these drugs on ERP's from different cortical sites seems unlikely.
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In one patient, bipolar recordings were obtained between several frontal sites. Similar positive potentials were recorded between a naming-related site in the posterior inferior frontal gyrus and two other sites where stimulation did not disrupt naming. One was in the middle portion of the same gyrus, and another was in the posterior middle frontal gyrus.
Selectively increased activity in the facial motor cortex during overt but not during silent naming has been recorded with regional cerebral blood flow measures also [B. Larsen, E. Skinhøj, N. A. Lassen, *Acta Neurol. Scand. Suppl.* **72**, 6 (1979)].
This nonspecific potential is most prominent at posterior sites, phase-reverses across the Sylvian fissure, and is stable across different stimuli and tasks.
Log spectral density for the 240- to 960-msec interval of the O1 ERP at the 5.56-Hz bandwidth centered at 8.33 Hz at site 7 (the fully anomic posterior site) is 0.81 compared with a range of 1.11 to 1.89 for nonanomic sites. The log values of spectral density at site 7 for the other stimuli are 0.83 for O2, 1.14 for L1, 1.62 for L2, and 1.65 for NF. The coherence between site 7 and the neighboring sites at this frequency is least following O1 and substantially greater for spatial and neutral flash inputs. For example, the coherence (at 8.33 Hz) between sites 7 and 9 is 0.00 for O1, 0.25 for L1, 0.90 for L2, and 0.80 for NF.
During silent naming, the activity of cortical region related to naming is differentiated from that of surrounding areas. Spectral analysis performed with SPECTRA [A. Barr, J. Goodknight, J. Sall, J. Helwig, *A User's Guide to SAS* (SAS Institute, Raleigh, 1976)]. Periodiograms were smoothed through the use of an approximate cosine window with 5.56-Hz bandwidth.
In one patient, desynchronization was evident at only one of two posterior sites associated with stimulation-evoked naming changes. In all other patients, such desynchronization was seen at all posterior sites associated with naming changes.
A variety of scalp EEG and ERP changes have been related to language. Often at least one report fails to confirm the finding [S. A. Hillyard and D. L. Woods, in *Handbook of Behavioral Neurobiology*, M. Gazzaniga, Ed. (Plenum, New York, 1979), vol. 2, p. 345; E. Donchin, M. Kutas, G. McCarthy, in *Lateralization in the Nervous System*, S. R. Harnard, R. W. Doty, L. Goldstein, J. Jaynes, G. Kruthamer, Eds. (Academic Press, New York, 1977), p. 330]. Several scalp EEG studies show suppression of 8- to 12-Hz activity during verbal tasks, but anatomic specificity of these studies is limited to the left hemisphere as a whole, and the suppression is not absolute but relative to the right hemisphere. Our findings of a potential shift in premotor and motor cortex preceding the onset of overt speech support the brain origin of similar scalp potentials [D. W. McAdam and H. A. Whitaker, *Science* **172**, 499 (1971)]. However, electromyographic changes preceded voice onset by more than 300 msec [B. Grozinger, H. H. Kornhuber, J. Kriebel, *Prog. Clin. Neurophysiol.* **3**, 87 (1977)]. Thus, although the potential shift preceding overt speech began as early as 680 msec before voice onset in our data, we did not routinely measure the electromyogram, and the onset in relation to speech muscle activity is uncertain. Also, interactions with cerebral respiratory potentials cannot be excluded (Grozinger *et al.*).
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# Circadian Variation in the Latency of Brainstem Responses and Its Relation to Body Temperature

Abstract. *The auditory brainstem response varies in a circadian rhythm that is negatively correlated with the circadian rhythm in oral temperature. The auditory brainstem responses and oral temperature were recorded every 3 hours from three healthy male subjects during a 2-day period. The data indicate that a reduction of 1°C in oral temperature is associated with an increase of 200 microseconds in the latency of wave V of the auditory brainstem response, and of 160 microseconds in the interval between waves I and V.*

