Gergen and MacLean's observations with extracellular recording (*1*). The fact that olfactory is less effective than septal stimulation could be explained if there were fewer impluses reaching the hippocampal cells in the former case or if there was a temporal dispersion of impulses. Or, compatible with the hypothesis stated in the introduction, it is possible that the major excitatory effect of olfactory impulses occurs at a greater distance from the trigger zone than that caused by the septal input.

The olfactory and septal pathways may be considered as representative inputs to the hippocampus from exteroceptive and interoceptive systems, respectively. Our experiments have revealed that stimulation of each input is effective in causing graded excitation of hippocampal neurons, with the notable difference that only the septal EPSP's are associated with cellular discharge. The duration of the EPSP's in each case may greatly exceed that reported for neocortical neurons (*7*). The hypothalamus, which has reciprocal connections with the septum (*8*), plays an important role in aversive, appetitive, visceral, and humoral reactions of an unconditional nature. In their paradigm for archicortical conditioning, Gergen and MacLean likened septal impulses to unconditional stimuli of classical conditioning, as these impulses are capable by themselves of discharging units (*1*). Olfactory and other stimuli of external origin, on the contrary, were pictured as analogous to conditioning stimuli, lacking the capacity, when at first acting alone, to cause discharge.

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Somatosensory Thalamic Neurons: Effects of Cortical Depression

Abstract. *Deafferented somatosensory thalamic neurons showed hyperactivity, followed by greatly reduced activity, after initiation of cortical spreading depression; local cooling of sensorimotor cortex was followed only by the inactive phase. Stimulation of contralateral midbrain reticular formation during the inactive phase failed to induce the typical increase in discharge rate of somatosensory thalamic neurons, but produced desynchronization in unaffected cortex. These results indicate that corticothalamic discharge is necessary for sustaining the ongoing activity of deafferented somatosensory thalamic neurons and for maintaining their responsiveness to stimulation of the reticular formation.*

Many sensory neurons within the central nervous system show an ongoing "spontaneous" discharge after elimination of specific sensory inflow (*1*, *2*). Fluctuations in excitability and in rate and pattern of discharge may occur, even when stimulus conditions are constant (*3*). Such observations provide functional evidence for convergence upon central sensory neurons of influences other than those originating within their receptive fields. The changes in single neuron activity associated with sleep and arousal or with desynchronization of the electrocorticogram (ECoG) are generally assumed to reflect activation by the brain stem reticular formation. However, convergence at subcortical relays must be investigated before effects at higher levels can be interpreted. Repetitive electrical stimulation of the midbrain reticular formation of the cat increases the rate of discharge of lateral geniculate neurons (*4*) and of neurons of the somatosensory relay nucleus ventralis posterior (VP)

