Brain Research, 185 (1980) 1–15

Research Reports

INTRACRANIAL SELF-STIMULATION IN RELATION TO THE ASCENDING DOPAMINERGIC SYSTEMS OF THE MIDBRAIN: A MOVEABLE ELECTRODE MAPPING STUDY

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(Accepted July 19th, 1979)

Key words: dopamine — self-stimulation — mapping — reward — moveable electrode

SUMMARY

Chronically implanted moveable electrodes were used to map the midbrain and caudal diencephalon for intracranial self-stimulation in relation to the ascending dopamine systems as revealed by fluorescence histochemistry. In the diencephalon the lowest self-stimulation thresholds and the highest response rates were in the areas traversed by the dopamine fiber bundles. In the midbrain, self-stimulation was restricted to the layer of dopamine containing cell bodies. Self-stimulation current thresholds and responses rates were proportional to the density of dopaminergic elements surrounding the electrode tip; the lowest thresholds and highest response rates were associated with the densest packing of dopaminergic neurons. However, not all portions of the dopamine cell groups supported self-stimulation. Self-stimulation was not obtained from the caudal poles of the A9 and A10 groups, nor from the A8 cell group.

These findings suggest that a certain population of dopaminergic neurons directly participates in what is probably a multiple-link circuitry subserving positive reinforcement.

INTRODUCTION

The finding of Olds and Milner that animals will work for electrical stimulation

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of some but not other parts of the brain[36] led to the view that neural circuits with some degree of specialization underly powerful control of behavior by rewarding stimuli. Speculations as to the neural substrate of reward have been greatly influenced by the fact that noradrenergic fibers are found near most intracranial self-stimulation (ICSS) sites and that drugs that interfere with noradrenergic function attenuate ICSS[12,13,25,46]. However, close examination of ICSS sites in the pons and caudal midbrain has shown that these sites are not well correlated with the boundaries or relative densities of noradrenergic elements near the electrode tips[11], and drugs that alter noradrenergic function generally cause a non-selective behavioral debilitation[22,52]. These and other recent data indicate that it is unlikely that stimulation is rewarding because it activates noradrenergic systems[6,7,9,10,29].

In the last several years an increasing amount of attention has focussed on the possible involvement of the midbrain dopamine systems in mediating ICSS[12,20,23,25,35,39,51]. Unlike lesions of the noradrenergic systems[6,7,9,10], lesions of the dopaminergic systems produce severe and often long-lasting deficits in ICSS[38,40,41]. Pharmacological agents that attenuate dopaminergic synaptic action also consistently reduce ICSS[30,35,43]. Although there seems to be no doubt that dopamine systems are involved in ICSS, there has been debate as to the nature of the involvement[21–24,43,50]. Since dopaminergic depletion has long been associated with the movement disorder of Parkinson's disease[26], it is not surprising that some workers have attributed the deficits in ICSS caused by dopamine blockers to reductions in motor or sensory motor abilities[9,21,43]. Others have argued that the patterns of ICSS deficits seen after dopamine blockade rule out explanation in terms of performance debility and suggest that in addition to any minor sedative or motor effects dopamine blockers must also attenuate the rewarding property of the stimulation[17,22–24,50,52].

If it is the case that activation of dopamine pathways is rewarding in its own right, it is not clear which dopamine pathways are involved. ICSS is generally obtained from the region of dopamine cell bodies in the mesencephalon, and from the fiber projections and terminal fields of these cells[2,8,12,26,27,31,32,37,38,44,45]. In mapping the region of dopamine cell bodies, however, histochemical methods for dopamine visualization have not been used; thus precise statements regarding the boundaries or relative densities of dopaminergic elements in relation to the location of the ICSS electrode tips cannot be made.

Precise localization of positive ICSS sites and determination of their relative sensitivity to current is of interest and importance, since it has recently been found that the dopamine cells of the groups A8, A9 and A10 of Dahlstrom and Fuxe[14] do not have discrete but rather have overlapping projection fields[15,18]. Thus it is now held that there is no meaningful distinction between the A8, A9 and A10 cell groups, although there are topographic differences in regional projection from the midbrain dopamine neurons[15,18,34]. Given the regional differences in projection of the dopamine cells, it might be reasonable to expect regional differences in self-stimulation from electrodes in different portions of the dopamine cell body region. In the present study a moveable electrode was used to map the dorsal-ventral boundaries of the mesencephalic dopamine cell group for ICSS, and rate-intensity functions were used to

determine the relative sensitivities of different ICSS sites within these boundaries. Fluorescence histochemistry was used to verify the electrode placements in relation to the dopamine cells and fibers.

METHODS

Surgery

Forty-eight male Sprague–Dawley rats weighing 250–400 g at the time of surgery were each implanted with a monopolar electrode that could be moved in 0.25 mm increments over a 2.0 mm range in the dorsal-ventral plane[49]. Electrode placements were systematically varied in a region which extended from the ventromedial hypothalamic nucleus through the caudal extent of the interpeduncular nucleus in the anterior-posterior plane and from the midline to the level of the internal capsule and lateral border of the substantia nigra in the medial-lateral plane. This region corresponds roughly to the following deGroot stereotaxic coordinates in relation to bregma: anterior-posterior, 0.0 to –5.0 mm; medial-lateral, 0.0 to 3.0 mm; and dorsal ventral –5.5 to –9.0 mm from the dural surface. In each animal a maximum 2 mm vertical penetration was explored within these boundaries. Greater detail of this mapping procedure has been reported earlier[11].

