals were killed, and the blind-sac model was not used for EEG studies in the conscious animal. For these studies we used an open carotid system with a fine catheter in the superior thyroid artery (see below) to minimize the occurrence of cerebral emboli from thrombi forming on the intra-arterial catheter.

For EEG studies, bipolar stainless steel electrodes were inserted into the dorsal hippocampal region and stainless steel screws were implanted on frontal and parietal skull regions (29) with the animal anesthetized with thiopentone and halothane (as above). After surgery, halothane was discontinued and the endotracheal tube removed. Animals recovered from anesthesia and appeared to be in normal health. After 1 wk, again under general anaesthesia as described above, a fine polyvinyl catheter was inserted into the left superior thyroid artery and the lumen was positioned at the junction of this vessel with the common carotid artery. The proximal end of the catheter was connected to an osmotic pump (Alzet 2ML1, Alza Palo Alto, CA) positioned in a subcutaneous pouch, with access to the catheter distal to the osmotic pump via a three-way tubing connector (20 G, Small Parts, FL) also positioned subcutaneously. The free end of the catheter system was left protruding through the skin at the back of the neck with the open end sealed. The intracarotid line was kept patent by continuous infusion of heparinized Ringer solution (1,000 units/ml) from the osmotic pump. The rabbit recovered from anesthesia.

On the following day, the rabbit was placed in a wooden box in a quiet laboratory (room temperature 20–22°C). An intravenous line was established via a marginal ear vein. The catheter leading to the carotid artery was connected to an arterial pressure transducer and also made available (via the 3-way tap) for intra-arterial administration of PBG. The EEG electrodes were connected via a headstage to the MacLab system, as previously described (29). Arterial pressure and EEG signals were digitized (100 Hz) and recorded with the MacLab system. The carotid arterial catheter was not available for arterial pressure recording during the period when it was used for PBG or Ringer injection. In addition, the fine caliber of the cannula meant that a pulsatile arterial pressure signal was not available on every occasion in which Ringer or PBG was injected into the carotid artery.

When the environment was quiet, the animal was still, and the hippocampal EEG registered an irregular pattern, PBG (0.2 ml, 1 mg/ml in Ringer solution) or vehicle was gently injected into either the left common carotid artery or into the marginal ear vein over a period of 2–3 s. Care was taken not to move the catheter during the injection period. Injections were repeated after intervals of ~3 min. If an obvious environmental stimulus occurred (e.g., a noise or a person entering the laboratory) or if the rabbit moved during or just after the injection period, the injection was aborted and the data were not included in our analysis. In some animals, PBG was administered first and then Ringer solution; in other animals we reversed the order.

The MacLab Chart records of hippocampal EEG were analyzed offline using the fast Fourier transform facility in IgorPro Software (WaveMetrics, Oregon). For each rabbit in each experimental condition, we selected four episodes of hippocampal EEG, each 25.60 s long. These four episodes were each divided into five epochs, each epoch being 5.12 s long. The injection was made toward the end of the first epoch so that the next four epochs were from the postinjection period. Both ends of each epoch were smoothed by a cosine function, and the magnitude of the real component of the Fourier transform of each epoch was obtained. Relative power spectra for corresponding epochs for each of the four episodes were averaged. The area of the power spectra for each EEG epoch occupied by theta rhythm (defined as 4–10 Hz) was expressed as a percentage of the total area (0–50 Hz) of the epoch. The parietal and frontal EEG traces were inspected by eye to determine whether or not the onset of hippocampal theta rhythm was associated with activation-desynchonization of the trace.

For each experimental condition (intracarotid or intravenous PBG or Ringer), the averaged hippocampal theta proportions for the five epochs were examined using analysis of variance with repeated measures. Statistical significance was set at the 0.05 level, and appropriate differences between epoch means were examined with Fisher's protected *t*-test.

RESULTS

In anesthetized rabbits, in both the open carotid and blind-sac preparations, injection of PBG into the common carotid artery caused a brisk increase in respiratory rate, commencing a few seconds after the injection and continuing for 20–30 s (Fig. 2). Arterial pressure and heart rate fell slightly (Fig. 2). We assessed the response to 0.2 ml of 0.1–5 mg/ml of PBG and found that a concentration of 1 mg/ml gave a reasonable respiratory effect.