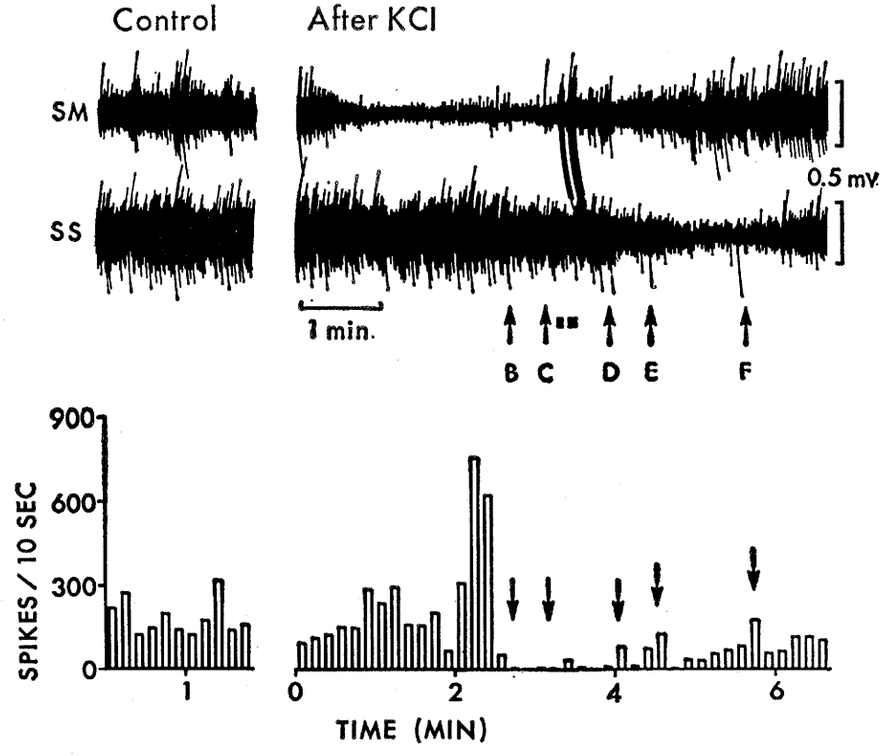

Fig. 1. Effect of cortical spreading depression on activity of a single VP neuron. Electrocorticographic recordings of sensorimotor (SM) and anterior suprasylvian (SS) cortex shown above. Histogram shows concurrent counts of neuron discharges in consecutive 10-second periods. Potassium chloride (2.5*M*) was applied to sensorimotor cortex after control run (left), a few seconds before start of experimental run (right). Arrows mark onsets of stimulus trains applied to contralateral reticular formation. Stimuli were 100 bidirectional pulses per second; each phase was 0.3 ma and lasted 0.1 msec. Rectangles mark periods of stimulation of afferent tracts in midbrain at 1.2-second intervals.

(*5*), and facilitates the response to a test stimulus applied to medial lemniscal afferent fibers (*6*). Direct projections of the reticular formation or indirectly relayed projections through the medial thalamic nuclei have been proposed as the routes mediating these thalamic effects, and several investigators have concluded that the role of corticofugal projections is unimportant (*1*, *7*). We designed experiments to determine whether changes of corticofugal activity affect the spontaneous discharge of individual VP neurons and their responses to stimulation of the midbrain reticular formation. Corticofugal activity was reversibly altered either by spreading depression (SD) or by local cooling.

Cats were prepared under ether anesthesia, followed by local infiltration of procaine and neuromuscular blockade with gallamine triethiodide. Small amounts (2 to 10 mg/kg) of sodium thiopental were given at irregular intervals to maintain a drowsy or slow-wave sleep ECoG. Activity of individual VP neurons was recorded with stereotaxically placed micropipettes (1 to 3 μ tip diameter) which were filled with 2.5*M* KCl. Data were stored on analog magnetic tape for subsequent analysis (*8*). Most electrode penetrations were through the medial portion of nucleus ventralis posterolateralis, which receives input predominantly from the contralateral forepaw. To eliminate centrally originating influences on VP neurons which might be indirectly mediated via the cuneate and gracile nuclei, these structures were thermocoagulated contralaterally. The effectiveness of deafferentation was demonstrated by the inability to evoke discharge of VP neurons by touch or manipulation of skin or joints. Because of the absence of peripheral input, VP neurons were functionally identified by short latency (for example, 0.9 to 2.0 msec) responses to stimulation of lateral midbrain ascending tracts and usually by antidromic invasion from forepaw somatosensory cortical area I (latency $\leq$ 0.8 msec) (*9*). Occasionally, neurons responded to very weak mechanical stimulation and, with short latency, to electrical stimulation of the contralateral forepaw despite extensive destruction of the contralateral medulla. Such neurons were probably innervated by projections from the lateral cervical relay (*10*) and were not included in this study. Neurons activated by stimulation of the face or whiskers also were not included. To minimize the possibility of direct stimulation of afferent fibers to VP, we stimulated the midbrain reticular formation contralaterally. Brains were frozen, sectioned, and stained with cresyl violet for histological verification of the location of electrode tracks.

