lus was determined by acoustically coupling the earmuff to a sound level meter (General Radio). The input to the sound level meter was monitored by oscilloscope to ensure proper phase relations. The spectral content of the stimuli was monitored by performing fast Fourier transforms (FFT's) on analog-to-digital representations of the stimuli. A 40-dB low-pass noise with a high cutoff of 450 Hz was present during all stimulation to minimize the possibility of recording a response to low-frequency auditory distortion.

Figure 1C shows the composite FFR's for five subjects to each of the stimuli; and Fig. 1D, the FFT spectrum of the responses. Composite FFR's are shown because the FFR amplitudes and phases were similar across subjects. The FFR correlates well with the periodicity of the waveform envelope: When a 200-Hz envelope periodicity was prominent (stimulus 1), a 200-Hz FFR occurred; when 200- and 400-Hz envelope periodicity was evident (stimulus 2), both 200- and 400-Hz FFR's occurred; when 400-Hz envelope periodicity was prominent (stimulus 3), a 400-Hz FFR occurred.

That the 400-Hz FFR to stimulus 3 did not correspond to the pitch perceived from this stimulus (200 Hz) indicates that the FFR is a reflection of envelope periodicity, but not of the pitch of the missing fundamental.

Although this result does not support temporally based pitch theories, it does indicate that envelope periodicity is an available cue for timbre perception and sound lateralization. Behaviorally, the cue of envelope periodicity is of special significance for the lateralization of high-frequency complex sounds. Therefore, if the FFR is truly a representation of envelope periodicity, it should occur for high-frequency complex stimuli as well as the low-frequency complex stimuli already studied. The stimulus of 3800 and 4200 Hz added in cosine phase provided a high-frequency complex stimulus with a prominent 400-Hz envelope periodicity (Fig. 2, A and B). When this stimulus was presented in the same manner as the previous ones, a clear 400-Hz FFR was recorded (Fig. 2, C and D). This periodicity information could serve as a cue for the lateralization of high-frequency stimuli with low-frequency envelopes.

The results show that the periodicity of the stimulus waveform envelope is represented by the FFR; this indicates that very early in the processing of sensory information, waveform periodicity is reflected. This finding supports the hypothesis that neural timing cues representing envelope periodicity may be used for timbre perception and sound lateralization. The results also show a lack of correspondence between the FFR and the pitch of the missing fundamental.

JOSEPH W. HALL III*
Duke University Medical Center, Durham, North Carolina 27710

References and Notes

1. A. Seebeck, *Ann. Phys. Chem.* **60**, 449 (1843).
2. H. L. F. von Helmholtz, *Sensations of Tone* (Longmans, New York, 1863).
3. W. Wundt, *Grundzuge der physiologischen Psychologie* (Engelman, Leipzig, 1880), vol. 1, pp. 315–317.
4. J. F. Schouten, *Proc. K. Ned. Akad. Wet.* **43**, 991 (1940).
5. J. C. R. Licklider, *J. Acoust. Soc. Am.* **26**, 945 (1954).
6. ———, *Experentia* **7**, 128 (1951). The time envelope of a complex stimulus varies directly with the cycle-by-cycle stimulus amplitude. The envelope is roughly described by an imaginary curve connecting adjacent peaks of the stimulus fine structure.
7. J. F. Schouten, R. J. Ritsma, B. L. Cardozo, *J. Acoust. Soc. Am.* **34**, 1418 (1962).
8. R. C. Mathes and R. L. Miller, *ibid.* **19**, 780 (1947); J. L. Goldstein, *ibid.* **41**, 458 (1967).
9. G. B. Henning, *ibid.* **55**, 1259 (1974); D. McFadden and E. G. Pasanen, *ibid.* **59**, 634 (1976).
10. J. C. Smith, J. T. Marsh, S. Greenburg, W. S. Brown, *Science* **201**, 639 (1978).
11. A stimulus artifact occurs in the electroencephalogram when the electrodes are placed near the earphone. This artifact is eliminated by removing the earphone from the proximity of the electrodes.
12. Supported by training grant 1 T32 Ag00029 from the National Institutes of Health. I thank B. Fry and G. Marsh for assistance and critical comments on an earlier version of this manuscript.
* Present address: Department of Audiology, University of North Carolina, Chapel Hill 27514.

