ing the time in which lidocaine is administered and is active. Significance of these data to the practitioner might be that in a diurnal animal such as man, increased susceptibility to the toxicity of lidocaine hydrochloride may occur more frequently in the activity phase of the animal's circadian cycle, and consequently time of day should be considered in the determination of each individual dose of lidocaine hydrochloride.

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13 February 1967

Thalamic Reticular System and Central Grey: Self-Stimulation

Abstract. *Rats will press a bar that brings about stimulation of midline thalamic reticular, periventricular, and central grey brain regions. In the latter two regions stimulation can also cause pain or fear.*

There is evidence to indicate that electrical stimulation of midline and intralaminar nuclei at low frequencies in the unanesthetized animal can induce sleep (*1*). In the same kind of preparation, stimulation at higher frequencies characteristically induces stereotyped motor movements or visual searching responses (*2*). Self-stimulation mapping studies of the brain have included few electrode placements within this area (*3, 4*). Nevertheless, on the basis of these studies investigators have suggested that self-stimulation is not characteristic of thalamic reticular system placements (*4, 5*). It has also been concluded that self-stimulation cannot be obtained with electrodes implanted in periventricular and central grey brain regions (*4, 6*). In contrast to these beliefs, the present study demonstrates that self-stimulation occurs with electrodes located within the thalamic reticular system, periventricular, and central grey regions of the brain.

Single, bipolar, enameled stainless-steel wire electrodes were implanted in rats, by techniques outlined previously (*7*). Each animal was assessed for self-stimulation in the Skinner box test. In this test a bar-press resulted in 60-cycle sine wave stimulation of the brain for a duration up to 0.5 second. Operant rates of responding without brain stimulation were established over four daily 15-minute sessions. On the fifth and subsequent days a bar-press closed a circuit that resulted in brain stimulation. Current levels were usually increased each day. On the basis of the Skinner box test the animals could be grouped into three classes. In the first class (SS) a current level was reached at which the animals consistently self-stimulated during the test periods. Bar-press rates ranged from 200 to 300 presses within the test period. Self-stimulation was usually accompanied by forced motor movements involving the forelimbs and neck. Observation of these animals in the Skinner box suggested that the brain stimulation had no noxious effects in spite of the fact that at high current levels the forced motor movements were sometimes intense enough to throw the animal about.

Animals in the second class (SS-P) also demonstrated self-stimulation behavior. In some cases, however, self-stimulation was obvious only after repeated test sessions at the same current level. Thus, Fig. 1 indicates no rise in response rate by an animal first tested at a particular stimulation intensity. Observation had suggested, however, that the stimulation had reached an intensity at which it was having some effect. Repeated sessions at the same intensity bore this out. Several SS-P animals exhibited this same behavior and in some instances bar-press rates rose by several hundred presses over sessions at the same stimulation intensity. Some animals in the SS-P group did show a rise in pressing rate when first tested at an effective current level. In some cases this rate was maintained or increased, while in others it was followed by a decrease, at higher current levels.

All SS-P rats as well as SS rats selfstimuated at above operant bar-press rates. Unlike SS subjects, however, self-stimulation was accompanied by signs

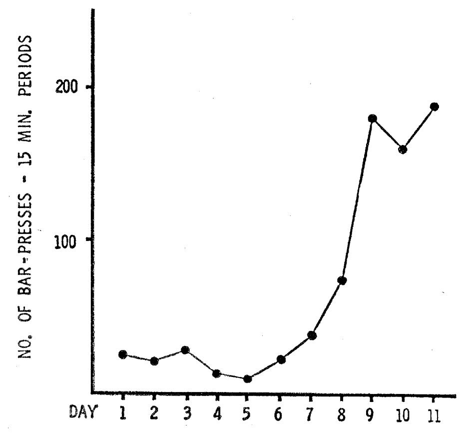

Fig. 1. Electrode in periventricular grey. Note slow rise in response rate over daily sessions at the same stimulus intensity.

of pain and fear (for example, shrieking) in SS-P animals. Usually when the shrieking reached the point where it accompanied each of a number of bar-presses the animal stopped manipulating the bar for several seconds, only to repeat the cycle again. Approach-avoidance behavior toward the bar was also noted.

Other observations also bore out the distinction between class SS and class SS-P animals. For example, many of these rats were placed in a rectangular box with a movable elevated platform. The weight of the animal on the platform closed a microswitch which initiated a train of 0.5-second-on, 0.5-second-off brain stimulation. At above-threshold currents SS animals would learn to move onto the platform and stay there. SS-P animals would move onto the platform and then off repeatedly. Limited use was made of experimenter-controlled brain stimulation. However, observation of SS animals during several seconds of on-off brain stimulation at above-threshold self-stimulation current levels did not indicate noxious effects. Such stimulation of SS-P animals resulted in running movements that were clearly indicative of pain or fear.