The effect of cortical SD on the activity of 25 VP neurons was studied in 15 cats. We induced SD by touching the pia with a capillary tube containing 2.5*M* KCl. The position of cortical recording electrodes and the site of initiation of SD were varied to aid in localizing the cortical origin of effects on thalamic neurons. The initial effect usually was desynchronization of the ECoG, accompanied by acceleration of the mean rate of discharge of a simultaneously recorded VP neuron and by disappearance of brief interspike intervals (< 5 msec). Such changes in rate and pattern of discharge resembled those occurring before SD during periods of spontaneous ECoG desynchronization or following repetitive stimulation of the midbrain reticular formation; these changes are characteristic responses of VP neurons to reticular activation (*5*). However, this initial *activation* phase was overshadowed by a further large increase in rate (*excitation* phase) lasting 10 to 150 seconds, followed by a longer period of reduced discharge (*inactive* phase). All VP neurons unequivocally influenced by SD showed this sequence of excitation and inactivity. During the recovery of spontaneous activity, the percentage of discharges which were in high-frequency bursts (*11*) was substantially higher than before SD, although the total number of both burst and non-burst spikes was reduced. The bursts were often concurrent with spindle-like waves recorded from sensorimotor (SM) cortex. The VP neuron of Fig. 1 was identified as a cortically projecting neuron because it was antidromically invaded with a latency of 0.75 msec following stimulation of the posterior sigmoid gyrus. About 2 minutes after KCl was applied to the same gyrus, the mean rate of discharge increased to an extremely high level (752 spikes in 10 seconds). The neuron had already entered the inactive phase before SD reached the posterior recording position. Responsiveness of the neuron to stimulation of the reticular formation was tested during this period (Fig. 2). Before SD (Fig. 2A), the mean rates of discharge for 10 seconds preceding and 10 seconds following the onset of stimulation were 11.8 and 24.1 per second, respectively. Subsequent histograms, corresponding in time to the arrows in Fig. 1, show virtual loss of response to stimulation during the inactive phase (Fig. 2, B and C) and gradual return of responsiveness when spontaneous activity returned (Fig. 2, D–F). During the early stages of recovery, stimulation of the reticular formation often seemed to accelerate recovery of neurons toward their control rate of discharge.

The neuron responded to lemniscal stimulation before SD with latencies of

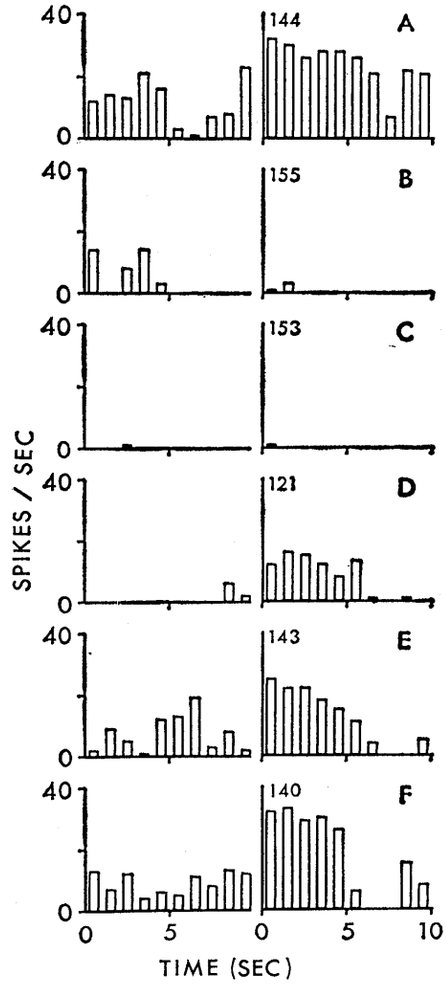

Fig. 2. Counts of single neuron discharges in ten consecutive 1-second periods preceding and immediately following onset of each reticular formation stimulus train. Neuron is same as in Fig. 1. Histogram A is from control run preceding Fig. 1; B–F correspond to arrows of Fig. 1. Vertical line marks onset of stimulus train; numerals indicate number of stimuli at 100 per second; incompleted portion of 1-second bin preceding stimulus train was discarded from each histogram.