Auditory brainstem responses (ABR's) are widely used for diagnostic purposes by neurologists and audiologists (*1*). The ABR's, first described by Jewett *et al.* (*2*), consist of five to seven waves (numbered I to VII) elicited in the brainstem by clicks presented in rapid succession. The ABR's are extracted by averaging signals from scalp recordings of the electroencephalogram. Although the origins of the potentials are not fully understood (*3*), the first five waves appear to be associated with neural activity at, or near, the first five relays in the auditory pathway (*4*). In persons with normal hearing the ABR's are remarkably stable and the latencies of the waves, particularly waves I, III, and V, are consistent across individuals (*5*). Latency deviations and, less often, amplitude deviations can indicate pathology in the auditory system (*6*). We present data suggesting that at least a portion of this variation in latency is related to the circadian rhythmicity of body temperature (*7*).

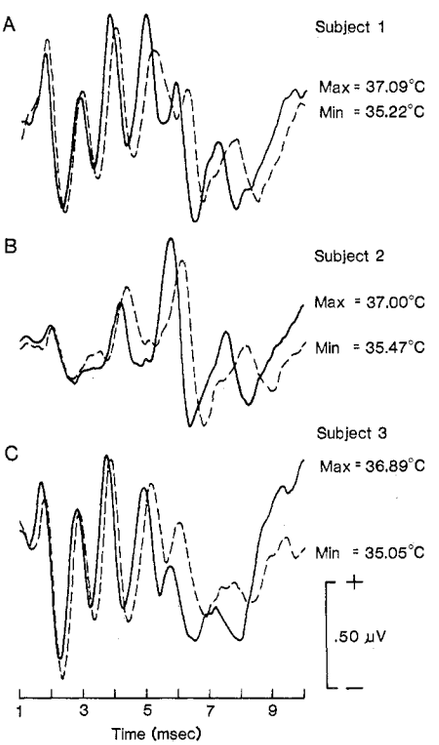


Fig. 1. Auditory brainstem responses recorded at the vertex in response to 4000 0.1-msec clicks, from each of three subjects at 65-dB hearing level. Solid lines represent ABR recorded when the subject's oral temperature was at a maximum in the experimental period; the dashed line was recorded when oral temperature was at a minimum. Positivity at the vertex relative to the mastoid is indicated by an upward deflection.

Several investigators have asserted that the latencies of the ABR's, particularly of wave V, increase with decreasing body temperature. They based their assertions on observations in nonhuman species where body temperature was changed artificially (*8, 9*), or on temperature measures taken from patients who were, for one reason or another, hypothermic (*10*). We report here that naturally occurring circadian variations in body temperature are correlated with similar changes in the latency of the ABR's.

Oral temperature and ABR's were recorded every 3 hours during a 51- to 54-hour period for a total of 17 recording sessions from each of three healthy male undergraduates (mean age, 20 years) who were paid for their participation. The initial recording session began at 1200, 1300, and 1400 hours (central standard time) and ended 2 days later at 1200, 1600, and 1400 hours for subjects 1, 2 and 3, respectively (*11*). The subjects were free to come and go during the day but slept overnight in the laboratory. They reported that they slept during most, if not all, of the recording sessions (*12*).

The EEG was recorded from a silver–silver chloride scalp electrode placed at the vertex (Cz) and referred to the mastoid process of the right ear. Subjects were grounded at the forehead. The vertex and reference electrodes were affixed with collodion. The short-stem scalp electrodes were placed on the subject before the first session and then reapplied after the seventh recording session. The ground electrode was reapplied every session. Electrode impedance was maintained well below 3 kilohms. The signals were amplified by Grass P511J amplifiers, set to a bandwidth of 100 to


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3000 Hz. Each ABR represents an average of 4000 trials digitized at the rate of 50,000 samples per second for 10 msec following click onset. Prior to being analyzed, the data were digitally low-pass-filtered at 3100 Hz (−3 dB).