Testing procedure

Following at least a 3 day postoperative recovery period the rats were trained to self-stimulate in standard operant chambers, each equipped with a lever that, when depressed, caused delivery of a 500 msec train of 60 Hz sine-wave stimulation (rms). Once responding became reliable the animals were switched to a rate-intensity testing paradigm. Each daily test session was 35 min in length during which current was reduced in 1.0 μA steps between successive 5 min segments until a current level was reached that failed to maintain a response rate of 10 responses per minute. This current level was defined as the threshold current intensity. At the end of 5 days in the rate-intensity paradigm the electrode was lowered 250 μm and the next stimulation site was tested similarly. Testing continued until the electrode reached its maximum ventral extent (a total travel of 2.0 mm), until the testing was terminated at a site of particular interest for histological examination, or until sites were found that did not support ICSS. Current intensity was adjusted at each site so that thresholds could be determined within 7 (5 min) rate-intensity test segments. Currents above 50 μA were never used. An earlier paper should be consulted for further details[11].

Histology

At the conclusion of testing, 26 of the animals were deeply anesthetized with sodium pentobarbital and perfused with physiological saline followed by 10% formalin. Brains were removed and stored for at least 3 days in 10% formalin; then frozen 40 μm sections were cut in the deGroot plane and stained with thionin. The remaining 22 animals were treated with a modification[11] of the glyoxylic acid method of Battenberg and Bloom[4] for the demonstration of catecholamines.

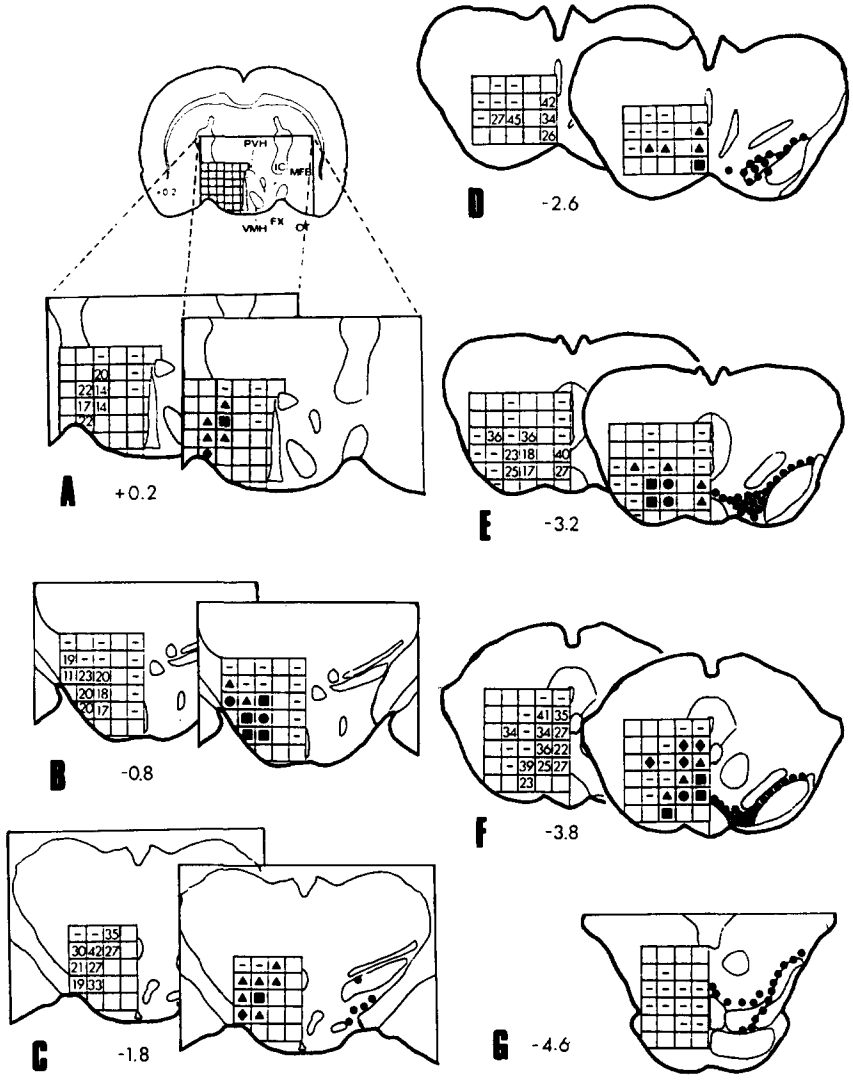

Fig. 1. Summary diagram of the 268 electrode sites tested for ICSS in all 48 animals. Data from 14, 7, 19 and 8 rats are summarized at the hypothalamic, rostral, middle and caudal substantia nigra levels, respectively. The numbers within each grid in the left-hand brain sections represent the median current intensities required to maintain responding at rates greater than 10 responses per minute at all electrode sites within the relevant portion of the grid. Each grid square represents an area of approximately 0.5 × 0.5 mm and contains from 2 to 8 stimulation sites. Open squares indicate that an area was not tested for ICSS, minus signs indicate that the area did not support ICSS. The characteristic response rate for each positive area is shown in the sections to the right: ● = 80 responses/min; ■ = 50–79 responses/min; ▲ = 20–49 responses/min; and ◆ = 5–19 responses/min. Numbers below each brain section indicate the distance posterior to bregma. The large black dots approximate the distribution of dopaminergic cell bodies.