24 January 1979; revised 5 July 1979

Baroreceptor Activation Reduces Reactivity to Noxious Stimulation: Implications for Hypertension

Abstract. *The hypothesis was tested that an acute rise of blood pressure may reduce reactivity to noxious stimuli through a baroreceptor-mediated reduction of cerebral arousal. When blood pressure was raised by an infusion of phenylephrine, rats showed less running to terminate or avoid noxious stimuli than during saline infusions. This effect was not seen in rats with denervated baroreceptors. The results suggest that a rise of blood pressure could have motivational consequences significant for human hypertension.*

Baroreceptor stimulation lowers blood pressure by reflex actions on the heart and blood vessels. In addition, such stimulation has a separate effect: it produces cortical and behavioral inhibition. We have suggested that this less well known effect may reinforce the learning of elevations in blood pressure (*1*). This experiment is an initial step toward exploring that hypothesis.

Weiss and Baker (*2*) investigated a form of fainting which resulted from inadvertent mechanical stimulation of the carotid region and determined that loss of consciousness in carotid syncope could occur without cerebral ischemia or a fall in blood pressure (*3*). Köch (*4*) reported that, in the dog, dilatation of a carotid cul de sac by an implanted balloon would produce prompt and deep sleep (*5*). Bonvallet *et al.* (*6*) reported extensively on the inhibitory electrophysiological sequels of stimulation of the baroreceptor nerves, and they showed these effects to be independent of hypotension. Lacey and co-workers (*7*) suggested that baroreceptor activation could be responsible for changes in response latency observed in vigilance tasks. Ádám and coworkers (*8*) showed that removal of the tonic influence of the carotid sinus by surgical denervation of rats resulted in reduced latency of a learned response and increased inappropriate responding to an unreinforced discriminative stimulus. They also demonstrated that agitated "neurotic" behavior could be more easily stress-induced in denervated rats. Bartorelli *et al.* (*9*) observed that reducing baroreceptor stimulation in decerebrate cats elicits sham rage, whereas increasing such stimulation inhibits it. In preliminary experiments we observed that denervated rats were more sensitive to a variety of noxious stimuli (*10*).

These results suggested a motivational effect of blood pressure that would be of general biological interest and possibly relevance to human hypertension. We designed the present experiment to measure blood pressure–induced changes in the escape-avoidance behavior of rats.

Escape running increases with aversiveness of the motivating stimulation (*11*). We therefore trained rats to escape a periodic aversive stimulus by running on the top of a treadwheel. Then we studied the effect of phenylephrine-induced hypertension on this behavior.

We used 16 male Sprague-Dawley rats (Charles River) weighing 300 to 350 g: ten intact and six with surgically denervated carotid and aortic arch baroreceptors (*12*). Denervation was confirmed by observing heart rate changes in response to an infusion of phenylephrine (*13*). One of the operated rats showed almost normal bradycardia to phenylephrine-in-

0036-8075/79/0921-1299$00.50/0

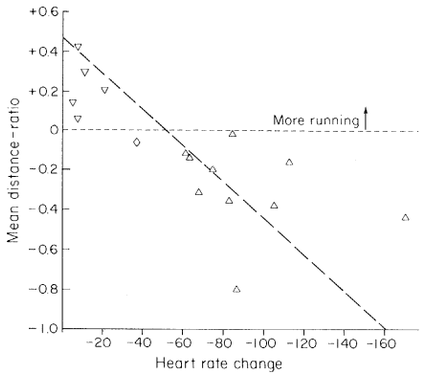

Fig. 1. Greater reduction in heart rate (beats per minute), as an index of baroreceptor activation, produces a decrease in running as indicated by the distance ratio. (△) Intact subjects; (▽) denervated subjects; (◇) partially denervated subject ($r = -.75$; $P < .001$).

duced blood pressure elevation and thus was only partially denervated. A cannula for infusion was implanted in the abdominal vena cava and one for monitoring blood pressure in the left renal artery after a unilateral nephrectomy (*14*). For administering highly controlled aversive stimulation, an electrode was implanted in the sensory nucleus of the trigeminal nerve (*15*).

