hours of continuous light. Inhibition of flowering is possible by the action of continuous light on leaves which are situated well below the leaves treated with short days. The inhibitor induced by continuous light must migrate from its origin toward the apex soon after it is produced. Inhibition by continuous light is not localized in the leaves; an inhibitor is transmitted to the apex without interfering with either the production or the translocation of the floral stimulus, but prevents flower bud formation at the growing point. The dominant role of this inhibition at the apex disappears after a certain time so that the stimulus can express itself; only then can the flowering processes proceed normally.

On the basis of these results and other work to be reported elsewhere (*6*), I suggest that the morphogenetic changes at the apex are regulated through competition between the flower-inhibiting and flower-promoting substances, both arising in the leaves and both acting at the apex.

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References and Notes

1. W. W. Schwabe, *Ann. Botany London* **20**, 1 (1956).
2. S. J. Wellensiek, *Proc. Koninkl. Ned. Akad. Wetenschap. Ser. C* **61**, 552 (1958).
3. ———, *Compt. Rend. Acad. Agr. France* **46**, 607 (1960).
4. S. C. Bhargava, *Proc. Koninkl. Ned. Akad. Wetenschap. Ser. C* **66**, 371 (1963).
5. G. Meijer, *Acta Botan. Neerl.* **6**, 395 (1957).
6. S. C. Bhargava, *Mededel. Landbouwhogeschool Wageningen* **64**, No. 12, 1, (1964).
7. This work is publication No. 258 from the Laboratorium voor Tuinbouwplantenteelt, Landbouwhogeschool, Wageningen, Netherlands.

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Spreading Depression and Recovery from Lateral Hypothalamic Damage

Abstract. *Spreading cortical depression reinstates aphagia and adipsia in rats recovered from lateral hypothalamic lesions. We suggest that cortical activity facilitates and maintains recovery by enhancing the activity of depressed, but intact, tissue adjacent to the lesions.*

Lateral hypothalamic lesions produce in rats an aphagia and adipsia from which they gradually recover (*1*). Such rats, at first, do not eat or drink, lose weight, and will die unless kept alive by intragastric tube-feeding. Then they progress to a stage of anorexia and adipsia, in which they eat wet and palatable foods, but not enough to maintain their weight. They still refuse to drink water, and die unless tube-feeding is continued. In a later stage of recovery, they regain their ability to regulate their caloric intake and maintain their weight but they remain adipsic—they still refuse to drink water. Eventually, however, they drink water, eat dry food, and appear completely recovered (*2*).

We do not fully understand how this recovery of function occurs. The tissue adjacent to the original lesions appears to be important: after complete recovery, additional lesions adjacent to the original lesions will again cause aphagia and adipsia (*2*). Therefore, it is possible that, in addition to the total destruction caused by a lesion, a temporary depression of activity is produced in the tissues adjacent to it. Such a temporary depression could be caused by local physical trauma—edema, partial poisoning of cells through deposition of metallic ions by the direct current used to produce our lesions (*3*), or by gliosis. In addition, a phenomenon such as "spinal shock" may occur; destruction of one region may cut off facilitating impulses to adjacent or related tissues, which are then unable to function (*4*). After some time, the depressed tissues recover their excitability and the symptoms disappear. By this reasoning, the activity of nervous tissue adjacent to lateral hypothalamic lesions is essential for the recovery of feeding and drinking.

The cerebral cortex appears to be important in maintaining lateral hypothalamic activity. During spreading cortical depression induced by KCl, the activity of cells in the lateral hypothalamus is greatly decreased (*5*). Spreading depression also eliminates self-stimulation in the lateral hypothalamus (*6*). Because the lateral hypothalamic areas that lie in the positive reward system are the same ones in which electrical stimulation induces feeding (*7*), it follows that spreading cortical depression should also decrease the activity of the feeding system. As shown by Bureš and his coworkers (*8*), aphagia and adipsia are produced in normal animals during spreading depression. In rats which have recovered from lateral hypothalamic lesions and which possess less remaining functional tissue in the feeding system, spreading depression should reinstate aphagia and adipsia, and the effect should be more pronounced than in normal animals. This is what we show in this report.

Two groups of Long-Evans hooded male rats each weighing 250 to 300 g were prepared. The experimental group consisted of six rats, fully recovered from lateral hypothalamic lesions (with the skull held level, the stereotaxic coordinates were: A 6.0, L 2.0, 8.0 mm down from cortex; anodal direct current, 1 ma, applied for 20 seconds). The average rate of recovery was 26 days (range 20 to 33 days), and recovery terminated an average of 15 days before the onset of spreading depression. Five control animals were used.