RESULTS

A total of 268 electrode placements were tested for ICSS. A summary diagram of the stimulation sites and the corresponding response rates and intensity thresholds is shown in relation to the location of the mesencephalic dopamine cells in Fig. 1. The results are described in relation to 4 major anterior-posterior levels: the hypothalamus and the levels of the rostral, middle and caudal thirds of the substantia nigra.

In the hypothalamus (Fig. 1A, B) ICSS was readily obtained with electrode sites in the area bounded laterally by the internal capsule and optic tract, dorsally by the zona incerta, medially by the fornix and ventrally by the base of the brain. Positive placements were within the region of catecholamine fibers which includes the dopamine fibers arising from the ventral tegmental nucleus of Tsai (VTN) and the medial portion of the substantia nigra, zona compacta[18,34]. Self-stimulation was usually found at a low threshold after a single electrode movement into or just through the zona incerta, and thresholds and response rates did not vary greatly as the electrode was passed through the positive region, until the base of the brain was approached. While minor differences in rate and threshold were seen, variations in both catecholamine intensity and in self-stimulation measures were minimal relative to those seen at the more caudal regions tested.

At the diencephalic-mesencephalic junction (Fig. 1C, D) ICSS was obtained from the midline to the medial edge of the internal capsule or to the lateral border of the substantia nigra pars compacta. ICSS was not obtained with stimulation sites more than 0.5 mm dorsal to the dopamine-containing cells. Self-stimulation thresholds dropped and response rates increased as electrodes were lowered from the medial lemniscus into the layer of dopamine containing cell bodies of the zona compacta. Animal 102 is good example (Fig. 2); this animal self-stimulated at only two tested sites with a threshold of 31 μA at the first site, in or just ventral to the medial lemniscus, and with a threshold of 22 μA at the second site, 0.25 mm lower in the zona compacta. The response rate doubled at the more ventral placement in this animal. Self-stimulation thresholds in the region of dopamine cell bodies at this level were generally not much lower than about 25 μA, whereas thresholds lower than 15 μA were frequently observed in the hypothalamus.

More caudally, at the middle third of the substantia nigra, ICSS was consistently obtained in and around the ventral tegmental nucleus of Tsai as well as in portions of the zona compacta. Fig. 3 shows a composite fluorescence photomicrograph of an electrode penetration, through the VTN; Fig. 4 shows a reconstruction of this penetration (no. 128) with the ICSS current thresholds and response rates at the sites tested. At this level the lowest thresholds and highest response rates occurred when the electrodes were in or on the edge of the VTN. Animal 128 (Fig. 3) is a representative case from a group of 7 animals with placements in this nucleus. This animal self-stimulated at 4 different sites along its electrode penetration. Current thresholds decreased (Fig. 4) and response rates increased as this animal's electrode was lowered into the VTN. Virtually identical patterns were seen in the other 6 animals with electrodes in this region. The density of dopaminergic elements within a 500 μm

