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## Hypothalamic Obesity: The Myth of the Ventromedial Nucleus

Abstract. *Lesions restricted to the ventromedial nucleus of the hypothalamus were neither necessary nor sufficient for, and did not contribute to, the production of hypothalamic obesity. Hypothalamic lesions and knife cuts that do produce obesity damage the nearby ventral noradrenergic bundle or its terminals.*

For over 30 years the ventromedial nucleus of the hypothalamus (VMN) has been linked in theory to the suppression of eating. There have been many reports of hyperphagia and obesity after destruction of the VMN (*1*). Both neurophysiological and anatomical evidence for connections between a presumed VMN satiety center and a lateral hypothalamic feeding center have been reported (*2*).

However, there is evidence that the overeating and obesity that once seemed associated with destruction of the VMN is not due to VMN damage per se, but rather to destruction of the nearby ventral noradrenergic bundle (*3*). The ventral noradrenergic bundle ascends from brainstem nuclei to innervate limbic areas, including several hypothalamic loci, but sends relatively few terminals to the VMN (*4*).

That VMN damage itself contributes to hypothalamic obesity is open to question. Lesions of the VMN that are produced by radio-frequency currents fail to produce obesity (*5*). Closer examination of the studies that do link VMN lesions to obesity reveals that the effective lesions overflow the bounds of the VMN, the largest lesions typically producing the fattest rats (*1*). Finally, lesions caudal or lateral to the VMN, parasagittal knife cuts rostrolateral to the VMN, and midbrain lesions can all produce obesity even though the VMN is left intact (*1*, *6*).

I now report that even under optimal testing conditions lesions restricted to the VMN, even iron depositing lesions (*5*), produce neither overeating nor obesity. The VMN lesions cause obesity only when they overflow the VMN, and the magnitude of the obesity is proportional to the amount of overflow.

Female albino rats ($N = 119$) were allowed free access to a highly palatable high fat diet (*7*) and tap water. Lesions were produced by passing an anodal direct current through platinum-iridium, stainless steel, or iron wire electrodes. The lesions were all aimed at the rostral tip of the VMN, with the use of stereotaxic coordinates that had previously been associated with rapid weight gains (*8*).

For the initial series of rats the bilateral lesions were produced by a current of 2 ma for 20 seconds (40 millicoulombs) as described in (*7*, *9*). The lesions that resulted from 40 mcoulomb were enormous (Fig. 1L), with iron electrode lesions by far the largest, and platinum-iridium the smallest (*10*). The lesioning dosages for subsequent groups of rats were therefore halved to 20 mcoulomb and for the iron and steel electrodes, halved again to 10 mcoulomb. Finally, to approximately match the size of the very large lesions produced by 40 mcoulomb delivered by iron or steel electrodes, platinum electrode lesions were made with 160 mcoulomb (*11*).

Lesions that fell entirely within the borders of the VMN and the intervening midline area (Fig. 1F) did not produce obesity. Weight gains for the five animals with these lesions fell within the range (0 to 1.6 g/day) of 17 sham-operated controls. Lesions that damaged both the VMN and the dorsomedial nucleus also did not cause obesity (Fig. 1C). In contrast, lesions that extended ventrally from the VMN did produce slight obesity (3.0 g/day) (Fig. 1G). This slight effect appears to be due to the damage ventral to the VMN. The failure to produce obesity with lesions completely restricted to the VMN occurred despite the use of all of the parameters that maximize postlesion weight gains, that is, female rats (*7*), heavy iron deposits from anodal current delivered through iron or steel electrodes (*5*), and a palatable high fat diet (*7*).

The brain areas destroyed by the 55 smallest lesions were compared. There was a common area for the lesions of the five rats with the greatest weight gains (9.0 to 12.6 g/day). These most effective of the smallest lesions all destroyed an area immediately rostral to the rostral tip of the VMN (Fig. 1A). It is precisely across this area that a group of noradrenergic fibers crosses the midline within the suprachiasmatic decussation. These noradrenergic fibers are thought to derive from the ventral ascending noradrenergic bundle (*4*). Small lesions located more dorsally or more caudally were less effective (Fig. 1, B and D) (*12*).