The stimuli were 0.1-msec rarefaction clicks presented to the right ear at the rate of 11 per second through TDH model 39 shielded headphones. A masking white noise at 30-dB hearing level (*13*) was presented to the left ear. During each session ABR's were obtained at two settings of click intensity: 65- and 45-dB hearing level (*13*). Oral temperature was recorded with a temperature probe (Yellow Springs Instrument model 401) placed under the tongue. Temperature was measured to within 1/10 of 1°C and was recorded before and after the presentation of each block of clicks. All correlations are based on temperature readings taken after each block of clicks.

In Fig. 1 we plot the ABR's elicited by the 65-dB hearing level clicks from the three subjects when oral temperature reached its maximum and minimum values during the experimental period (*14*). The pattern of the ABR's that we recorded is similar to that observed by other investigators (*15*). When oral temperature is at its maximum value, the latency of the ABR components is evidently shorter than when oral temperature is at its minimum value. We present a more detailed view of the relation between ABR latency and oral temperature in Fig. 2 where, for subject 3, we plot the latencies of ABR waves I, III, and V, and oral temperatures against the time of day at which the measurements were taken (*16*). The latencies vary with a period of about 24 hours. Moreover, the changes in latency correlate negatively with oral temperature.

In Table 1 we show that there was a significant negative correlation ($P < .01$) between the latency of the ABR's and oral temperature in all three subjects (*17*). Although the correlation for wave I is lower than that for waves III and V, the correlation is significantly different from zero ($P < .05$) in two of the three subjects. The slope of the function relating latency to oral temperature indicates that, in the three subjects we studied, a reduction of 1°C in body temperature corresponds to a 200-μsec increase in latency of wave V. In general, the later the wave the steeper the slope of the function. These values may indicate that the effect of temperature increases with increasing number of synapses in the auditory system.

When the latency of wave I is subtracted from the latency of succeeding waves an estimate is obtained of the duration of postcochlear processes. Interpeak latencies (IPL) are, therefore, often reported in ABR studies. Aberrant IPL values presumably indicate impaired central conduction and can be of use in localizing interruptions of the peripheral auditory system (*1, 6*). Table 1 shows that there was a high negative correlation between oral temperature and IPL. Here, again, the correlation between oral temperature and ABR latency increases with increasing latency of the component.

Table 1. Relation between wave latency and oral temperature for the three subjects.

| Wave | Subject | Correlation* | Slope† | $P$‡ |
|---|---|---|---|---|
| | | *Latency to peaks* | | |
| I | 1 | − .4528 | − .03 | .0653 |
| | 2 | − .6693 | − .06 | .0035 |
| | 3 | − .7356 | − .05 | .0010 |
| III | 1 | − .8389 | − .10 | .0001 |
| | 2 | − .8679 | − .14 | .0000 |
| | 3 | − .8932 | − .09 | .0000 |
| V | 1 | − .8989 | − .22 | .0000 |
| | 2 | − .9089 | − .23 | .0000 |
| | 3 | − .9056 | − .17 | .0000 |
| | | *Interpeak latencies* | | |
| I to III | 1 | − .8267 | − .07 | .0001 |
| | 2 | − .6944 | − .08 | .0023 |
| | 3 | − .5487 | − .04 | .0215 |
| III to V | 1 | − .8520 | − .12 | .0001 |
| | 2 | − .7410 | − .09 | .0001 |
| | 3 | − .7601 | − .08 | .0006 |
| I to V | 1 | − .8953 | − .18 | .0000 |
| | 2 | − .8405 | − .17 | .0001 |
| | 3 | − .7937 | − .11 | .0003 |

*Pearson product moment. †The slope of the regression equation relating latency to oral temperature is $L = bT + k$, where $L$ is latency in milliseconds, $b$ is the value of the slope in the table, $T$ is temperature in degrees Celsius, and $k$ is a constant. ‡The probability of obtaining the reported correlation when the correlation in the population equals zero.