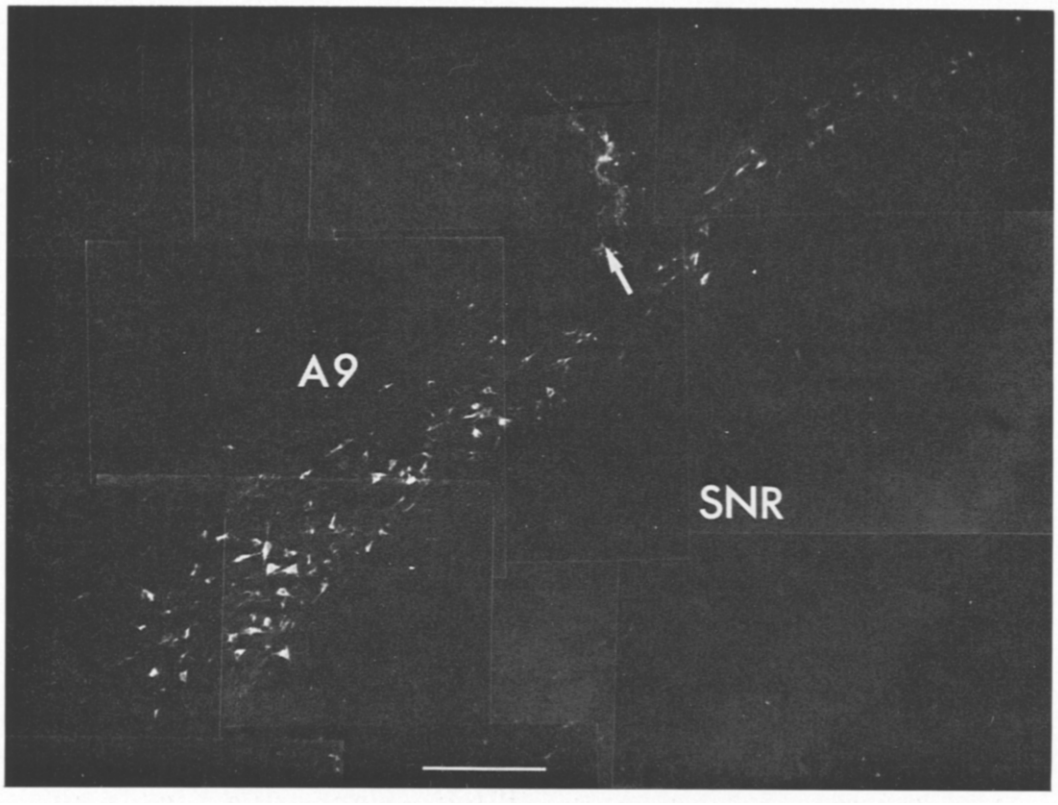

Fig. 2. Fluorescence photomontage of an electrode penetration in the rostral portion of the zona compacta (animal no. 102). The two most ventrally tested electrode sites in this penetration supported ICSS. Indicator bar = 250 μm. SNR, substantia nigra, zona reticulata.

radius around each electrode site tested in these 7 animals that were treated for catecholamine fluorescence was rated on a 3-point subjective scale[1] and related to ICSS thresholds. A highly significant negative correlation (Spearman rho = –0.70, $P < 0.01$) was found; the lowest ICSS thresholds were in the areas richest in dopamine-containing neurons.

More laterally at this level the probability of obtaining ICSS decreased. One animal (no. 134, Fig. 7) self-stimulated at a site that appeared to be in or just dorsal to the zona compacta. The current threshold at this site was 32 μA, which was moderately high. With a single move of the electrode (0.25 mm) ICSS was lost at currents up to 50 μA, though low currents (20 μA) continued to elicit motor responses such as neck extension, thus indicating a functional electrode. The dopamine neurons in this lateral zone form a thin layer, and the negative site was found to be just ventral to the zona compacta, within the zona reticulata. As had been the case of two stimulation sites at more rostral levels (Fig. 1D) the zona reticulata was found not to support ICSS. An electrode penetration from an animal (no. 129) that failed to self-stimulate at any of 4 different stimulation sites within the zona reticulata is shown in Fig. 7. A total of 21 different stimulation sites obtained from 7 animals with electrode

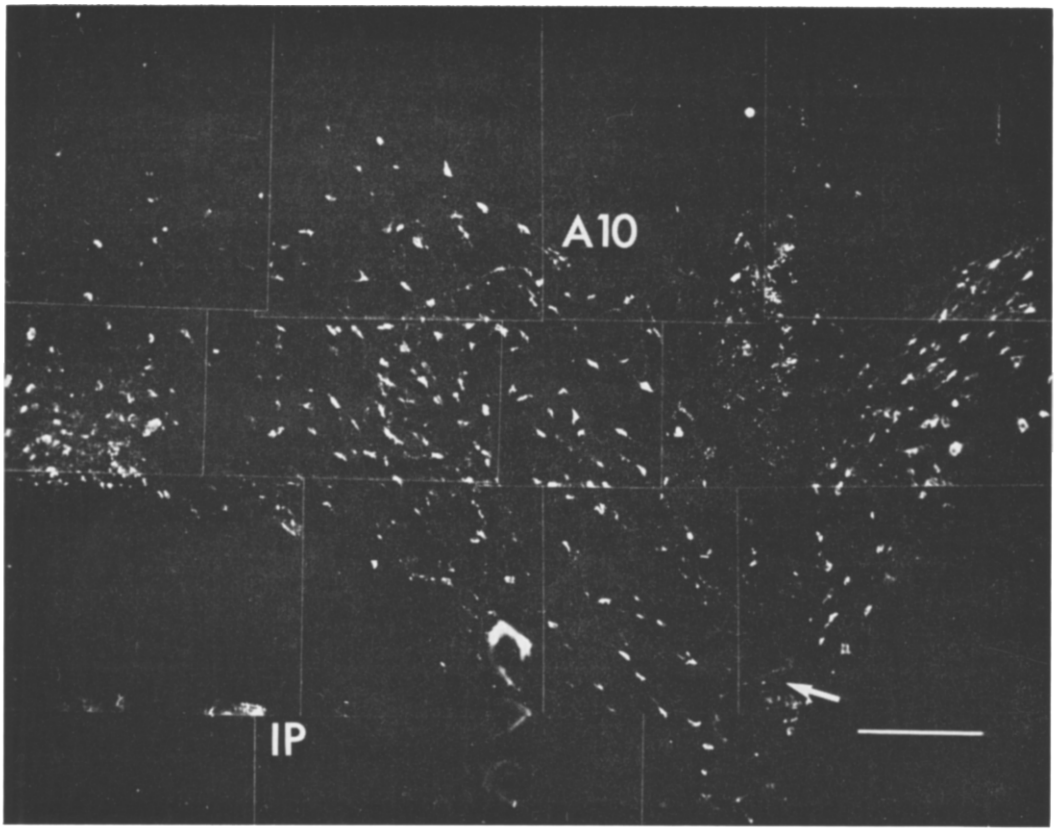

Fig. 3. Fluorescence photomontage of the electrode track in animal no. 128. Arrow indicates electrode tip. Indicator bar = 250 μm. IP, interpeduncular nucleus.