In both groups of animals, using the method developed by Bureš (*8*), we exposed the dura of both cerebral hemispheres by drilling a 5-mm hole in the skull directly over the midline suture, or in some animals, two such holes as close as possible to the midline. If a piece of filter paper large enough to fill the hole in the skull is soaked in 25 percent KCl and is placed directly on the dura, waves of depolarization are produced which spread over the entire cerebral cortex and diminish spontaneous cortical activity for 3 to 4 hours (*8*). The depression is believed to be largely confined to the cerebral cortex of that hemisphere (*8*) although there are reports of it spreading into the striatum (*9*). Animals trained previously to avoid shock do not do so during spreading depression (*8*). This is so reliable an indicator that we routinely monitored the effectiveness of cortical depression by testing the animal's ability to turn a wheel to avoid shock. After 3 to 4 hours, all animals regained this ability. To allow repeated applications of KCl in the same animal, in a method similar to that of Russell and Ochs (*10*), we placed stainless steel tubes (5 mm inside diameter and 6 to 7 mm long) on the skull surrounding each hole and fixed them permanently to the skull with screws and dental cement. Each tube was threaded internally to receive a stainless steel screw so that the opening in the skull could be capped tightly to prevent drying of the dura.

To insure that they would eat readily at the time of testing, all animals received no food for one day and limited food thereafter to keep their weight at approximately 85 percent of normal. Filter paper was placed on the dura and was then soaked with 0.05 ml of 25 percent KCl dripped into each dural cap with a hypodermic syringe.

In some tests, instead of KCl solution, 14 mg of crystalline KCl was applied directly to the dura. The caps were then resealed with their screw tops. The animals were replaced in individual cages and, 10 minutes later, given free access to water in a Richter tube, dry Purina pellets scattered in the cage, and 25 ml of eggnog in a Syracuse watch glass on the cage floor. Their behavior, particularly their feeding and drinking, was observed continuously for the next 36 hours. Body weight and food and water intake were measured daily thereafter.

In the control rats, the effect of spreading depression on feeding and drinking was quite clear. In the first hour or so, they occasionally showed reflexive licking of smooth surfaces: they licked the smooth outer side of the glass dish or the flat surfaces of the Purina pellets. If they encountered the rough end of a pellet, they sometimes showed reflex gnawing. But, if the dish or pellet was moved away a few centimeters, the animals made no attempt to find them, and only licked or gnawed when they happened to contact them accidentally. Otherwise, they ignored all food and water (*8*). After 2 to 3 hours, the animals usually began to eat liquid diet. The liquid diet was removed at that time, and they usually did not eat pellets or drink water until 6 to 8 hours after the onset of depression. At that time, those previously trained would press a bar to obtain pellets of food. They ate repeatedly from that time on, so that after 24 hours, as shown in Fig. 1 (bottom), they had ingested a normal daily quantity of food and water, gained weight, and appeared normal. Within 4 to 5 days (ranging from 3 to 6 days), they had regained their normal (prior to deprivation) weight.

In rats with lateral hypothalamic lesions, there was a much more pronounced effect on food and water intake. One animal did not eat or drink for 4 days following the depression. Its weight loss, when added to that already sustained during its deprivation before depression, was so great that it died without recovering. A second animal was maintained by tube-feeding for 8 days after cortical depression. As shown in Fig. 1 (top), it was aphagic and adipsic for 6 days, anorexic and adipsic for 2 more days, and then it recovered the ability to regulate its intake of liquid diet. It was weaned to sweet, less-nutritive fluid and ate pellets on the 16th day. Finally, after 21 days, it drank water and maintained its weight on dry food, but it did not reach its normal weight until 27 days after the onset of spreading depression. The other four animals with lateral hypothalamic lesions showed lesser effects but all were much more affected than the control rats. Except for sporadic nibbling, they did not eat or drink anything for at least 24 hours, then took liquid diet within the next day. They did not drink water and eat dry food until the 3rd day after depression. Their food and water intake was greatly depressed for several days thereafter, and they typically did not regain their normal weight for 15 days (10 to 24 days). After the animals had fully recovered, spreading depression was produced again in all the control rats and two of the least affected experimental animals by means of crystalline KCl. As before, the food and water intake was always more severely depressed in the animals with lateral hypothalamic lesions than in the control animals. In animals recovered from lateral hypothalamic lesions, therefore, the syndrome of aphagia and adipsia was reinstated by spreading cortical depression.