In conscious rabbits, manipulation of the intravenous or intra-arterial line occasionally disturbed the animal so that slight movement occurred and the proportion of hippocampal theta rhythm increased for both PBG and Ringer administration. These episodes

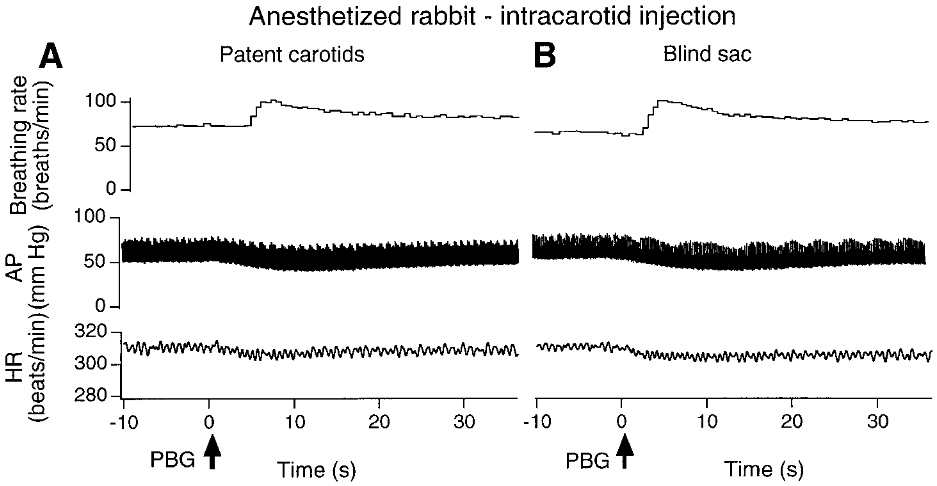

Fig. 2. Effect of intracarotid injection of PBG (0.2 ml of 1 mg/ml) on breathing rate, arterial pressure (AP), and heart rate (HR) in anesthetized rabbits with both carotids patent (*A*) or in a blind-sac preparation (*B*).

were omitted from analysis. Injection of PBG (0.2 ml of 1 mg/ml) did not cause observable bodily movement in its own right.

Injection of PBG into the common carotid artery (n = 6 rabbits) caused hippocampal EEG to express a theta rhythm dominant pattern, commencing durng the first postinjection epoch and continuing throughout the following three epochs (Figs. 3 and 4 and Table 1). Injection of PBG into the common carotid artery also caused a fall in arterial pressure and a bradycardia commencing ~3 s after the onset of the injection. Arterial pressure fell from 63 ± 4 mmHg before intracarotid injection of PBG to 47 ± 5 mmHg 10 s after injection of PBG (n = 8 injections in 4 rabbits, $P < 0.01$). As can be seen in Fig. 4, theta rhythm clearly increased in the hippocampal EEG before the fall in arterial pressure commenced. Injection of Ringer solution into the common carotid artery (n = 6 rabbits) did not change the proportion of hippocampal EEG theta rhythm in any of the postinjection epochs (Fig. 3, Table