Larger lesions produced far greater weight gains. If the thalamus and the nigro-striatal dopamine pathway at the extreme lateral edge of the hypothalamus (*4*) were spared, then the bigger the lesion, the greater the initial rate of weight gain. For example, a large platinum electrode lesion spared the VMN but produced rapid weight gains of 10.6 g/day (Fig. 1E). The correlation between lesion size and weight gain is illustrated by the representative series of lesion reconstructions in Fig. 1, F to L.

The wide area encompassed by the most effective lesions includes the wide area in the rostral hypothalamus to or through which the ventral ascending noradrenergic bundle projects (*4*). Many of the most effective lesions extended so far laterally that they appear to have damaged the medial edge of the ventral bundle itself (Fig. 1, K and L), thus producing especially rapid weight gains as high as 18.8 g/day. When the lesion was even larger than this (Fig. 1M) the nigro-striatal bundle (*4*) was damaged, and weight gains were minimal. This would be expected, since nigro-striatal lesions produce aphagia (*13*).

I found that when obesity is produced with parasagittal knife cuts (*14, 15*), the greatest weight gains require long cuts. Thus 3-mm cuts are more effective than 2-mm cuts which are more effective than 1-mm cuts (unpublished data). It thus appears that fibers projecting diffusely to more than one area are involved in hypothalamic obesity. The parasagittal knife cuts are only effective if they include the area lateral to the dorsal supraoptic commissure (Ganser), precisely the frontal level of the most effective small lesions of Fig. 1 (*15*). The parasagittal knife cuts that produce obesity apparently sever noradrenergic fibers as they turn medially from the ventral bundle to innervate numerous rostral hypothalamic structures. In further support of the notion that ventral bundle damage mediates hypothalamic obesity, it has been shown that obesity results from combining a unilateral parasagittal knife cut (or unilateral medial hypothalamic lesion) with a contralateral ventral bundle lesion (*3*).

It is perplexing that electrolytic or chemical damage to the ventral noradrenergic bundle or to its terminal areas produces overeating, while electrical or noradrenergic stimulation of the same loci also produces eating. Booth (*16*) has observed that the loci (presumably terminals) at which noradrenergic stimulation produces eating lie rostral to the loci (presumably ascending fibers) at which electrical stimulation produces eating. Other reports have localized the optimal locus for eating induced by electrical stimulation at the paraventricular nucleus (*17*). This structure receives a major proportion of the hypothalamic noradrenergic terminals (*4, 16*). Even the release of endogenous transmitter by small localized 6-hydroxydopamine infusions into the hypothalamus can produce eating (*18*).

A resolution of the paradox whereby lesioning or stimulation of the ventral bundle both produce eating may lie in the recent demonstration by Margules *et al.* (*19*) that norepinephrine applied to the perifornical medial forebrain bundle (ventral noradrenergic bundle) can either enhance or suppress eating depending on when it is administered during the daily circadian cycle. During the day norepinephrine does enhance eating, but at night it suppresses eating (*20*).

In conclusion, many of the lesioning or stimulating procedures that produce excessive eating appear to share in common damage, blockade, or stimulation to the ventral ascending noradrenergic bundle or its terminals. The VMN is merely a prominent landmark in the vicinity of effective loci.