It is commonly thought that spreading depression is fully reversible (*8*). It may be difficult, therefore, to understand why aphagia and adipsia per-

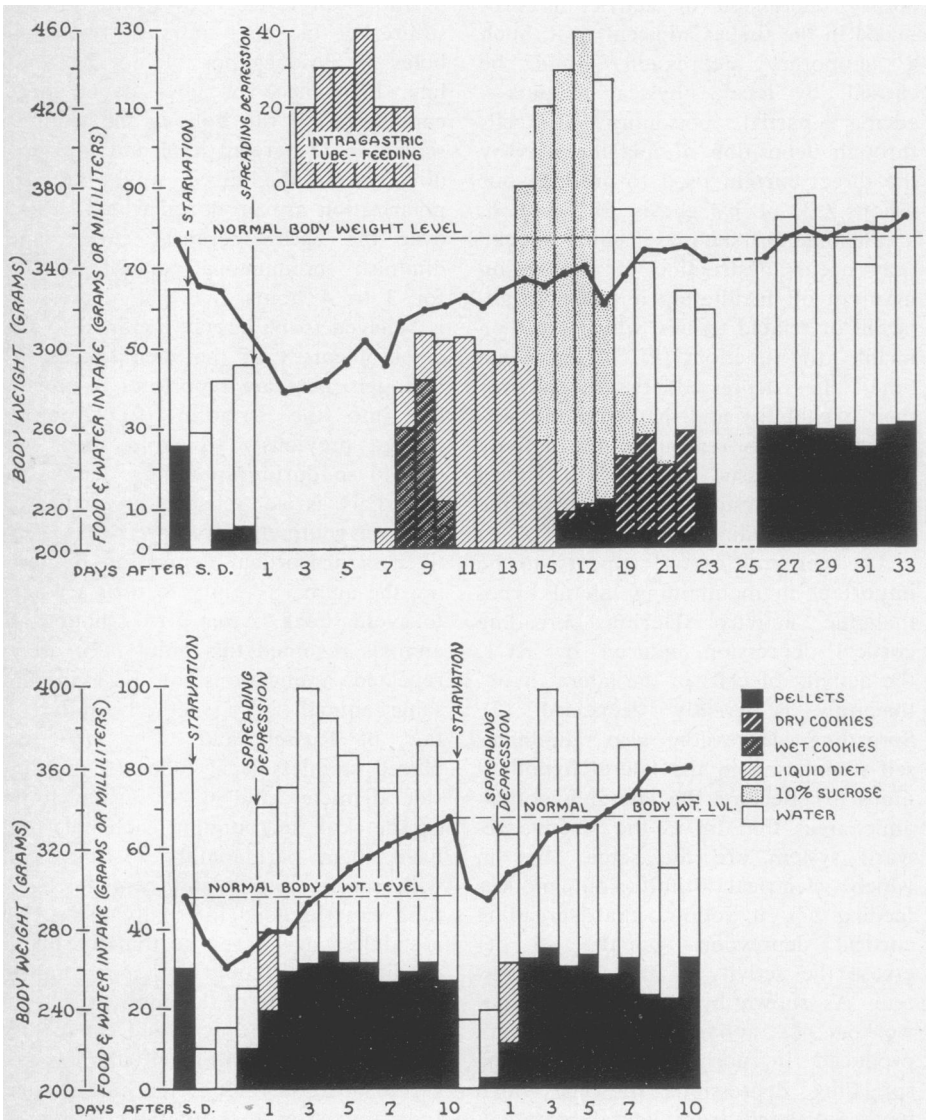

Fig. 1. Daily body weight and food and water intake after the onset of spreading depression. The height of each bar on any day represents the cumulative intake of all substances on that day (30 g of food plus 50 ml of water equals a total height of 80). (Top) Prolonged aphagia and adipsia reinstated in a rat recovered from lateral hypothalamic lesions. During recovery, the rat was weaned from wet cookies to a liquid diet, and from a liquid diet to pellets and water. (Bottom) In a control rat, on two occasions, spreading depression had little effect on the food and water intake.

sisted so long in some of our animals that had recovered from lateral hypothalamic lesions. There are at least two possible explanations. (i) Perhaps recovery from spreading depression is sometimes not as complete as is generally assumed. With our method, we often found some cortical damage, though relatively slight, in the area of application of KCl. Our animals, having a reduced amount of functional tissue in the lateral hypothalamus, revealed the deficit, whereas unoperated animals were not so sensitive. Perhaps this reduction in the amount of serviceable tissue is also why the regulation of food and water intake is easily disturbed in animals recovered from lateral hypothalamic lesions (*2*). Other methods, such as surgical removal of neocortex, should therefore be used to study this problem. (ii) Even if complete cortical recovery is assumed, it is possible that recovery of normal lateral hypothalamic activity, after removal of cortical facilitation, depends on the amount of serviceable tissue present. With a reduction in such tissue, recovery of normal activity is much slower. One might then expect spreading depression to reinstate other subcortical syndromes in which recovery occurs. Our more recent work supports this view: after recovery, the hyper-emotionality of septal lesions is clearly reinstated for about 2 weeks by one administration of spreading depression. However, in contrast to lateral hypothalamic animals, rats with septal lesions show no exaggerated impairment of feeding or drinking after spreading depression. This is a control for a possible enhanced effect of spreading depression on feeding and drinking in animals with dura puncture and lesions in other parts of the brain. Our findings, therefore, when taken together with the evidence that spreading depression decreases the activity of cells in the lateral hypothalamus, suggest that cortical activity may facilitate and maintain recovery from lateral hypothalamic lesions by enhancing the activity of depressed but intact tissue adjacent to those lesions.