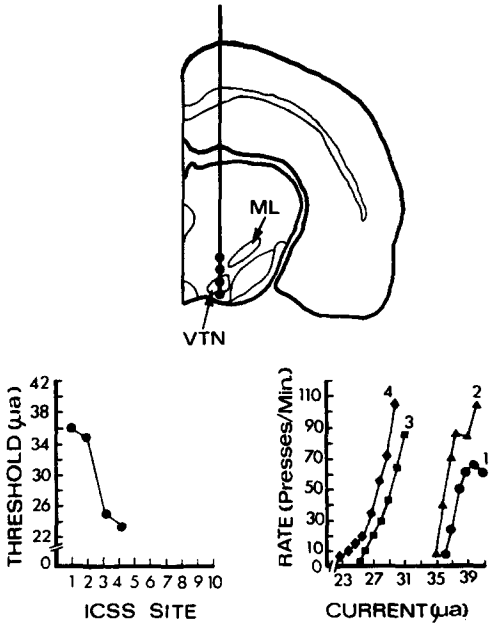

Fig. 4. Schematic representation of the electrode penetration in animal 128. The bottom figures show the ICSS current thresholds (left) and rate-intensity functions (right) at each of the 4 electrode sites tested. ML, medial lemniscus. VTN, ventral tegmental nucleus of Tsai.

placements in the zona reticulata all failed to support ICSS (Fig. 1D, E, F). As in the case of animal 134, three of these animals self-stimulated when the electrode was in zona compacta, but failed to self-stimulate as soon as the electrode was moved into zona reticulata.

Some electrodes in the lateral portions of the zona compacta did not support ICSS at this level. For example an electrode placement located approximately 2.5 mm lateral to the midline failed to support ICSS (no. 117, Figs. 5, 7); this animal should be compared to animals at more rostral levels (e.g. no. 102, Fig. 2). An anomolous placement which supported ICSS was seen at this level in animal 138 (Fig. 7). This animal self-stimulated with a threshold of 34 μA at a site dorsal to the medial lemniscus; when the electrode was lowered ICSS was no longer seen though the electrode was still dorsal to the zona compacta. Testing was discontinued in this animal without penetration of the dopamine cell layer. A second case of ICSS dorsal to the dopamine cells in the region of intended testing was seen more caudally.

At the level of the caudal third of the substantia nigra (Fig. 1F, G) ICSS was no longer obtained from electrode placements in the zona compacta, and at the most