The treadwheel is 60 cm in diameter, 15 cm wide, and freely turning (*16*). On it, blood pressure and heart rate can be recorded without need for a swivel while a rat secured in an enclosure by only the base of its tail can run ad libitum. All animals were trained to rotate the wheel at least 10 cm to terminate trigeminal nucleus (TN) stimulation (*17*). During the experiment, a rat could either escape from the TN stimulation by turning the treadwheel 10 cm, which immediately terminated current delivery and began the 180-second intertrial interval, or altogether avoid the stimulation for an additional 180 seconds by turning 5 cm during the 5-second prestimulus interval. Otherwise, the stimulation was continued for a maximum of 60 seconds. In each daily session, ten stimulation trials were followed by three extinction trials (no stimulation). On half of the testing days, blood pressure was elevated by infusing phenylephrine into the vena cava; on the others, physiological saline was infused.

Phenylephrine and saline control days were matched in pairs and counterbalanced for order of occurrence. For any matched pair of days, the current levels used for the TN stimulation trials were identical. Immediately before starting the schedule, we gave a sufficient dose of phenylephrine to initially elevate blood pressure by 20 to 55 mm-Hg (*18*). Throughout the ten TN stimulation trials and the three extinction trials of each phenylephrine session, average blood pressure of the intact rats was 31.2 mm-Hg above and heart rate 93.1 beat/min below the preinfusion baseline, and for the successfully denervated rats 49.25 mm-Hg above and 15.2 beat/min below baseline. During saline sessions, across all trials for the intact rats, average blood pressure and heart rate, respectively, were 1.9 mm-Hg and 4.4 beat/min below baseline.

We obtained data from 44 matched pairs of sessions for the ten intact rats and for 25 matched pairs for the five successfully denervated rats. Distance run was measured for both the TN stimulation and the extinction trials. Because our design compared the distance run (D_{PE}) during each elevated blood pressure session with the distance run (D_{SC}) on the corresponding saline control session matched for stimulation intensity, we calculated the running distance difference ratio

$$\frac{(D_{PE}) - (D_{SC})}{(D_{PE}) + (D_{SC})}$$

for each pair of sessions. A negative ratio indicates that the rat ran more on the normotension (saline) day than on the matched hypertension (phenylephrine) day, a ratio of 0.0 means equal running, and a positive ratio indicates less running on the saline day.

Our hypothesis that intact rats would run less to escape or avoid TN stimulation on days when their blood pressure was elevated by phenylephrine was found to be correct ($P < .01$) (*19*). Surgically denervated animals did not show this effect; thus, blood pressure elevation reduced running by the intact subjects more than by denervated controls ($P < .01$) (*20*). Apparently, eliminating baroreceptor function by surgical denervation, as evidenced by a lack of phenylephrine-induced bradycardia (*13*), is sufficient to attenuate the effect of the blood pressure elevation on the aversiveness of the TN stimulation or on some other component of the running response.

In extinction, intact rats continued to run less during the phenylephrine sessions than the saline control sessions. In fact, this effect in extinction was reliably greater than that during the TN stimulation trials ($P < .02$) (*19*) and the difference between the denervated and intact subjects was maintained ($P < .01$) (*20*). Perseveration of established escape responding into extinction is conventionally interpreted as an indication of heightened fear (*21*).

We attempted to elevate blood pressure by the same amount for all subjects by individually adjusting the phenylephrine dose (*18*): there was no relationship between the distance ratio and either the blood pressure change (correlation coefficient $r = .0$) or the dose of phenylephrine ($r = .11$).