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References and Notes

1. B. K. Anand and J. R. Brobeck, *Yale J. Biol. Med.* **24**, 123 (1951); P. Teitelbaum and E. Stellar, *Science* **120**, 894 (1954).
2. P. Teitelbaum and A. N. Epstein, *Psychol. Rev.* **69**, 74 (1962).
3. V. Rowland, W. J. MacIntyre, T. G. Bidder, *J. Neurosurg.* **27**, 55 (1960).
4. C. S. Sherrington, *The Integrative Action of the Nervous System* (Yale University Press, New Haven, 1906).
5. O. Burešová, J. Bureš, E. Fifková, W. Rudiger, *Proceedings of the Conference on Central and Peripheral Mechanisms of Motor Functions*, E. Gutmann and P. Huik, Eds. (Czechoslovac Academy of Science, Prague, 1963).
6. J. Bureš, O. Burešová, E. Fifková, J. Olds, M. E. Olds, R. P. Travis, *Physiol. Bohemosl.* **10**, 321 (1961).
7. B. G. Hoebel and P. Teitelbaum, *Science* **135**, 375 (1962).
8. J. Bureš and O. Burešová, *Electroencephalog. Clin. Neurophysiol.* **13**, 359 (1960).
9. E. Fifková and J. Syka, *Exptl. Neurol.* **9**, 355 (1964).
10. J. S. Russell and S. Ochs, *Brain* **86**, 37 (1963).
11. This research was supported by NSF research grant 24386 and PHS international postdoctoral fellowship grant FF 666. One of us (J.C.) is currently an international postdoctoral fellow at the Department of Psychology, University of Pennsylvania.

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Lateralization of Sounds at the Unstimulated Ear Opposite a Noise-Adapted Ear

Abstract. *We have discovered conditions of monaural stimulation under which a sound image can be located toward the contralateral, unstimulated ear; the phenomenon helps to clarify divergent experimental results. A tentative model is presented, together with some testable psychophysiological consequences.*

Auditory fatigue (we shall call it adaptation) is a temporary change in the functional state of the ear. Various psychophysical measures may be used to assess this change (*1*); a common procedure is shown in Fig. 1. The observer is seated in an anechoic chamber. Noise stimuli are presented dichotically (that is, separately to each ear) for a brief period. By means of an attenuator the subject adjusts the intensity of the noise in one ear so that, for a fixed intensity in the other ear, the two intensities appear equal.

Instead of this so-called simultaneous dichotic loudness balance, the subject's task may be to adjust the variable noise so that a fused sound image is centered between the two ears; this median-plane lateralization balance is the method we used. A fixed period is allowed for the balance to be made, and a brief rest period separates successive balances. After an initial series of balances, the adapting stimulus remains on in one ear (the adapting ear). At the end of the adapting period, the stimulus is momentarily introduced to the unadapted (control) ear as in the preadaptation balances; the adapted ear continues to be stimulated. As adaptation proceeds, the subject adjusts the intensity of the comparison (probe) stimulus to progressively lower levels. Subtracting the mean difference of the adaptation balances from the mean difference of the preadaptation balances gives a measure of adaptation in decibels (db). In making simultaneous dichotic balances it is assumed that the control ear is adapted very little by the comparison stimulus and that judgments of lateralization or loudness yield the same results (*2*).

Various experimenters have determined auditory adaptation for pure tones and noises (*3–5*); all agree that adaptation increases with the intensity of the adapting stimulus, reaching asymptote for any intensity somewhere between 3 and 10 minutes, taking longer for higher intensities, and longer for noises than for tones. The simultaneous method, used by all but one worker, required from 15 to 30 seconds for a balance. Von Békésy (*4*) found 18 db of adaptation after 2-minute stimulation with an 800-cy/sec tone at about 90 db SPL (sound pressure level), by measuring with a 200-msec probe immediately after cessation of the adapting tone. Yet adaptation was only 3 db and 1 db after 2 and 5 seconds of recovery, respectively. The rapid, exponential recovery suggested that an allowance of 15 seconds for making a simultaneous balance would lead to underestimation of the amount of adaptation.

To avoid this difficulty we used a 500-msec pulse of noise in the control ear. Preadaptation balances were made by turning on the 500-msec probe in both ears at the same time, the probe being set at a random intensity in the control ear and at a fixed intensity in the ear to be adapted. The listener judged whether the fused intracranial sound image was left or right of the median plane. Fifteen seconds separated each trial. [Recovery from the probe is complete in about 100 msec (*6*).] After 10 minutes of noise in one ear, during