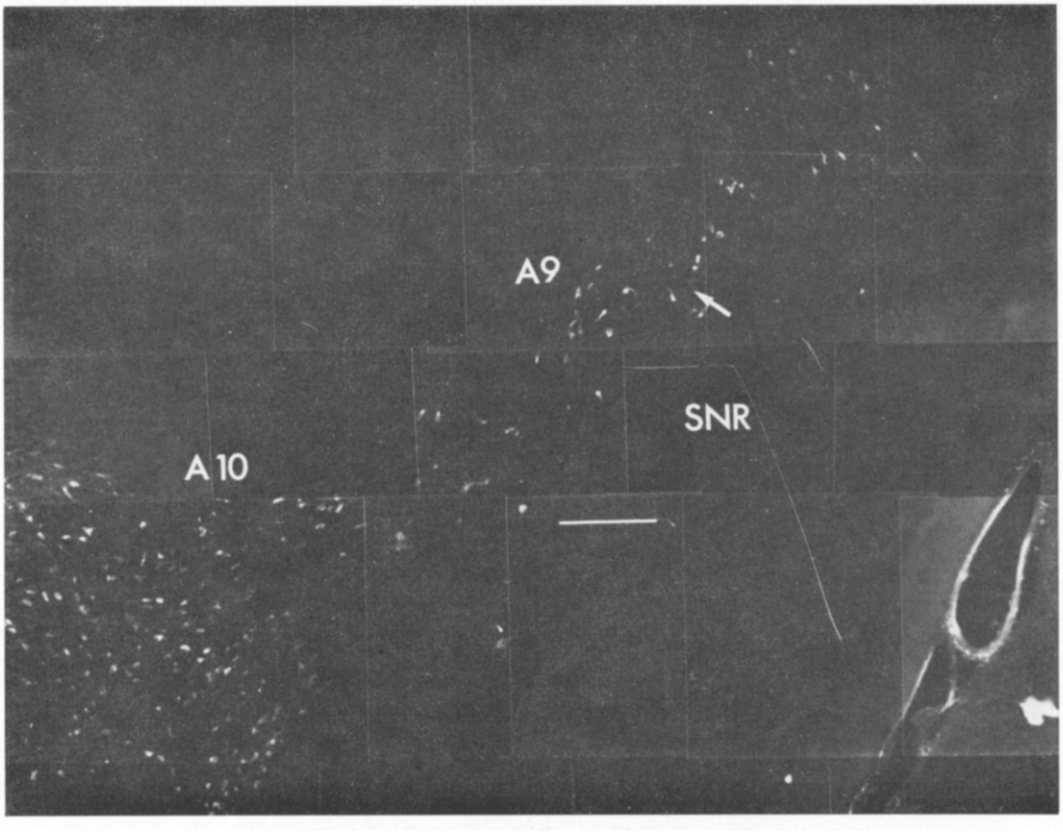

Fig. 5. Fluorescence photomontage of an electrode penetration in the caudal portion of the zona compacta (animal no. 117). Arrow indicates electrode tip. None of the electrode sites in this penetration supported ICSS. Indicator bar = 250 μm.

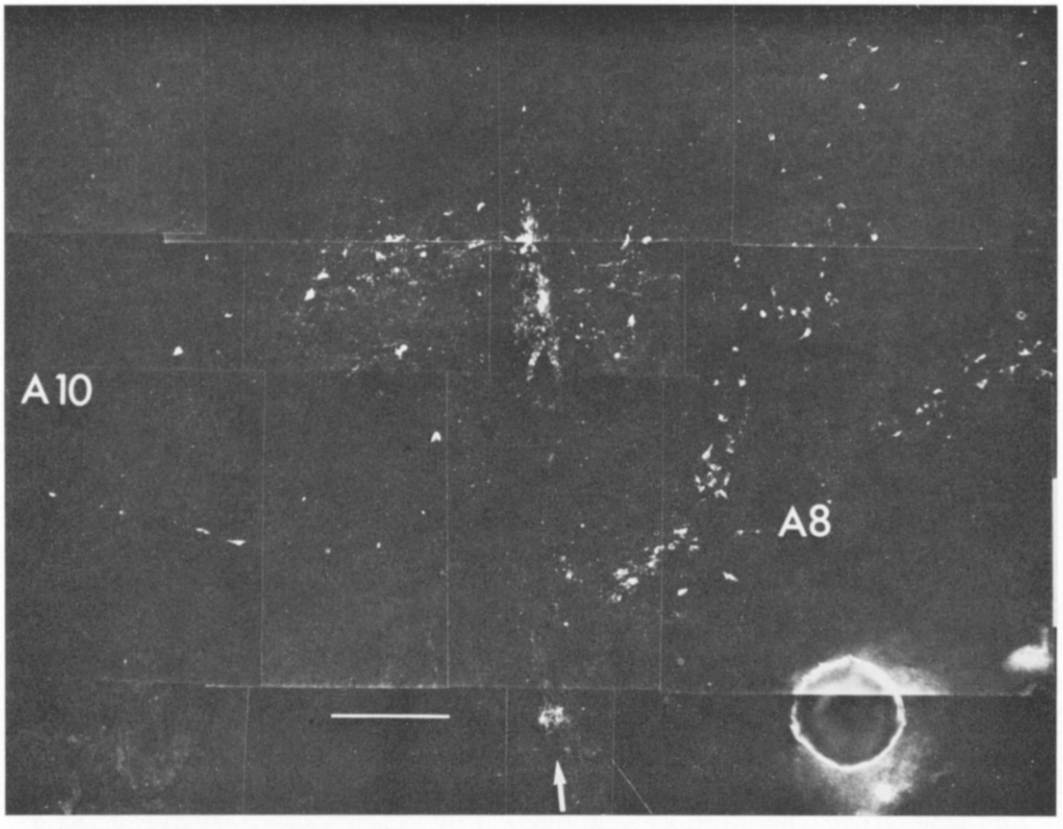

Fig. 6. Fluorescence photomontage of an electrode penetration in the A8 cell group (animal no. 131). Arrow indicates electrode tip. None of the electrode sites tested in this penetration supported ICSS. Indicator bar = 250 μm.

caudal level was no longer seen in relation to the dopamine cells around the interpeduncular nucleus. Negative sites were found at the caudal poles of the A9 and A10 regions and throughout the A8 region. A thionin stained section of an electrode penetration through the caudal pole of the A10 region is shown in Fig. 7 (no. 115). This animal failed to display ICSS at any of the 7 sites tested. A fluorescence photomicrograph of a more laterally located penetration in the A8 region is shown in Fig. 6; no ICSS was seen in this penetration.

DISCUSSION

The results of the present mapping study are generally consistent with the view that dopaminergic neurons may mediate ICSS in the ventral midbrain and hypothalamus[25,39,51].