0.9 to 1.2 msec and to each of 11 stimuli, applied during the inactive phase, with latencies of 0.9 to 1.0 msec. In additional experiments with this and other neurons, we detected reduced excitability only in the early part of the inactive phase, by finding either an increased threshold, a transient increase in latency, or a transient failure to respond to a constant stimulus. The increase in threshold was less than 10 percent in an experiment in which the measurements were completed during the first half of an inactive phase lasting approximately 4.5 minutes.

When SD was initiated in SM cortex, the changes in VP neuron discharge frequently preceded spread of SD to the ECoG electrode on the suprasylvian or lateral gyrus, 3 to 10 mm posterior to SM cortex (Fig. 1). Furthermore, when records were taken from the same neuron, the latency for the excitation phase was much shorter (60.5 seconds) when the KCl was applied to the posterior sigmoid gyrus about 2 mm from the cruciate sulcus than when it was applied to somatosensory area II near the suprasylvian sulcus (402 seconds). The observed latency includes propagation time tangentially from the site of initiation to the location of cortical neurons mediating the excitation phase in VP. In addition, the latency includes a radial component of spread (at the same velocity as the tangential component) because SD initially invades the superficial layers (*12*). In the experiment yielding a minimum latency of 60.5 seconds, the observed propagation velocity was 1.6 mm/min for four trials; this was probably an underestimate because either one or two sulci were interposed. If it is assumed that the true velocity was as much as 3 mm/min, the tangential spread was less than 3 mm from the site of application of KCl. These results suggest that the excitation phase begins while the wavefront of SD is within the posterior sigmoid or pericruciate cortex.

Because of the complex effects of SD, we also tested the effect of lowering the temperature of SM cortex on seven VP neurons in three cats. Cooling was produced by vaporization of ethyl chloride under reduced pressure in a small chamber. The surface in contact with the brain was an electrically insulated silver disk (9 mm in diameter) to which a recording electrode and a thermocouple were cemented. The effects of cooling SM cortex are shown in Fig. 3. No excitation phase appeared during cooling (except in one instance when SD also resulted). When the temperature of the pial surface was lowered, the mean rate of discharge decreased from 10.3 per second before cooling to 2.9 per second in the 1st minute and 0.9 per second in the 2nd minute after the onset of cooling. During this time, the fraction of discharges forming high-frequency bursts increased from 23 percent before cooling to 63 percent during the 1st minute and 84 percent during the 2nd minute of cooling. The length of high-frequency bursts increased only slightly, from 3.0 spikes per burst before cooling to 3.4 spikes per burst in the 2nd minute after the onset of cooling. The high-frequency bursts were often related to the occurrence of spindle-like waves which were recorded from the cooled SM cortex but which did not appear at the suprasylvian recording electrode. Such changes in neuron firing pattern were similar to those observed during recovery from SD, and occurred during the period of reduced responsiveness to stimulation of the reticular formation.

