single injection of 0.1 to 1 mg of purified enterogastrone significantly reduced food-intake during the first 30 to 60 minutes, when some mice ate almost nothing. There was no decrease in intake during later periods, but the cumulative changes remained evident after 4 hours. Two different batches of enterogastrone showed this effect; it reduced intake whether it was injected intravenously, subcutaneously without carrier, or subcutaneously in a vehicle containing 16 percent gelatin and 0.5 percent phenol. Two peptide preparations from hog duodenum each had a slight effect when it was measured at 30 minutes, but the cumulative reduction was not observed between 1 and 4 hours later; their minor effects may be attributable to slight contamination with enterogastrone. Similarly, a material purified from the pig colonic mucosa, by the concentration procedure used for enterogastrone, had no effect on intake. Administration of other substances such as glucagon, secretin, glucose, and bovine serum albumin had no effects under the conditions employed. The anorexigen chlorphentermine-HCl (Pre-Sate), administered intravenously at 300 μg per mouse, significantly reduced intake during the first 30 minutes, and its cumulative effects were significant for as long as 2 hours.

The activity of duodenal enterogastrone fractions was apparently not due to toxicity or pyrogen-like properties; they did not elicit abnormal behavior in the mice or cause fever; mice injected with enterogastrone appeared to be active, healthy, and quite normal except for failure to eat after 17 hours of fasting. While it is still possible that the anorexic effect of our preparations is due to nonspecific toxic effects of enterogastrone or a contaminant present in these preparations, our studies suggest that enterogastrone may be involved in inhibition of feeding. Inhibition may be in some way related to elimination of gastric hunger contractions, since it is known that, when given to dogs in doses of 0.5 mg/kg, these enterogastrone preparations inhibit gastric motility and histamine-induced augmentation of secretion of pepsin and hydrochloric acid (*5, 7*) for as long as 1 hour. About 0.1 mg of enterogastrone was needed to inhibit significantly appetite in mice, or about seven times more (expressed per unit body weight) than the dose required to affect gastric secretion in dogs. However, many hormones able to exert more than one biologic effect show greatly different activities with respect to different responses; for example, doses of vasopressin required to obtain an effect on blood pressure in rats are at least 100 times larger than those necessary for an antidiuretic effect.

It is not clear, regarding all factors involved in control of food-intake, how the reflexes are signaled to the hypothalamic portion of the brain (*1, 2, 4*) to produce cessation of eating. The mechanisms of regulation of intake are most likely interrelated, and many various factors such as glucose utilization and energy balance (*1, 2*) and distention of the stomach (*4*) could be involved in inhibition of feeding or apparent satiety (*1–4*). It is also interesting that intraperitoneal administration of large amounts of glucose had no effect on food-intake in fasted mice; this finding is in agreement with those of Grossman and Janowitz (*4, 6*). Glucagon also was ineffective. It has been reported that administration of glucose or glucagon inhibits gastric hunger contractions in men and rats (*2, 8*). This problem is complex, since it is the rate of glucose utilization, and not the level of glucose, that is associated with cessation of gastric contractions (*2*). Moreover, under certain conditions gastric contractions may not be indicative of or necessary for the hunger state (*2*). It is possible therefore that enterogastrone did not exert all its effects through inhibition of gastric contractions, and that it acted, at least in part, humorally on the central nervous system. Although our studies suggest a role for enterogastrone in the overall complex relations of appetite control, they do not prove that secretion of enterogastrone under physiologic conditions affects food intake; much further work will be necessary to assess the importance of these preliminary findings.