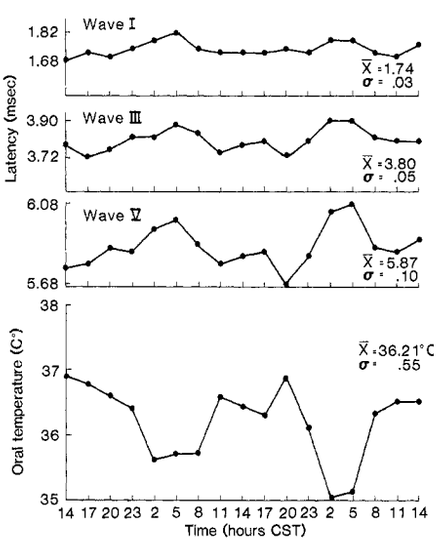


Fig. 2. Latencies of waves I, III, and V of the ABR and oral temperature, recorded from subject 1 and plotted against the time of the recording session. Note that ordinate of latency curves reflects the individual subject and wave latencies. The maximum and minimum values are indicated on the ordinates.

Demonstrating a correlation between oral temperature and ABR latency does not imply that oral temperature causes the change in ABR latency. However, active manipulation of body temperature affects the latency of eighth nerve action potential recorded at the round window (*18*) and of ABR latency (*8*). Furthermore, it is well established that reductions in body temperature slow most biological reactions (*19*), including neural transmission time (*20*). These reports, when considered with our data, suggest that the changes in body temperature cause the changes in ABR latency. Whether this is indeed the case remains to be determined.

The data we report may bear on the controversy concerning the effects of acute ethanol ingestion on ABR latency. Squires and his colleagues (*21, 22*) reported that ethanol intoxication increased ABR latency in rats and cats as well as in humans. These investigators suggested that ethanol, a central nervous system depressant, increases sensory transmission time at the medullary level (cochlear nucleus or superior olive). However, Jones *et al.* (*9*), in studies controlling carefully for small changes (1°C) in body temperature, failed to replicate the findings of Squires' group. According to Jones *et al.* (*9*) the latency shift can be attributed, largely, if not entirely, to the effect of ethanol on body temperature rather than to the direct effect of ethanol on the central nervous system. Our data indicate that small changes (±1°C) in oral temperature apparently induce changes in ABR latency of the same order that ethanol induced in

Squires' study (170 μsec for wave V). It is clear, therefore, that investigators should control, or at least monitor, body temperature in studies of ABR latency (*23, 24*).

The mechanisms underlying the correlation of body temperature and ABR latency are unknown. Temperature might affect ABR latency by retarding receptor activity, neuronal conduction, or synaptic transmission at any point up to and including the inferior colliculus (*18, 19*). By varying stimulus and organismic variables, and observing corresponding changes in the rhythm, it may be possible to determine the locus of the effects. The ABR's may thus be useful for investigating the effects of body temperature on neural activity in the human.