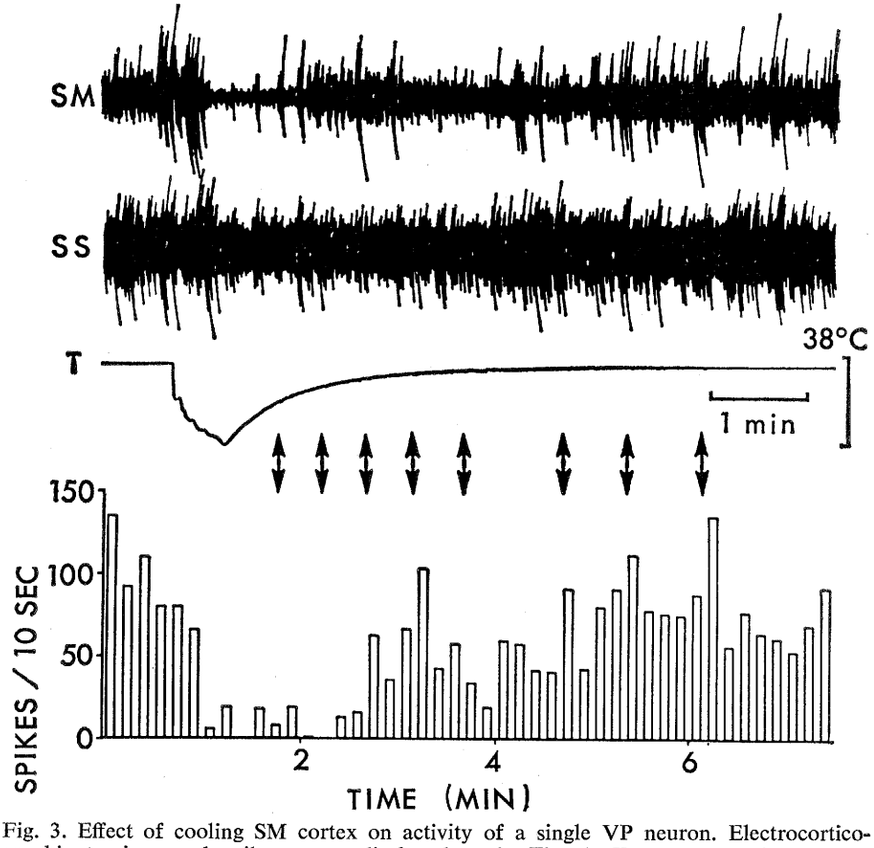

Fig. 3. Effect of cooling SM cortex on activity of a single VP neuron. Electrocorticographic tracings and spike counts displayed as in Fig. 1. Temperature change (T) measured by thermocouple cemented to surface of cooling chamber in contact with pia; irregularities of T during cooling resulted from the injection of successive increments of ethyl chloride into the chamber. Arrows mark onsets of reticular formation trains containing 168 or 169 stimuli at 100 per second; each phase of the bidirectional stimuli was 0.4 ma and lasted 0.1 msec. The neuron failed to respond to the first and second stimulus trains during rewarming but responded to the third and to subsequent trials.

The phases of increased activity of VP neurons during SD might result either from corticofugal facilitation or from the withdrawal of tonic corticofugal inhibition (*13*). However, the failure of cortical cooling to cause increased discharge of VP neurons suggests that hyperactivity during SD does not result from the withdrawal of corticofugal inhibition, but is due to the brief (2 to 3 seconds) high-frequency discharge of cortical neurons in the advancing wavefront of the SD (*14*). Such corticofugal discharge may activate the reticular formation (*15*) and thus evoke the initial activation phase of VP neurons. The excitation phase evidently reflects a more intense excitatory input to VP than results from reticular activation alone, suggesting that the wavefront of the SD has reached the specific corticothalamic neurons projecting directly or through thalamic interneurons to the VP neuron being studied (*16, 17*).

Clearly the inactive phase cannot be explained by a general depression of the "ascending reticular system" because ECoG desynchronization (occurring either spontaneously or following stimulation of the reticular formation) was observed in cortex 1 cm or more from the site of depression. This inference is consistent with the finding of Bureš *et al.* (*18*) that in the unanesthetized rat most reticular neurons only increased in rate during SD. (By contrast, the majority of medial thalamic neurons they studied showed only an inactive phase.) Neither synaptic fatigue (for example, transmitter depletion) nor delayed inhibition, caused by the high level of corticofugal discharge, adequately account for the inactive phase, because it was readily observed during cortical cooling without a preceding phase of hyperactivity. The mean rates of discharge attained during SD excitation exceeded those occurring either spontaneously or in response to stimulation of the reticular formation. However, some innervated neurons may be driven at comparable rates for many seconds by peripheral stimulation but return quickly to the control rate of discharge following such stimulation (*19*).