Beginning with the hypothalamus, the area that supported ICSS (Fig. 1A, B) is known to be traversed by dopaminergic fibers from the ventral tegmental nucleus of Tsai and the medial portion of the zona compacta[18,34]. In the perifornical region are

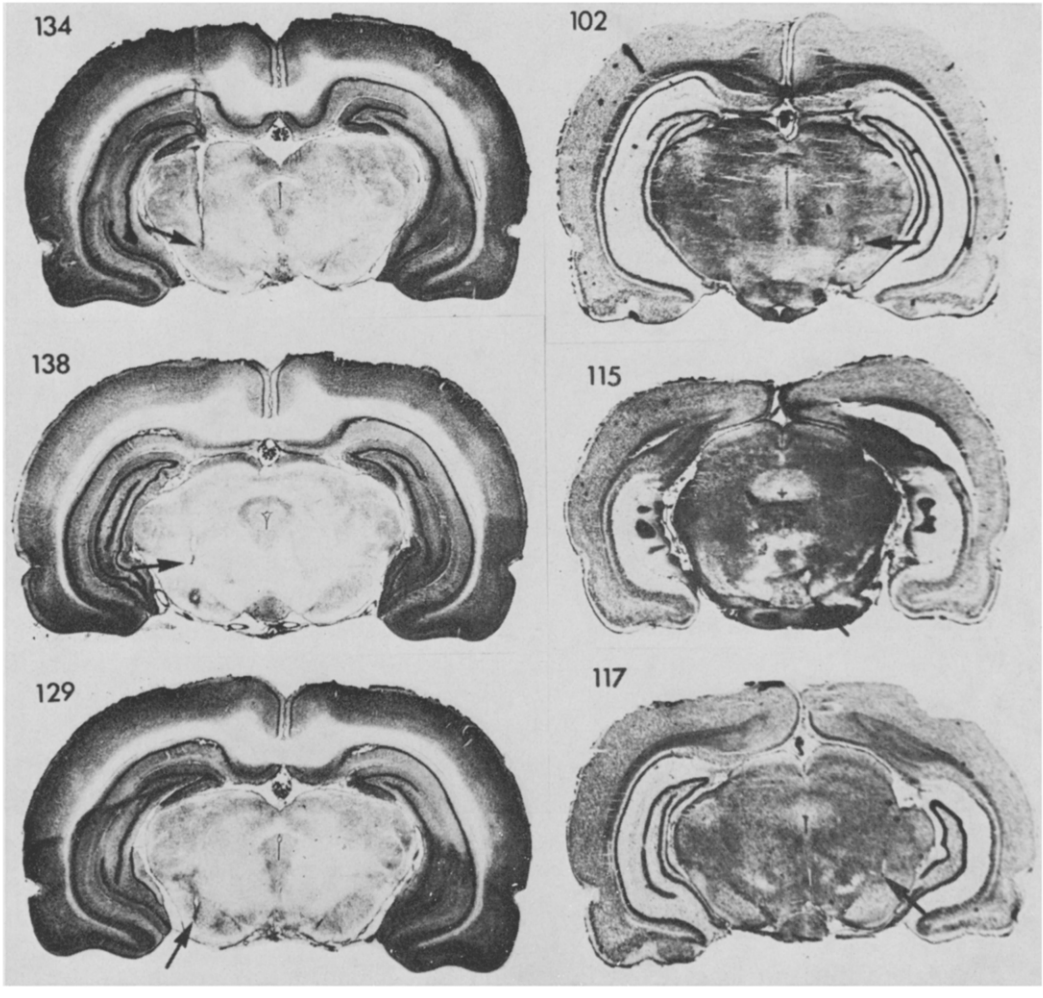

Fig. 7. Thionin-stained sections showing electrode placements in animals 102, 117, 134, 138, 115 and 129. Arrows indicate the most ventral penetration of the electrodes.

located fibers from the medial portion of the VTN while at the tip of the internal capsule are located fibers arising from the lateral portion of the VTN and most medial portion of the zona compacta[18]. These fibers appear uniformly distributed throughout the hypothalamic region that supported ICSS. From inspection of Fig. 1A and B it can be seen that the ICSS current thresholds and response rates were fairly uniform in this region. Since the stimulation currents used to map the hypothalamus were generally low (25 μA), the best explanation of the relatively uniform thresholds and response rates is that the ICSS-related fibers are uniformly distributed throughout the region that supported ICSS. The distribution of dopamine fibers fits this description reasonably well.

The strongest evidence for the dopamine hypothesis comes from the close correspondence between positive sites and the loci of dopamine cell bodies in the

dorsal-ventral plane. When ICSS was obtained, it was seen as the electrode reached the dorsal boundary of the dopamine cells (with the exception of the two animals in which ICSS was seen dorsal to the dopamine cell group). Invariably ICSS was lost as the electrode passed into the zona reticulata (e.g. no. 134, Fig. 7). The abruptness of transition between ICSS sites and negative sites indicates that the spread of current was not great and that the borders of the ICSS substrate are closely confined to the region of the dopamine cell layer. This observation is further supported by the fact that ICSS was not obtained from the interpeduncular nucleus, the medial lemniscus or the red nucleus, structures which border the dopamine cell layer. The failure to obtain ICSS from the caudal and caudo-lateral portions of the dopamine cell group does not fit with the notion that all dopamine neurons mediate ICSS in the region of the substantia nigra. This point merits discussion in further detail. With the exception of the regional differences just noted, the present data are in general agreement with the results of previous ICSS mapping studies[2,12,16,27,31,37,42]. The fact that earlier workers have not noted regional differences between the anterior and posterior and the medial and lateral portions of the dopamine cell region can probably be attributed to methodological factors. In previous mapping studies fluorescence histochemical methods have not been employed, and histological reconstructions, sometimes based on unstained material[31,32], have been represented on one or two coronal sections which fail to indicate potentially substantial anterior-posterior variations in electrode placement[12]. In our data regional differences were carefully sought, and were clear. It could be argued that our failure to obtain ICSS from all of the most posterior placements and from some parts of the lateral zona compacta reflected a failure to activate a sufficient number of dopamine neurons, since in these regions the cells are less numerous than at more medial regions. This explanation seems unlikely since negative sites in the zona compacta and caudal ventral tegmental area were found despite the use of stimulation currents of double the intensity needed in the anterolateral zona compacta where cell density is equally sparse.