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4. Wave I probably reflects eight nerve action potentials; waves II to V are presumed to be generated by the cochlear nucleus, superior olive, lateral lemnicus, and inferior colliculus, respectively (*3*).
5. The mean (± standard deviations) latency (in milliseconds) of waves I to V observed in our laboratory were 1.79 ± 0.11, 3.00 ± 0.14, 3.97 ± 0.14, 5.17 ± 0.21, and 6.00 ± 0.16, respectively, at 64-dB hearing level based on 80 observations (eight subjects, ten recordings). The interpeak latencies for waves I to III and III to V were 2.18 ± 0.11 and 2.02 ± 0.29, respectively. All components of the ABR can be observed at the appropriate latencies.
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11. Because of equipment malfunction, data from the tenth recording session of subject 2 were unusable. A session at 1600 hours was therefore added for a total of 17 recordings.
12. Sessions lasted 30 to 45 minutes. The subjects were instructed to relax and sleep if they could during the recording period. M. Amadeo and C. Shagass [*Psychophysiology* **10**, 244 (1973)] reported that there is little or no change in the amplitude and latency of the ABR's from waking to sleep.
13. Hearing level threshold was established on the basis of the mean level of intensity at which three staff members could no longer detect the presence of continuous white noise. The hearing level for click stimuli delivered at 11 per second was established in a similar manner.
14. The latency determinations were made by a trained observer, who did not know the purposes of the experiment. Peaks were identified in a computer display of the ABR's by positioning a cursor at the peaks. The latency value at the cursor was identified by the computer. Latency was determined with 0.02-msec resolution.
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16. The 45-dB hearing level clicks elicited ABR's in which only wave V was distinct; wave I was not discernible for all subjects. The latency of wave V showed the same pattern for variation during the 24-hour period although they were longer, corresponding to the well-established effect of stimulus intensity on response latency [T. W. Picton, D. L. Woods, B. A. Baribeau-Braun, T. M. G. Healey, *J. Otolaryngol.* **6**, 90 (1977)].
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23. While Squires *et al.* (*21*) did attempt to control for body temperature they ignored differences less than 1°C.
24. Although it is well established that acute ethanol intoxication impairs body temperature regulation in man and rodents [G. Freund, in *Biochemistry and Pharmacology of Ethanol*, E. Majchrowiez and E. P. Noble, Eds. (Plenum, New York, 1979), pp. 439–452; J. Hirvonen, in *Body Temperature: Regulation, Drug Effect, and Therapeutic Implications*, P. Lomax and E. Schonbaum, Eds. (Dekker, New York, 1979), pp. 561–585], at present there are no data from which it is possible to infer the amount of ethanol an individual needs to ingest to reduce body temperature by 1°C.
25. Supported by the Office of Naval Research (contract N00014-76-C-0002) with funds provided by the Defense Advanced Research Projects Agency; Air Force Office of Scientific Research (contract F49620-79C-0233); Wright Patterson AFB (contract F33615-79C-0512); Illinois Department of Developmental Disabilities (grant D-D8020-02); and the Environmental Protection Agency (contract R8056 28010). V. L. Towle participated in the initial phases of this study and helped in developing our ABR recording procedures. We thank P. Seegar for helping with data analyses and C. Wickens and E. Satinoff for helpful comments.
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## GABA Analogues Activate Channels of Different Duration on Cultured Mouse Spinal Neurons

Abstract. *Voltage-clamp recordings from mouse spinal neurons grown in culture were used to study the membrane current fluctuations induced by 12 substances structurally similar to γ-aminobutyric acid (GABA). Fluctuation analysis provided estimates of the electrical properties of the elementary events underlying these responses. Estimates of the mean conductance of channels activated by all of the substances except glycine did not differ significantly from that estimated for GABA, whereas mean durations of agonist-activated channels all differed significantly from that found for GABA. The results indicate that all of the substances tested except glycine activate channels of similar conductance but of different durations.*

γ-Aminobutyric acid (GABA) is an amino acid endogenous to a variety of nervous systems, where it is thought to function as a neurotransmitter, inhibiting excitability through an increase in $Cl^-$ ion conductance (*1*). This inhibitory action, shared by a number of naturally occurring amino acids, can also be mimicked by a variety of synthetic substances thought to resemble the GABA molecule stabilized in different configurations (*1*). The advent of fluctuation analysis and single-channel recording techniques has shown that the elementary events associated with the macroscopic effects of neurotransmitters can be described quantitatively in terms of the electrical dimensions of ion channel events (*2*). We have applied fluctuation analysis to the membrane responses induced by GABA, glycine, taurine, and a number of synthetic substances in cultured mouse spinal neurons and report that all of the agonists except glycine activate ion channels of similar conductance but variable duration.

Mouse spinal neurons were grown in tissue culture according to methods previously described (*3, 4*). At the time of the experiment, normal maintenance medium was replaced by Hanks balanced salt solution containing 1 m*M* $CaCl_2$, 10 m*M* $MgCl_2$, and 1 μ*M* tetrodotoxin to eliminate all evoked synaptic activity and allow clearer study of the pharmacologic responses. The recording medium and the drug solutions were all buffered to *p*H 7.4 with 25 m*M* Hepes. Intracellular recordings under voltage clamp were made at room temperature (23° ± 1°C) on the modified stage of an inverted phase microscope through the use of two


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