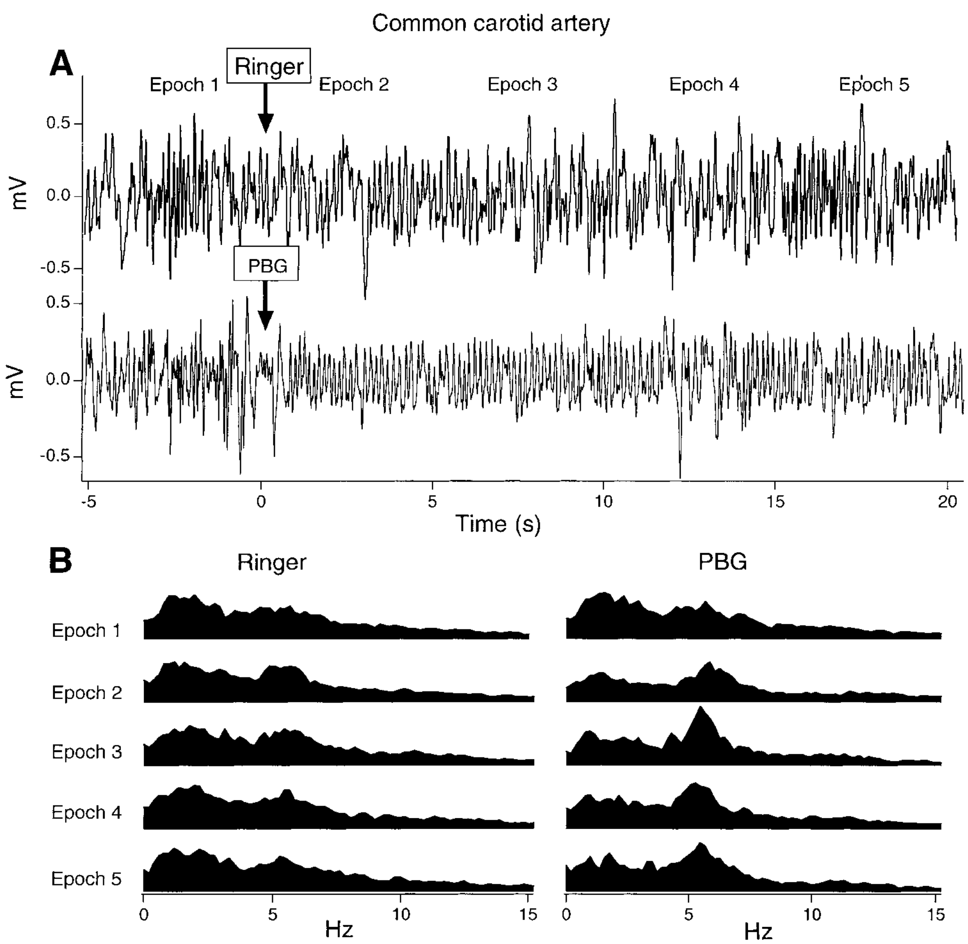

Fig. 3. *A*: hippocampal electroencephalogram (EEG) traces before and after injection of either Ringer or PBG (0.2 ml of 1 mg/ml) into common carotid artery in conscious rabbit. *B*: power spectra derived from Fourier analysis of hippocampal EEG recordings. Intracarotid injection of Ringer or PBG occurred at beginning of *epoch 2*.

