The stability of the Cu-peat complex, particularly at low salt concentrations, would result in extremely small quantities of soluble ionic Cu(II) in most soils.

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16 August 1955

Modification of Electric Activity in Cochlear Nucleus during "Attention" in Unanesthetized Cats

Attention involves the selective awareness of certain sensory messages with the simultaneous suppression of others. Our sense organs are activated by a great variety of sensory stimuli, but relatively few evoke conscious sensation at any given moment. It is common experience that there is a pronounced reduction of extraneous sensory awareness when our attention is concentrated on some particular matter. During the attentive state, it seems as though the brain integrates for consciousness only a limited amount of sensory information, specifically, those impulses concerned with the object of attention.

An interference with impulses initiated by sensory stimuli other than those pertaining to the subject of attention seems to be an obvious possibility. It is clear that this afferent blockade might occur at any point along the classical sensory pathways from receptors to the cortical receiving areas, or else perhaps in the recently disclosed extraclassical sensory paths that traverse the brain-stem reticular system (*1*).

Recent evidence indicates the existence of central mechanisms that regulate sensory transmission. It has been shown that appropriate stimulation of the brain-stem reticular system will inhibit afferent conduction between the first- and second-order neurons in all three principal somatic paths (*2–4*). During central anesthesia, the afferent-evoked potentials in the first sensory relays are enhanced. This appears to be due to the release of a tonic descending inhibitory influence that operates during wakefulness and requires the functional integrity of the brain-stem reticular formation.

The possibility that a selective central inhibitory mechanism might operate during attention for filtering sensory impulses was tested by studying (*5*) afferent transmission in the second- or third-order neurons of the auditory pathway (cochlear nucleus) in unanesthetized, unrestrained cats during experimentally elicited attentive behavior. Bipolar stainless steel electrodes with a total diameter of 0.5 mm were implanted stereotaxically in the dorsal cochlear nucleus through a small hole bored in the skull. The electrode was fixed to the skull with dental cement. A minimum of 1 week elapsed between the operation and the first electroencephalographic recordings. Electric impulses in the form of short bursts of rectangular waves (0.01 to 0.02 sec) at a frequency of 1000 to 5000 cy/sec were delivered to a loudspeaker near the cats at an intensity comfortable to human observers in the same environment.

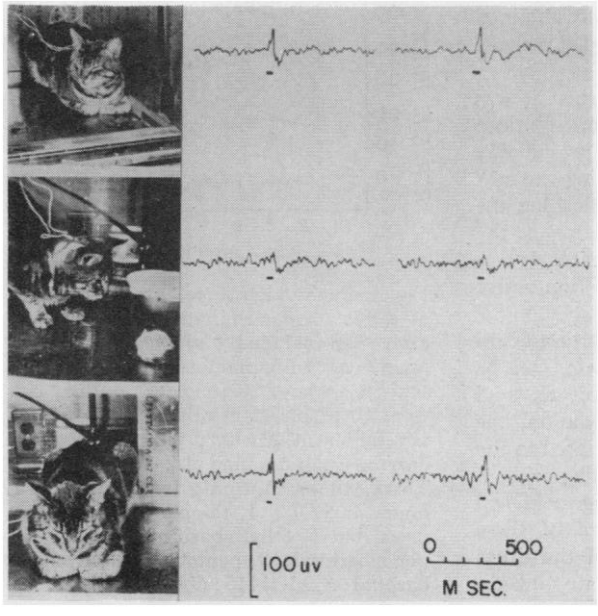

Fig. 1. Direct recording of click responses in the cochlear nucleus during three periods; the photographs were taken simultaneously. (Top and bottom) Cat is relaxed; the click responses are large. (Middle) While the cat is visually attentive to the mice in the jar, the click responses are diminished in amplitude.