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Resistance Shifts Accompanying the Evoked Cortical Response in the Cat

Abstract. *Clicks and flashes that evoke an electrical response from the auditory or visual cortex also evoke a resistance shift in the tissue. The resistance shift, a drop followed by a rise in resistance, closely follows the temporal pattern of the electrical response recorded simultaneously through the same electrodes. While several experimental manipulations produce corresponding changes in the amplitudes of both electrical response and resistance shift, the resistance shift is more sensitive to alterations in cortical temperature and anesthetic level. The two responses behave distinctly differently as a function of the depth of the electrode in the cortex.*

Since Cole and Curtis first measured impedance changes during activity of nerve cells (*1*), numerous authors have studied the impedance of brain tissue and the changes induced in it by electrical stimulation, spreading depression, asphyxia, ischemia, and even by normal activities such as sleep and learning (*2*). Resistive and capacitive changes of the order of several percent of the resting value with a time course of seconds or minutes have been reported. The measurements to be presented here show resistance changes sev-

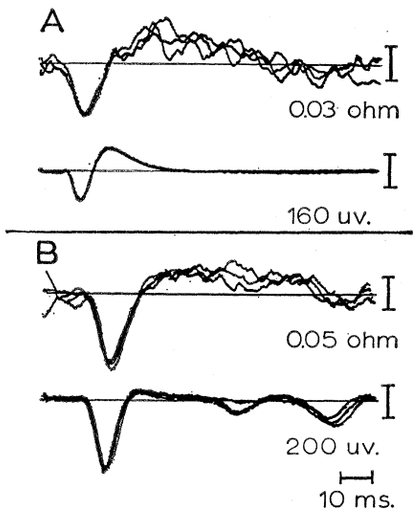

Fig. 1. Simultaneous recordings of resistance shift (upper trace, decrease downward) and evoked response at auditory cortex to click (A) and visual cortex to flash (B). Each trace is sum of responses to 128 stimuli at 1.25 per second (clicks) and 4 per second (flashes); three successive sums are superimposed. Cortical depth electrode is at about 1 mm (A), 2 mm (B), and records positivity upward.

eral orders of magnitude smaller taking place on a millisecond time scale.

Forty-six adult cats under sodium pentobarbital or chloralose anesthesia were used in this study. The ectosylvian cortex (and in some cases the lateral gyrus) was exposed and a plaster of paris wall constructed around the opening to confine the pool of mineral oil that covered the cortex. Temperature of this pool was automatically controlled to within about 0.5°C over the range 31° to 41°C. A platinum (occasionally silver) wire, 0.8 mm in diameter, insulated except for 0.25 mm at the sharpened tip, was inserted into the cortex to serve as the active electrode. The indifferent lead was either a platinum plate resting on the cortex nearby, or the headholder. These electrodes were connected to one arm of a wheatstone bridge and signals of frequencies between 1 and 100 khz (usually 10 khz) at current densities ranging between 10^{-9} and 10^{-12} amp per square micron were applied through them for making impedance measurements. A lock-in amplifier detected the unbalance signal from the bridge when the interelectrode impedance (interface plus tissue) differed from that of parallel resistance and capacitance decades in the adjacent arm. The phase sensitivity of the amplifier permitted separate determination of the resistive and reactive components of the impedance shifts since deviations of these two components from their resting values produced unbalance signals 90 degrees out of phase with each other.

The same electrodes were used to record the brain electrical activity by connecting them through a low pass filter (to remove the bridge signal) to the electrophysiological recording equipment. Effects of the bridge signal and of the filter on the shape of the evoked response were demonstrated to be negligible.

An average response computer was used to sum both the evoked resistance shift and the evoked response simultaneously. Since the signal-to-noise ratio for the resistance shift was less than unity at the output of the lock-in amplifier, between 64 and 512 responses were summed to enhance the signal. The resolution of this system was such that impedance changes of the order of one part in 10^5 were clearly visible.

The resting resistance of cat cortex varied widely depending upon the type and depth of the anesthetic, the state of the preparation, and other factors. The measurements to be reported here were all made during intervals throughout which the resting resistance drifted less than .05 percent per minute. This resting value was ordinarily around 2000 ohms (at 10 khz) independent of the location of the indifferent electrode, but varied from cat to cat between about 1500 and 2500 ohms.