Although reduction of corticothalamic discharge is associated with reduced activity of VP neurons, our experiments do not directly differentiate between reduced direct excitatory drive and reduced inhibition of tonically active inhibitory interneurons (disinhibition). Either mechanism would lead to reduced facilitation of VP neurons. However, because increased inhibition of tonic inhibition probably could not alone account for the very high level of discharge during the excitation phase we conclude that the dominant effect exerted by corticothalamic neurons is synaptic excitation.

Therefore, the relatively small decrease in excitability that was observed during the early part of the inactive phase probably resulted from reduced synaptic facilitation. Our finding that depression of sigmoid gyrus and adjacent cortex leads to reduced VP neuron activity is consistent with anatomical evidence that this region of cortex projects to VP (*17*). The data imply that the response of VP neurons to reticular formation stimulation requires corticothalamic facilitation. Either reticular activation of VP is mediated solely by corticothalamic neurons, or the response requires the summation of corticothalamic with reticulothalamic discharge. Further investigation is required to differentiate between these alternatives.

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9. Ability of neurons to respond to consecutive stimuli at 500 per second is a useful criterion for identifying an antidromic response, even though antidromic impulses sometimes fail to invade the soma-dendrite region of VP neurons because the cortical stimulus train also evokes postsynaptic inhibition (*16*). We did not apply this criterion in this study because such stimulation may also evoke convulsive afterdischarge in the unanesthetized or lightly anesthetized cortex. However, VP neurons responding to stimulation of somatosensory cortex with latencies of 0.5 to 0.9 msec in cats anesthetized with barbiturate rarely fail to follow four minimally suprathreshold stimuli at 500 per second. Use of the latency criterion alone is unlikely to have resulted in our classifying some interneurons as cortically projecting, but may have resulted in our failure to classify some antidromically invaded neurons with slowly conducting axons as cortically projecting.
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Lateral Hypothalamic Stimulation in Satiated Rats: The Rewarding Effects of Self-Induced Drinking

Abstract. *It is well known that thirsty rats will press a lever for water. The purpose of the present experiment was to demonstrate that, when water is freely available, nonthirsty rats will press a lever for thirst. Three satiated rats, bearing permanently implanted electrodes, were trained to press a lever which caused stimulation to be applied to an area of the lateral hypothalamus which induces thirst. The animals were tested with and without water available. Two of the rats pressed the lever to induce thirst only when water was available. Thus, thirst-inducing stimulation was not rewarding by itself, but only in combination with drinking.*

Thirsty laboratory animals readily learn to engage in responses (for example, pressing levers) which are followed by the presentation of water which they drink. The responses are usually said to be motivated by thirst and reinforced by drinking, and the experiment is said to demonstrate the reinforcement principle or law of effect. However, empirically all that can be said is that thirsty animals respond in order to obtain water, while satiated animals do not; that is, the simultaneous presence of thirst and water constitutes a rewarding situation. The empirical "law" is that responses followed by this combination tend to increase in frequency of occurrence. In this case the law is demonstrated by supplying the animal with one member of the combination (thirst) and presenting the second member (water) after the animal presses the lever. However, it is also logically possible to demonstrate this law by interchanging the members of the combination, that is, by supplying the animals with water, and inducing thirst each time the animal presses the lever. The rapid induction of thirst by electrical stimulation of the lateral hypothalamus (*1*) provides a means of testing this possibility.

Five inexperienced albino rats were implanted with two monopolar stainless steel electrodes placed one on each side of the brain in the lateral hypothalamus (Krieg coordinates: 1.0 mm posterior to bregma, 1.4 mm lateral from the midline, and 8.2 mm below the superior surface of the skull). Also an indifferent electrode consisting of an uninsulated stainless steel wire (5 mm