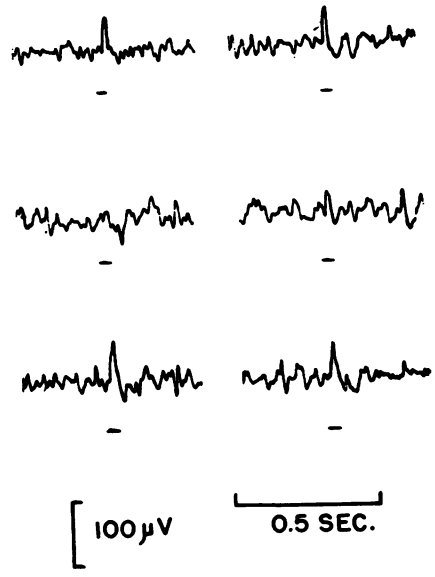

Fig. 2. Click responses recorded from the cochlear nucleus of the cat. (Top) cat is relaxed; (middle) cat is attentively sniffing an olfactory stimulus; (bottom) cat is relaxed again. Note the reduced amplitude of the click responses when the animal is sniffing.

Three types of sensory modalities were used to attract the animal's attention: visual, olfactory, and somatic. As is illustrated in Fig. 1, during presentation of visual stimuli (two mice in a closed bottle), the auditory responses in the cochlear nucleus were greatly reduced in comparison with the control responses; they were practically abolished as long as the visual stimuli elicited behavioral evidence of attention. When the mice were removed, the auditory responses returned to the same order of magnitude as the initial controls. An olfactory stimulus that attracted the animal's attention produced a similar blocking effect. While the cat was attentively sniffing tubing through which fish odors were being delivered, the auditory potential in the cochlear nucleus was practically absent (Fig. 2). After the stimulus had been removed and when the cat appeared to be relaxed once more, the auditorily evoked responses in the cochlear nucleus were of the same magnitude as they had been prior to the olfactory stimulation. Similarly, a nociceptive shock delivered to the forepaw of the cat—a shock that apparently distracted the animal's attention—resulted in marked reduction of auditorily evoked responses in the cochlear nucleus.

If this sensory inhibition during attentive behavior, as demonstrated in the auditory pathway, occurs in all other sen-

sory paths except the ones concerned with the object of attention, such an inhibitory mechanism might lead to favoring of the attended object by the selective exclusion of incoming signals. It is conceivable not only that such a selective sensory inhibition might operate simultaneously for various sensory modalities, leaving one or more unaffected but that the selectivity could extend to some discriminable aspects of any single modality—for example, to one tone and not to others. This suggestion finds support in the recent demonstration that sensory "habituation" may occur to a particular tone—that is, a slowly developing inhibitory effect on auditorily evoked potentials observed in the cochlear nucleus on prolonged repetition of a given tone, an influence that does not affect other frequencies that are novel to the animal (*6*). The pathway by which this inhibitory influence acts on incoming auditory impulses remains to be determined, but experiments now in progress have shown that during electric stimulation of the midbrain reticular formation, the auditory potential in the cochlear nucleus is depressed (*7*).

The present observations suggest that the blocking of afferent impulses in the lower portions of a sensory path may be a mechanism whereby sensory stimuli out of the scope of attention can be markedly reduced while they are still in their trajectory toward higher levels of the central nervous system. This central inhibitory mechanism may, therefore, play an important role in selective exclusion of sensory messages along their passage toward mechanisms of perception and consciousness. In a recent symposium on brain mechanisms and consciousness, Adrian pointed out that "the signals from the sense organs must be treated differently when we attend to them and when we do not, and if we could decide where and how the divergence arises we should be nearer to understanding how the level of consciousness is reached" (*8*).

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Effect of Barbiturates on Acetylation

Several different groups of investigators have recently attempted to demonstrate a biochemical action of barbiturates and other central nervous system depressants. After McLennan and Elliott (*1*) showed that acetylcholine synthesis by brain slices was inhibited by these agents, interest focused on the study of acetylation reactions generally, either in tissue slices or in relatively purified enzyme systems. The results of these studies, however, have been distinctly at variance with one another so that it has not been possible to draw any clear conclusions other than that the experimental methods offered some unseen difficulties (*2–4*). Experiments carried out in this laboratory may shed some light on this problem.