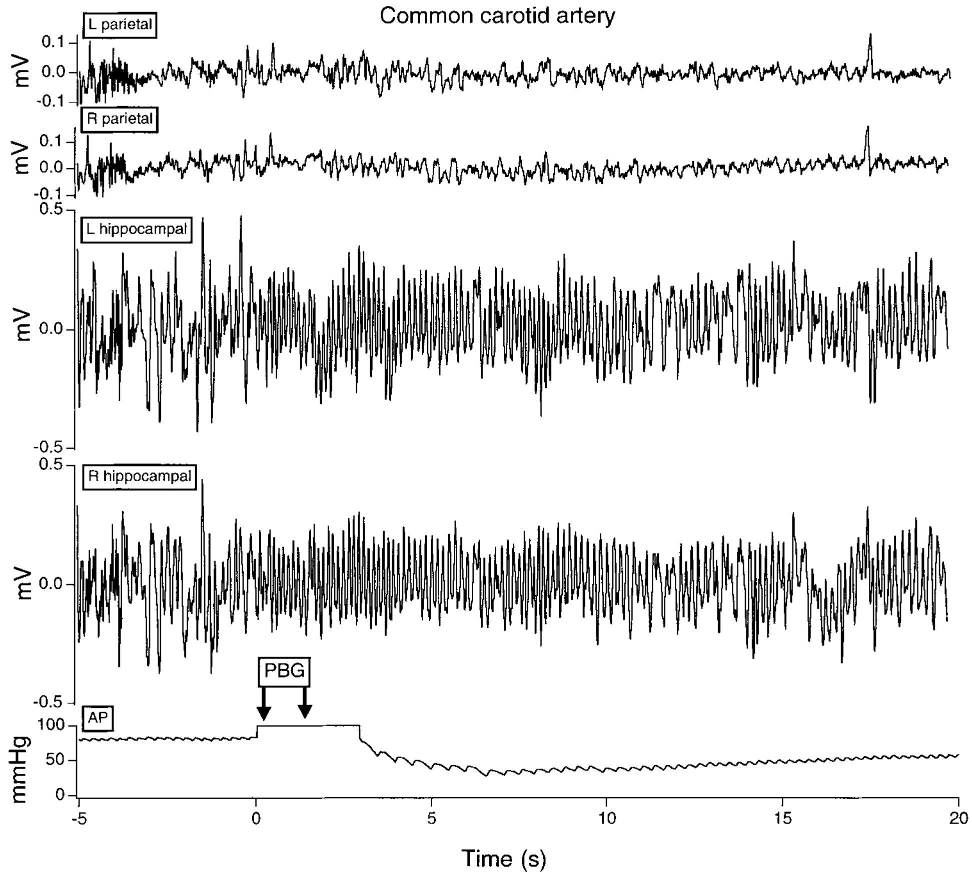

Fig. 4. EEG traces from bilateral parietal extradural electrodes and from bilateral intrahippocampal electrodes before and after injection of PBG (0.2 ml of 1 mg/ml) into common carotid artery. Phasic arterial pressure is illustrated in *bottom* trace.

1). Similarly, intracarotid Ringer injections did not change arterial pressure (63 ± 5 mmHg before injection and 63 ± 5 mmHg 10 s after injection, $n = 8$ measurements in 4 rabbits).

Injection of PBG into the marginal ear vein ($n = 4$ rabbits) caused hippocampal EEG to express a theta rhythm dominant pattern commencing at the second postinjection epoch and continuing throughout the remaining two epochs (Fig. 5, Table 1). In all cases, PBG-induced hippocampal theta activity was bilaterally symmetrical, as shown in Fig. 4. Injection of Ringer solution into the marginal ear vein ($n = 4$) did not significantly change the hippocampal EEG theta rhythm expression (Fig. 5, Table 1).

When injection of PBG caused the appearance of theta rhythm in the hippocampal EEG, the frontal and parietal EEG signal displayed lower voltage faster rhythms, indicative of activation-desynchonization (Fig. 5).

Table 1. *The proportion (%) of theta rhythm (4–10 Hz) area compared with total area in the Fourier power spectrum of the hippocampal EEG for different experimental conditions*

	Power Proportion (%) of Theta Rhythm in Hippocampal EEG				
	Epoch 1	*Epoch 2*	*Epoch 3*	*Epoch 4*	*Epoch 5*
Common carotid artery injection (n = 6 rabbits)					
Ringer ($n = 6$)	41 ± 2	40 ± 3	41 ± 5	40 ± 4	39 ± 4
PBG ($n = 6$)	39 ± 2	47 ± 4†	49 ± 5†	46 ± 5*	46 ± 3*
Marginal ear vein injection (n = 4 rabbits)					
Ringer ($n = 4$)	40 ± 4	41 ± 5	42 ± 4	40 ± 5	40 ± 6
PBG ($n = 4$)	41 ± 4	41 ± 6	51 ± 5*	52 ± 4*	49 ± 6*

Values are means ± SE. Phenylbiguanide (PBG) or Ringer was injected at the beginning of *epoch 2*. Significantly greater than the corresponding value for *epoch 1*: $*P < 0.05$; $†P < 0.01$ (analysis of variance for repeated measures). EEG, electroencephalogram.

DISCUSSION

Our study demonstrates that PBG, administered into the common carotid artery or into the marginal ear vein in the conscious rabbit, causes hippocampal EEG to change to a predominant theta pattern accompanied by activation-desynchonization of the neocortical EEG without any obvious change in the behavior of the animal. Our previous study (29), also in the conscious rabbit, demonstrated that similar hippocampal EEG changes occur when the rabbit is alerted by a significant stimulus in the external environment. We therefore consider that the appearance of hippocampal theta rhythm in response to administration of PBG implies that the animal has been alerted by events in the internal physiological environment.