The cortical resistance changes following sensory stimulation are shown in Fig. 1. In A, recorded from auditory cortex, the click evokes a resistance shift (ERS) of about 0.05 ohm as well as an electrical response (ER) of several hundred microvolts. In B, recorded from visual cortex of another cat, flashes evoke an ERS and an ER comparable in magnitude to those produced by clicks at auditory cortex. Shifts in capacitive reactance were generally at least one order of magnitude smaller; only the ERS will be discussed here.

Both the click and flash ER in Fig. 1 display the latency, polarity, and waveshape characteristics well known for responses recorded from anesthetized cats in these locations. The latency of the ERS is the same as that of the ER in both cases, and while in some experiments the onset of the ERS may precede or follow that of the ER by a few milliseconds, no consistent difference seems to exist. The initial deflection in the ERS always shows a decrease in resistance, regardless of the depth of the electrode in the cortex; its duration and waveshape usually resemble the early positive deflection normally recorded by a surface electrode in the same area. As shown in Fig. 1, the initial resistance decrease in the ERS is regularly followed by a resistance increase that ends about 100 msec after the stimulus. The amplitude of the recorded ERS depends, finally, upon the bridge frequency used. If the value of this shift (in ohms) at 10 khz is called 1, its amplitude at 1 khz is about 3, and at 100 khz 0.25.

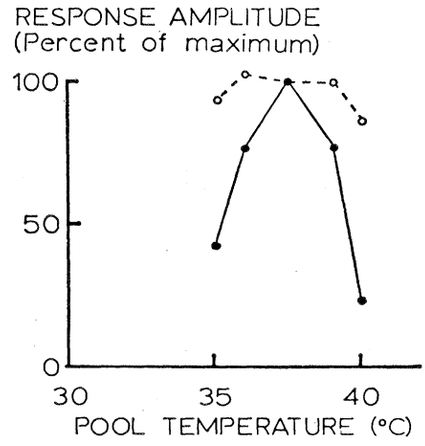

Fig. 2. Amplitude of resistance shift (closed circles) and evoked response (open circles) as a function of oil-pool temperature. Each point represents sum of 128 responses to clicks at 1.3-second intervals recorded from electrode about 1 mm deep in auditory cortex.

The obviously similar time courses shown in Fig. 1 for the ERS and ER suggest a similar physiological mechanism for both. Such a conclusion is supported by the results of experiments where responses to stimuli of graded intensity were delivered: the early components of ER and ERS grow in amplitude at approximately the same rate. Furthermore, the amplitude reduction of the response to a second stimulus closely following the first (so-called recovery curve) is approximately the same function of the interstimulus interval for both ERS and ER.

A number of additional facts, however, argue that separate mechanisms may underly the two phenomena. First, at different locations on the cortical surface the resistance shift always displays the same time course (within a few milliseconds) and polarity whereas the evoked response varies considerably with location. Second, as the recording electrode penetrates the cortex the ER

diminishes in amplitude and usually reverses its polarity; the ERS, by contrast, increases in amplitude with penetration into the cortex to approximately the inversion point of the ER, then diminishes to disappear at a depth where the electrode presumably penetrates white matter. Third, either warming or cooling the oil bath (± 5°C) away from 37°C has little effect upon the amplitude of the ER, but strikingly reduces the ERS amplitude, as Fig. 2 illustrates. Such dissociations between the two phenomena can also be demonstrated with manipulations of anesthetic depth and type, trauma, and asphyxia; for example, in recordings made on animals near death the ERS may disappear while the ER is still clearly present. When an animal finally stops breathing, the baseline resistance of its brain rises over a period of 20 to 30 minutes to reach final values around 6000 (versus 2000 at 1 khz), 5000 (versus 1500 at 10 khz), and 4000 (versus 1300 at 100 khz) ohms.