The acetylation system that was studied was that described by Kaplan and Lipmann—namely, the acetylation of arylamines by a pigeon liver enzyme in the presence of adenosine triphosphate (ATP) and coenzyme A (coA) (*5*). Both the crude coA and purified coA were used (Nutritional Biochemicals and Pabst Laboratories, 300 units/mg, 75 percent pure). The analytic procedure for sulfanilamide was that of Bratton and Marshall (*6*), using a photoelectric colorimeter. Similar results were obtained from the use of the pure and the crude coA preparations.

Purified coA was stable when it was kept cold and dry, but aqueous solutions rapidly lost their activity, presumably through oxidation. By dissolving the coA in 1.0*M* cysteine at *p*H 6.8, flushing the vessel with nitrogen, and storing in the freezing chamber of a refrigerator, it was possible to keep the coA solution active for 1 to 2 weeks.

The effect of various barbiturates on this "pure" acetylating system can be seen in Fig. 1. All the barbituric acid derivatives used inhibit acetylation, the amount of inhibition being related to the concentration of the drugs. The concentrations used included the range achieved pharmacologically in the use of these agents as anesthetics. One of the drugs was a convulsant barbiturate, 1,3-dimethylbutyl barbituric acid (*7*), and it too inhibits acetylation. Also tested were MC 1415 (2,2-diethyl-1,3-propanediol) and MC 2973 (2,2-diethyl-1,4-butanediol (*8*). Neither of these substances produces any significant inhibition of acetylation.

With respect to the mechanism of inhibition, addition of extra purified coA will alleviate the inhibition, but addition of extra ATP to the incubating mixture will not (Table 1). Addition of magnesium ions increases the inhibition by barbiturates rather markedly, perhaps by activating some residual ATPase, which may still contaminate the enzyme preparation. When the enzyme system from liver is further fractionated, it has been shown that it is stimulated, rather than inhibited, by magnesium (*9*).

The results presented, in agreement

Table 1. Effect of coA and ATP on inhibition of acetylation by phenobarbital.

coA (units)	ATP (μmole)	Phenobarbital ($10^{-3}M$)	Acetylation (%)	Inhibition (%)
Experiment 1				
0	4	0	0	
1.5	4	0	64.8	
1.5	4	1	50.0	22.8
3.0	4	0	75.1	
3.0	4	1	73.6	2.0
Experiment 2				
0	4	0	0	
1.5	4	0	70.8	
1.5	4	5	41.6	41.2
1.5	8	5	38.0	46.3

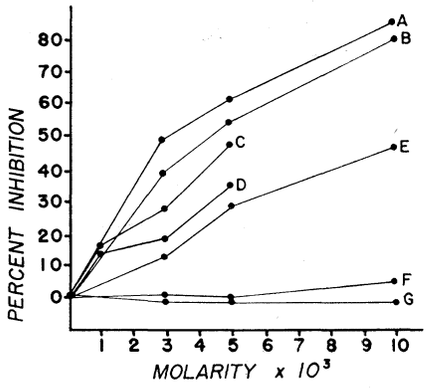

Fig. 1. Each value represents the average of duplicate determinations. Contents of each tube included 4 μmole of ATP, 0.4 μmole of sulfanilamide, 25 μmole of sodium acetate, 20 μmole of sodium citrate, 10 μmole of cysteine, 150 μmole of tris buffer at *p*H 8.3, 0.25 ml of aged enzyme solution, and 1.2 units of coA. Total volume 1.0 ml; incubated for 2 hours at 37°C. *A*, thiopental; *B*, 1,3-dimethylbutyl ethyl barbituric acid; *C*, phenobarbital; *D*, pentobarbital; *E*, amobarbital; *F*, MC1415; *G*, MC2973.