Figure 1 shows the relationship between the hypertension-induced change in heart rate and the distance ratio averaged across all trials (TN stimulation and extinction) for all rats, including the partially denervated one. As bradycardia, an indicator of baroreceptor activity (*13*), increased, the average distance ratio became more negative; that is, running during phenylephrine sessions decreased relative to saline sessions ($r = -.75$; $P < .01$). Also note that the average distance ratio for the ten intact rats was less than zero and for the five denervated rats greater than zero. Thus, when the TN stimulation trials and the extinction trials are combined, there is no overlap of the distance ratios for the intact and the completely denervated rats.

Hypertension-induced baroreceptor activity thus reduced escape-avoidance running either by attenuating the aversiveness of noxious trigeminal stimulation or by an unknown action on some other link in the response system. Although a direct action on muscular tone cannot be excluded, the former explanation is more consistent with our preliminary observations (*10*) and with a variety of studies in which others have obtained parallel results for miscellaneous response measures, including direct electrophysiological observation of cortical inhibition (*6*). Furthermore, the results on the behavioral effects of clonidine, an antihypertensive drug that is known to increase the gain of the baroreceptor reflex, are entirely consistent with the hypothesis that baroreceptor activation reduces the aversiveness or motivational consequences of noxious stimulation (*22*).

Combined with recent reports that squirrel monkeys, baboons (*23*), and human paraplegics (*24*) can learn to sustain significantly increased blood pressure, these results suggest a pathophysiological mechanism that could manifest itself as elevation of blood pressure in response to incessant aversive stimulation (*25*). Thus, some hypertension may begin as an instrumentally learned blood pressure response for which the reward is a baroreceptor-mediated reduction in

anxiety or in the aversiveness of ambient noxious stimuli. This hypothesis (*1*) can be reconciled with many observations about essential hypertension (*26*).

B. R. DWORKIN
R. J. FILEWICH
N. E. MILLER
N. CRAIGMYLE
Rockefeller University, New York 10021
T. G. PICKERING
Cardiovascular Hypertension Center, New York Hospital–Cornell Medical Center, New York 10021