Most animals of our third group (U)

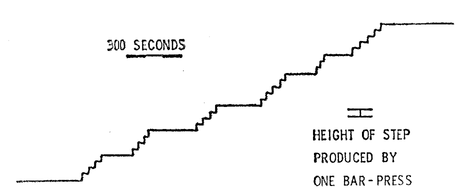

Fig. 2. Electrode in central grey. Representative portion from a prolonged 200-minute test session. Bar-press rate is low but regular, indicating self-stimulation.

responded to stimulation in a manner clearly indicating pain or fear. Unlike SS-P animals, however, high above-operant press rates could not be demonstrated at any current intensity in the regular 15-minute Skinner box test sessions. It is possible, however, that at least two of the five rats included in the U group could be appropriately placed in the SS-P group if manner, rather than rate, of bar-pressing is considered. Thus one of these animals, given a prolonged 200-minute test session, pressed at an average rate of only once per minute. Nevertheless, pressing did not occur at random. From Fig. 2 it can be seen that this animal with an electrode in dorsal central grey tended to press in clusters of about four at regular intervals. Moreover, the time between presses within a cluster tended toward constancy. In some clusters the intervals between each bar-press varied from 28 to 32 seconds. During these latter intervals the animal adopted a frozen posture, as if attending to some aftereffect of the stimulus. Probably the timing of responses within a cluster was closely tied to the duration of the aftereffect. The self-stimulation behavior of such animals seems no less significant than that of the SS-P animal which pressed 1100 times in a 15-minute session.

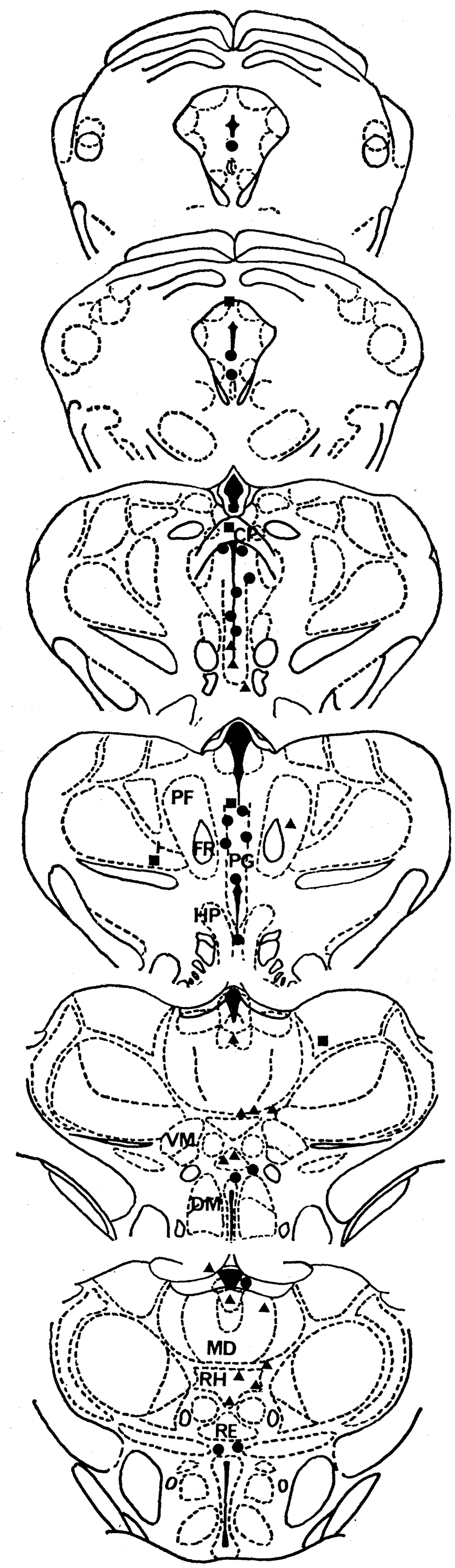

Fig. 3. Electrode tip locations of SS (triangle), SS-P (circle), and U (square) animals. Coronal sections slightly modified from König and Klippel (*11*).

At the conclusion of testing, the animals were killed and electrode placements (Fig. 3) were ascertained from cresyl violet or cresyl violet–luxol fast blue stained brain sections. The tips of the electrodes of several SS animals were located in centralis medialis, centralis lateralis, rhomboidalis, and reuniens, and one tip was located in nucleus parafascicularis. These SS placements correspond to nuclei making up the thalamic reticular system (*8*). Most SS-P placements were located in periventricular and central grey brain regions.

Functions proposed for the thalamic reticular system include sleep, consciousness, control of cortical rhythms, epilepsy, attention, learning, and nonspecific motivation. While such proposals are not mutually exclusive, such a long list seems compatible with our belief that there is little understanding of the functional significance of the thalamic reticular system. At the risk of adding to this list of supposed functions we feel that the present investigation indicates that the system is involved in specific motivational processes. Our contention is based on strong evidence indicating that self-stimulation always includes activation of specific motivational processes (*9*).

Many reports (for example, *4, 6*) indicate that stimulation of the periventricular fibers and central grey is noxious. Experiments and theories have been based on the belief that self-stimulation cannot be obtained from electrodes implanted within this area (*6, 10*). The present study indicates, however, that the self-stimulation effect is also consistently found in this region.

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Quasar 3C 446

Variations in optical light have been observed (*1*) in several quasi-stellar objects (quasars). Although no certain evidence has yet been obtained of variations within a month, the occurrence of fluctuations with shorter intervals has been suggested (*2*).

During the second week of October 1966 a photographic patrol of quasar 3C 446 was initiated at the Bethany Observing Station of Yale University Observatory, using the new 40-inch (1-m) telescope. This particular object was selected after Sandage's observation in July 1966 that it had brightened considerably since October 1964. This note announces our discovery of light variations having a considerably shorter period than the periods we have mentioned. Figure 1, covering a period of 2 months, shows significant variations in light over intervals of the order of 1 day.