Mechanisms postulated for the evoked resistance shift must account for its two phases, an abrupt decrease followed by a more prolonged rise. The normal coincidence of ERS and ER (Fig. 1) suggests that events associated with depolarization of cortical neurons following the sensory input from the thalamus are critical. The simplest explanation of the ERS might therefore hold that reductions in membrane resistivity associated with depolarization of cortical neurons lie at the basis of the phenomenon. This argument is supported by the fact that the ERS reaches its maximum in the region of the pyramidal cell bodies where extensive neuronal membrane depolarizations might be expected. Such an explanation might serve the resistance decrease but no reported measurements show a resistance rise connected with neuronal membrane depolarization or recovery; an additional hypothesis would therefore be required to explain the later phase of increasing resistance in the ERS.

The dissociation between ER and ERS caused by temperature, trauma, and anesthesia, however, argues against a simple neuron depolarization theory, since the ERS may disappear when evidence of unchanged depolarization (a stable ER) exists. Hence other possibilities should be considered. Alterations in the extracellular space through which the measuring current flows is an outstanding possibility. Theoretically the measured resistance of brain would decrease if the extracellular space were to increase in volume or in ionic concentration. Evidence exists that such alterations in volume and composition do take place, though their time course as thus far measured is long compared to the events in the ERS. The diminution of ERS magnitude with increasing bridge frequency is not inconsistent with this possibility, since membrane capacitance would tend to shunt the extracellular path at higher frequencies, and only lower frequencies would detect changes in the extracellular fluid. Less likely possibilities involve changes of membrane resistance in cells other than those engaged in producing the ER. These would include neurons not discharging and glial cells. Synaptically depolarized or hyperpolarized neurons show conductivity increases (*3*); the ERS might depend upon such events in dendritic membrane (which may be more sensitive to anoxia and temperature change than the soma). Glial cells also alter their conductivity when stimulated, showing an initial increase followed by a decrease (*4*), but with a time course many times longer than required to explain the ERS described here for cats.

The remaining current paths that might alter cortical conductivity flow through intracellular fluids, and the blood vessels with their contents. It is unlikely that the ERS would depend upon changes in these factors.

The mechanism or mechanisms responsible for the ERS cannot be determined from the experimental evidence at hand. Neither the early resistance drop nor the later resistance increase can convincingly be assigned to neuronal events responsible for the elaboration of the sensory evoked response.

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Aminoacidemias: Effects on Maze Performance and Cerebral Serotonin

Abstract. *The feeding of high dietary supplements of* L-*phenylalanine (7 percent) and* L-*leucine (7 percent) to weanling rats is associated with poor performance in a multiple-T, water-escape maze. Supplements high in* L-*tryptophan (5 percent), on the other hand, result in maze performance which is superior to that of controls. Adding 5 percent tryptophan to the high-phenylalanine diet reverses the behavioral deficit. The quality of maze performance correlated with the cerebral content of serotonin.*

Considerable evidence has accumulated to demonstrate the impairment of maze performance subsequent to the administration of excessive dietary phenylalanine (*1–6*). We have found weanling rats on phenylketogenic diets to be less proficient than controls in mastering a multiple-T water maze (*2*). The water-escape reinforcement precluded the need for water- or food-deprivation which would have introduced additional uncontrolled variables. We also reported preliminarily on the effectiveness of tryptophan in improving performance (*2*). The behavioral deficit induced by phenylketogenic diets was confirmed by Polidora and his coworkers (*3–5*), and malnutrition was eliminated as a critical variable by pair-feeding techniques (*4*).

Behavioral effects have been ascribed to other amino acids when present in high concentrations in blood. Leucine has been associated with a severe degree of mental retardation in humans (*6*), and reversible changes in behavior have been noted in normal subjects following oral administration of high levels of L-tryptophan (*7*). Phenylalanine, leucine, and tryptophan have pronounced effects also on cerebral indole metabolism. Phenylalanine (*1*) and leu-