References and Notes

1. N. E. Miller and B. R. Dworkin, in *Biofeedback: Theory and Research*, G. E. Schwartz and J. Beatty, Eds. (Academic Press, New York, 1977), p. 129.
2. S. Weiss and J. P. Baker, *Medicine* **12**, 297 (1933).
3. E. B. Ferris, R. B. Capps, S. Weiss, *ibid.* **14**, 424 (1935); W. G. Lennox, R. A. Gibbs, E. L. Gibbs, *Arch. Neurol. Psychiatry* **34**, 1001 (1935).
4. E. B. Köch, *Klin. Wochenschr.* **11**, 225 (1932); in *Die Irradiation Autonomer Reflex*, A. Schweitzer, Ed. (Karger, Basel, 1937), p. 287.
5. In the Balinese Islands, carotid massage is used to induce sleep [E. Schlager and T. Meier, *Acta Trop.* **4**, 127 (1947)].
6. "The main point that arises from these observations is that the afferents from the baro-sensitive sino-carotid areas are capable of producing considerable decreases in the amount of electro-cortical activity, and to do it independently of any variations in blood pressure or the level of circulating adrenalin. The role of these afferents, then, goes very much beyond that of regulators of vasomotor tonus and the adrenalin-secreting bulbar centers" [M. Bonvallet, P. Dell, G. Hiebel, *C.R. Soc. Biol.* **147**, 1166 (1953); p. 1168 (our translation)].
7. J. I. Lacey, J. Kagen, B. C. Lacey, H. A. Moss, in *Expression of the Emotions in Man*, P. H. Knapp, Ed. (Academic Press, New York, 1970), p. 205; B. C. Lacey and J. I. Lacey, in *Cardiovascular Psychophysiology*, P. A. Obrist, A. H. Black, J. Brener, L. V. DiCara, Eds. (Aldine, Chicago, 1974), p. 538.
8. G. Ádám, A. Béla, É. Koó, J. I. Szekely, *Acta Physiol. Acad. Sci. Hung.* **23**, 339 (1963); J. I. Szekely, É. Koó, G. Ádám, *ibid.*, p. 343.
9. C. Bartorelli, E. Bizzi, A. Libretti, A. Zanchetti, *Arch. Ital. Biol.* **98**, 308 (1960).
10. These experiments were performed as projects by undergraduate students. Comparing baroreceptor-denervated rats with sham-operated controls, M. Flaum demonstrated that denervated rats had a lower threshold to avoid quinine-adulterated water; D. Erle showed that denervated rats on a Sidman schedule had increased responding rates to foot shock; and P. Henry demonstrated that denervated rats had lower thresholds for escape from a hot floor in a thermal shuttle apparatus.
11. B. A. Campbell and D. Kraeling, *J. Exp. Psychol.* **45**, 97 (1953).
12. We dissected the adventitia from each carotid bifurcation and severed the sympathetic chain approximately 0.7 cm caudal to the carotid bifurcation, just posterior to the superior cervical ganglion and superior laryngeal nerve. The surfaces of the arteries in the region of the bifurcation were cauterized. We took particular care not to damage the vagus nerve. After 2 months' convalescence, the experiment started. At the start of the experiment, the average mean arterial pressure for the intact rats was 116.2 ± 14.9 and for the denervated rats 113.8 ± 22.9 mm-Hg. Thus, the denervated rats were not hypertensive. Krieger reported that most rats were hypertensive 2 months after denervation, but his methods of measurement were quite different [see E. M. Krieger, *Circ. Res.* **15**, 511 (1964)].
13. The attenuation of this reflex indicates the extent of the denervation [H. S. Smyth, P. Sleight, G. W. Pickering, *ibid.* **24**, 109 (1969)].
14. B. R. Dworkin, R. J. Filewich, J. da Costa, E. Eissenberg, N. E. Miller, *Am. J. Physiol.*, in press.
15. A hole was made in the skull by using a dual-bar Kopf stereotaxic instrument with the incisor bar at 10.00 mm. A stainless steel Formvar-insulated electrode 0.0127 cm in diameter with 0.5-mm exposure at the tip was entered at an angle of 9° anterior from vertical to prevent cerebellar damage, with deGroot coordinates 1.3 mm anterior-posterior and 2.4 mm lateral [L. J. Pellegrino and A. J. Cushman, *Stereotaxic Atlas of the Rat Brain* (Appleton-Century-Crofts, New York, 1967)]. As the electrode was lowered during implantation, under light anesthesia, a suprathreshold current was passed at various depths within the nucleus (8.3 to 9.0 mm from the incisor bar). At the point of the largest algesic response, the electrode was cemented in place. Scalp retraction, drilling of skull holes, and so on, were accomplished under deep anesthesia. Rats will learn to run, press a lever, or stop drinking (even though water-deprived for 24 hours) to escape from 20- to 45-μA stimulation, and higher intensities elicit nonperseverating squeals, activity, and freezing. Trigeminal nucleus stimulation is similar to foot or tail shock, but gives closer control of the stimulus parameters and relatively constant thresholds.
16. J. M. Weiss, H. I. Glazer, L. Pohorecky, W. H. Bailey, L. Schneider, in *The Psychobiology of Depressive Disorders: Implications for the Effects of Stress*, R. Depue, Ed. (Academic Press, New York, in press).
17. The current was increased in 1-μA increments until elapsed time from TN stimulation onset to offset was consistently 40 seconds or less.
18. Phenylephrine concentrations were 3.0 or 5.0 mg/ml; a bolus was 2.0 to 8.0 μl.
19. Randomization test for matched pairs, two-tailed, $N = 10$.
20. The comparison between the intact and denervated groups was with a Mann-Whitney U test, two-tailed, $N = 10, 5$.
21. L. J. Kamin, *J. Comp. Physiol. Psychol.* **49**, 420 (1956); R. A. Rescorla and R. L. Solomon, *Psychol. Rev.* **74**, 151 (1967), see pp. 172–177.
22. The increase in the gain is a consequence of both facilitation of the effect of the baroreceptors in the brain and near doubling of the firing rate of individual baroreceptor fibers at a given arterial pressure [P. Sleight, M. J. West, P. I. Korner, J. R. Oliver, J. P. Chalmers, J. L. Robinson, *Arch. Int. Pharmacodyn. Ther.* **214**, 4 (1975)]. In rats, clonidine prolongs chlorohydrate sleeping time, inhibits exploratory activity, and reduces rotorod performance, pain-induced aggression, and conditioned avoidance behavior [R. Laverty and K. M. Taylor, *Br. J. Pharmacol.* **35**, 253 (1969)]. The principal behavioral side effect in humans is sleepiness [G. Onestri, A. B. Schwartz, K. E. Kim, V. Paz-Martinez, C. Swartz, *Circ. Res. Suppl. II* (1971), p. 53].
23. H. Benson, J. A. Herd, W. H. Morse, R. T. Kelleher, *Am. J. Physiol.* **217**, 30 (1969); A. H. Harris, W. J. Gilliam, J. D. Findley, J. V. Brady, *Science* **182**, 175 (1973).
24. N. E. Miller and B. R. Dworkin, in *Neurophysiological Mechanisms of Goal-Directed Behavior and Learning*, R. F. Thompson, Ed., in press.
25. A. R. Lorimer, P. W. Macfarlane, G. Provan, T. Duffy, T. D. V. Lawrie, *Cardiovasc. Res.* **5**, 169 (1971), R. Friedman and J. Iwai, *Science* **193**, 161 (1976); A. Jonsson and L. Hansson, *Lancet* **1977-1**, 86 (1977).
26. M. H. Davies, *J. Chronic Dis.* **24**, 239 (1971).
27. We thank D. J. Reis for advice, C. Kaufmann for work in early phases of the study, and J. da Costa for performing surgery. Supported by PHS research grant HL 21532 awarded to N.E.M. and by a special grant from the Institute of Rehabilitation Medicine, New York University Medical Center, awarded to B.R.D. R.J.F. was supported by a postdoctoral fellowship from PHS grant MH 15125.