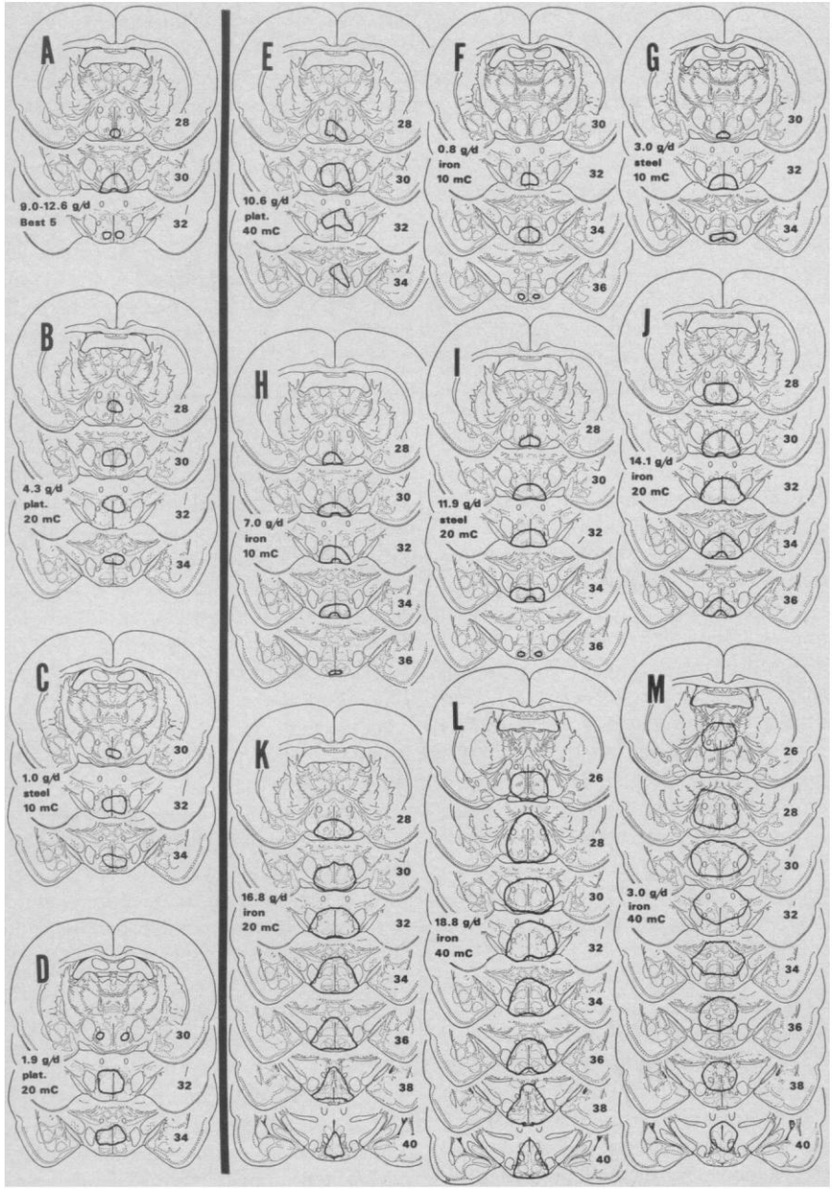


Fig. 1. Reconstructions of representative lesions, prepared as described in (*11*), and superimposed on even-numbered plates (plates 26 to 40) modified from the Konig and Klippel rat brain atlas. Weight gains per day for 2 weeks after surgery were computed as in (*7*). The VMN appears in plates 32 through 40. (A) Common area of destruction for the five greatest weight gains among the 55 smallest lesions. At level 30, the largest of these five lesions only slightly exceeded the common area. For (B) to (M) see text. Abbreviations: *g/d*, grams per day; *mC*, millicoulombs.


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8. With the top of the incisor bar 3.0 mm below the ear bar center, the electrode tip was placed 6.5 mm anterior to the ear bar center, 0.5 mm lateral, and 8.1 or 8.3 mm below the dura. The conical exposed electrode tips were 0.5 mm long.
9. To determine the influence, if any, of lesioning current (as opposed to the total amount of millicoulombs delivered), half of these rats received the same 40 mcoulomb slowly as 100 $\mu$a for 400 seconds.
10. In order to produce stainless steel and platinum-iridium electrode anodal lesions of equivalent size, the number of coulombs is tripled when going from stainless steel to platinum-iridium.
11. The size of the lesions was determined without reference to weight gains, by projecting appropriately magnified cresyl violet–stained sections directly onto the frontal plates of the Konig and Klippel atlas and then tracing at 0.4-mm intervals the absent normal tissue. I used all of the even-numbered atlas plates through the extent of the lesion. Tracing the absent normal tissue instead of the periphery of the apparent lesion scar corrected for shrinkage into the lesion cavity. Shrinkage and scar tissue were greatest with the iron and steel lesions, especially the iron.
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21. P. M. Quackenbush provided technical assistance, and G. Kapatos reviewed the manuscript. A preliminary report of this work was presented to the Eastern Psychological Association, Washington, D.C., May 1973.