We found a clear difference in the latency of onset of the theta activity depending on the route of administration of the PBG. When the drug was administered into the common carotid artery, onset of theta rhythm occurred 1–3 s after the injection, ~5 s earlier than

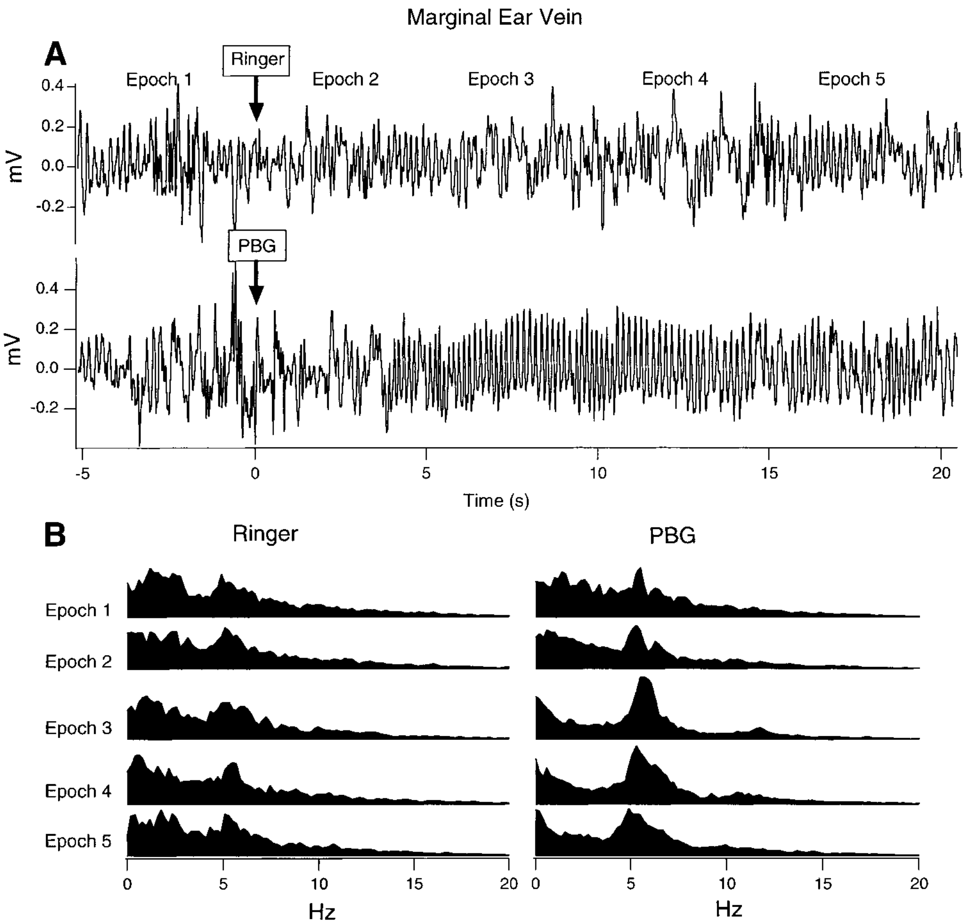

Fig. 5. *A*: hippocampal EEG traces before and after injection of either Ringer or PBG (0.2 ml of 1 mg/ml) into marginal ear vein in conscious rabbit. *B*: power spectra derived from Fourier analysis of hippocampal EEG recordings. Intracarotid injection of Ringer or PBG occurred at beginning of *epoch 2*.

occurred after intravenous injection. This earlier onset of theta suggests that intracarotid PBG acts on chemoreceptors in the arterial territory. The respiratory effects noted in our open carotid and blind-sac experiments in anesthetized rabbits confirm that the dose of PBG used activates carotid chemoreceptors in rabbits, as has been previously demonstrated (27). If PBG crossed the blood brain barrier (this is unlikely) in the open carotid situation, injection of the drug into the common carotid might result in a direct action on the ipsilateral forebrain. However, in our conscious rabbit studies, it was clear that induction of hippocampal theta rhythm occurred bilaterally and symmetrically. Thus we consider it likely that the occurrence of hippocampal theta rhythm after intracarotid PBG reflects activation of carotid chemoreceptors by this agent. In rats, there is direct evidence that PBG and 5HT stimulate arterial chemoreceptor endings, but not baroreceptor endings (10, 26).