12 February 1979; revised 30 April 1979

Floras and Oxygen

McLean (*1*, p. 1061) claims that "the importance of terrestrial plants in the overall world productivity in the geologic past has not been recognized" in earlier papers on the control of atmospheric oxygen, and that this greater primary productivity means that the control of the partial pressure of oxygen must occur predominantly on land. The first claim is false (*2, 3*), and the second is inadequately supported.

Like some earlier investigators, McLean fails to consider the necessary (*3*) concentration-dependent regulation of oxygen. Photosynthesis, like any reaction, produces no net change in oxidation. Almost all the oxygen from photosynthesis later reoxidizes the carbon reduced photosynthetically. Any net change in free oxygen is equal to the difference between the amount of reduced carbon buried and the amount of previously buried carbon that is oxidized. (Other reactions are coupled to this or are now minor.) The way in which the regulation occurs is not yet clear in detail, but most nonephemeral reduced carbon is deposited in ocean sediments. Much of this reduced carbon comes from the land. Therefore, to the extent that regulation of free oxygen occurs by way of the deposition of reduced carbon, we must look to marine processes. Even a sudden excess deposition of 10^{12} metric tons of reduced carbon in coal swamps left by a retreating sea would decrease the partial pressure of oxygen by less than 0.0005 atm. To the probably smaller extent that regulation occurs by erosion, by oxidation of detrital carbon before it is redeposited, we must look primarily to the continents. But McLean's argument is irrelevant to either case. With respect to regulation, we must focus on the sinks of free oxygen rather than on their sources.

With respect to temporary changes in free oxygen, an increase in land area by eustatic regression should give a somewhat greater net input after the reoxidation of unburied carbon. However, regression would also increase erosion and therefore the amount of previously buried carbon available to be reoxidized. From the inadequate data I know, either effect might predominate.

LEIGH VAN VALEN
Department of Biology, University of Chicago, Chicago, Illinois 60637

References

1. D. M. McLean, *Science* **200**, 1060 (1978).
2. J. H. Ryther, *Nature (London)* **227**, 374 (1970).
3. L. Van Valen, *Science* **171**, 439 (1971).

12 June 1978; revised 10 April 1979

0036-8075/79/0921-1301$00.50/0