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# Morphine Action at Central Nervous System Sites in Rat: Analgesia or Hyperalgesia Depending on Site and Dose


Abstract. *Morphine was injected via fine-gauge cannulas permanently implanted in various subcortical sites in the rat brain. In this way the blood-brain barrier was avoided and precise quantities of the drug were delivered to the intended sites. Ten micrograms of morphine in the posterior hypothalamus resulted in significant analgesia, while the same dose injected into the medial septum, the caudate, or the periaqueductal gray matter yielded hyperalgesia. The morphine-produced hyperalgesia at the last-mentioned site was accompanied by stereotyped violent circular leaps, an effect of morphine not previously reported. Thus, intracerebral injections of morphine differ significantly from systemic injections and produce either analgesia or hyperalgesia, depending on site and dose.*


One of the major therapeutic uses of morphine has been for its analgesic action. Yet, little is known about sites in the central nervous system (CNS) which mediate the analgesic action of the drug. Attempts to relate a pattern of morphine distribution in the CNS with its analgesic effects in the intact animal after systemic injections have produced disappointing results (*1*).

A technique of potential value in the search for anatomic sites of morphine action is microinjection by means of permanently implanted intracerebral cannulas. This technique has been used in few morphine studies (*2*, *3*), although it has been applied extensively and fruitfully in neuropsychological studies of brain mechanisms controlling motivation (*4*). This method has the advantage of avoiding the blood-brain barrier [only about 0.1 percent of the systemically administered dose gains access to the CNS (*1*)] and permits precise quantities of the drug to be delivered into the intended site.

In the present studies, the microinjection method was used to administer morphine to discrete subcortical sites, and the analgesic action of morphine at these sites was evaluated. Injections of 10 $\mu$g of morphine into the posterior hypothalamus and into the third ventricle yielded dose-dependent analgesia, while injections at three other sites, the medial septal nucleus, the caudate nucleus, and the periaqueductal gray matter, yielded hyperalgesia (*5*).

In the first experiment, 78 adult male albino Wistar rats, 200 to 250 g at the time of surgery, were randomly assigned to one of nine groups. All animals except controls were stereotaxically implanted with bilateral 30-gauge stainless steel cannulas at least 1 week before testing. The cannula tip was implanted 1 mm above the intended site. For the injection, a 35-gauge stainless steel needle affixed to a 10-$\mu$l Hamilton syringe was inserted into the cannula, with the needle tip extending 1 mm beyond the cannula tip. The volume injected into each site was 0.5 $\mu$l. The needle was withdrawn after 45 seconds to allow adequate absorption by the surrounding tissue and thus lessen the likelihood of the fluid being drawn back into the cannula or over the outer wall of the cannula and thus diffusing to other sites. Analgesia testing followed the injection either immediately or after a 20-minute delay; the time factor made no difference in the results. All animals were given habituation sessions (including mock injections and a 10-minute confinement in the experimental chamber) for 3 days to acclimatize them to the procedure before testing.

Analgesia was evaluated by a modified flinch-jump test. Ten sets of shocks were presented to the animal in alternating ascending and descending series. Shock intensity ranged from 0 to 2.2 ma in ten approximately equal steps. Shocks, delivered via a noiseless shock scrambler to the grid floor of the experimental chamber, lasted 1 second, and occurred at 30-second intervals. The animal was viewed through a one-way observation window by the experi-