Although intracarotid PBG clearly induced an alerting type hippocampal EEG rhythm in the doses used, we did not observe any dramatic "sham rage" response such as the one reported after injection of lobeline into a carotid blind sac in decerebrate cats (4). Similarly, Daly and Taton (11) evidently did not observe marked behavioral effects with injections of cyanide into the carotid body region in rabbits. Rats do show behavioral arousal in this situation (15) so that there appears to be species differences in the behavioral manifestations of alerting reactions. Similarly, in our previous study using intravenous administration of PBG (17), rats exhibited transient behavioral activation (the animals started to climb the wall of the cage), but rabbits remained immobile and apparently calm, although, as demonstrated in the present study, intravenous PBG also activates EEG indices of arousal. In humans, chemoreceptor activation by intravenous lobeline is associated with an unpleasant feeling in the upper chest and throat (16, 24).

Data from our previous study (17) confirm that in rabbits intravenous PBG causes a marked reduction in arterial pressure and heart rate (Bezold-Jarisch reflex). It is possible that the EEG changes observed after intravenous injections of PBG could at least partially reflect the fall in arterial pressure, possibly via effects on the baroreceptors (1) or (less likely) by altering cerebral blood flow. Increases or decreases in arterial pressure can arouse lambs from sleep by baroreceptor-mediated mechanisms, a process that is accompanied by desynchronization of the neocortical EEG (18). In contrast, after intracarotid PBG, the EEG change occurred within a couple of seconds, an effect that clearly preceded any fall in arterial pressure.

Carotid chemoreceptor afferents enter the brain via the carotid sinus and glossopharyngeal nerves. In rabbits, as in other species, the major termination site of the carotid sinus nerve is the nucleus tractus solitarius, but there is also a direct termination in the spinal nucleus of the trigeminal nerve as well as a direct projection to the ventrolateral medulla oblongata caudal to the level of the area postrema (6). Studies in anesthetized animals have reported experimental manipulations in the nucleus tractus solitarius that synchronize the neocortical EEG, changes opposite to those usually seen in arousal (9, 20, 21, 25). So far, no studies have related hippocampal theta activity to the function of the nucleus tractus solitarius. However, neuronal activity in a number of brain stem regions (including the locus coeruleus and the dorsal raphe nucleus) can induce theta activity in the hippocampal EEG (2, 3, 28). Our demonstration that activation of carotid chemoreceptors causes hippocampal theta activity suggests that there may be a functional "alerting" connection between relevant neurons in the nucleus tractus solitarius and the hippocampus.

Our present study adds to the body of evidence supporting the view that arterial chemoreceptor activation normally alerts the individual. As noted in the introduction, the underlying cause of at least some cases of SIDS may well be some defect in the brain stem circuitry mediating this response. This fundamental defect would render the infant more vulnerable to situations that compromise the airway (e.g., sleeping in the prone position). Our limited understanding of the actual brain stem circuitry involved in chemoreceptor-induced arousal makes it difficult to interpret the pathological finding from SIDS victims (14). Hypothesis-driven postmortem studies, directed at specific brain stem regions, are more likely to demonstrate a neuropathological abnormality. We have previously used the fos procedure to study central pathways activated by intravenous PBG in the conscious rabbit (17). Further investigation of the brain stem circuitry activated by intracarotid administration of this agent may provide specific hypotheses for the location of neuropathological changes in SIDS victims.

Perspectives

Over the years, different investigators have considered the behavioral arousal responses elicited by stimulation of peripheral chemoreceptors. Such responses make physiological sense, because changing the position of the nose and/or mouth is clearly vital when the patency of the upper airways is compromised by a particular position of the head. Moving from one environment to another may well improve the quality of the inspired air. In rabbits, appearance of theta rhythm in the hippocampal EEG is a sign that the animal has detected a significant environmental event (29), although there may be little or no overt behavioral response. The selective cutaneous vasoconstriction that accompanies the alerted EEG state no longer occurs in rabbits with inactivated neuronal function in the region of the amygdala (30) so that this region of the brain acts to integrate the response to possibly dangerous events in the external environment. Our present study demonstrates that the hippocampal EEG also displays theta activity when activation of peripheral chemoreceptors signals the occurrence of potentially dangerous events in the internal environment. The chemoreceptor-derived neural signals travel to the brain in the carotid sinus nerve. We have recently mapped the central termination sites of this nerve in the rabbit (6), and it may be possible to elucidate the ascending brain stem pathway mediating the alerting response to peripheral chemoreceptor stimulation. This knowledge may well prove relevant to our understanding of some cases of SIDS.

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