The more plausible explanation for regional differences in ICSS within the mesencephalic dopamine cell group is that different portions of the group have differing terminal projections and presumably different functions. The most anterior midbrain dopamine neurons project to the most anterior portions of their target nuclei, while the most posterior cells project to the most posterior portions of the same nuclei[18]. A similar organization is seen in the medial-lateral plane, with the most medial of the dopamine cells projecting medially and the most lateral of the cells projecting to more lateral terminal fields[18]. The positive ICSS sites in the present study correspond to the region of cells projecting to the more anterior portions of the striatum, limbic system and cortex while the dopamine neuronal population that did not support ICSS projects to caudal portions of striatum, limbic system and cortex. It is interesting to note that the highest rates of ICSS have been reported from the anterior rather than the posterior portions of both striatum[38] and entorhinal cortex[8], which receive innervation from the dopamine cell regions that were positive for ICSS in the present study.

The dopamine cell groups also have a topographical organization in the dorsal-ventral plane. The dorsal layer of dopamine neurons in zona compacta projects to the

limbic forebrain where the ventral layer projects to the striatum[19]. Unfortunately the resolution of the mapping paradigm is not sufficient to say which layer was positive for ICSS. The ventral steps of the mapping (0.25 mm) and the degree of probable current spread were too great in relation to the thickness of the dopamine cell body layer (0.25 mm) to determine whether ICSS correlated best with one or the other of the sublayers of zona compacta.

While there have been previous reports of ICSS from the zona reticulata[12,31, 32,45], most of these electrode placements were either in close proximity to the ventral tegmental area or just at the border between the zona compacta and zona reticulata. Moreover, the most ventral layer of dopamine-containing neurons have dendrites which radiate ventrally into the zona reticulata. Thus the ICSS which has been reported from zona reticulata may result from current spread to neurons in zona compacta and the ventral tegmental area. This possibility seems even more plausible since confirmation of zona reticulata ICSS sites has not been too precise; the studies in question did not involve fluorescence histochemistry for definition of the layers of monoamine-containing neurons and in some cases involved unstained histological sections. These facts together with the rather poor resolution offered by fixed electrodes in defining anatomical boundaries, when taken with our clear failure to obtain ICSS from the zona reticulata at 21 different electrode sites, suggest that the zona reticulata itself does not support ICSS.

The discrepancies between earlier studies and the present observations on zona reticulata draw attention to some of the advantages of using a moveable, rather than a fixed, stimulating electrode. First, multiple stimulation sites can be tested in each animal giving a greater data yield for a given investment in surgery and animal training. In the present study 268 different electrode sites were tested in 48 rats; more than 5 times the total number that would have been tested with conventional fixed electrodes. Second, and more importantly, moveable electrodes allow a more precise delineation of the anatomical boundaries between regions that support ICSS and regions that do not support ICSS than is possible with fixed electrodes. The typical pattern of ICSS observed in a moveable electrode penetration which begins above the critical substrate is that at the most dorsally tested stimulation site ICSS is either not obtained, or the ICSS is obtained only with high stimulation currents and is characterized by low response rates. With subsequent moves of the electrode there usually appears a sudden drop in ICSS thresholds and a concomitant increase in response rates. This pattern reverses once the electrode tip reaches the most ventral boundaries of the ICSS region; thresholds begin to increase and response rates begin to decrease, and finally ICSS is lost altogether. The transition between positive and negative ICSS regions is best illustrated in the region of the dopamine-containing cell bodies of the zona compacta where, as discussed above, ICSS thresholds decreased as the electrode approached the dopamine containing cell bodies and the ICSS ceased once the electrode tip passed through the zona compacta and entered the zona reticulata (e.g. no. 134, Fig. 7). Fixed electrodes, with one tested site per animal, do not allow this degree of resolution. Finally, whereas with fixed electrodes ICSS rates and current thresholds must always be compared between animals, the moveable electrode

paradigm allows intra- as well as inter-animal comparisons. Thus, for example, it is frequently possible to verify that an animal has learned the ICSS task from data at one stimulation site, and thus place great confidence on the inference that other sites are negative. The failure to obtain ICSS may in some cases reflect emotionality or insufficient training; demonstration of good responding with other stimulation sites in the same animal can rule such factors out. The moveable electrode thus appears to be a powerful tool for investigating anatomical correlates of ICSS as well as other stimulation-induced behaviors[49].

The present study has two main findings. First the correlation between ICSS sites and the more rostral zona compacta and ventral tegmental dopamine cell regions is very strong. Moreover, ICSS rates and thresholds in these regions appear to be proportional to the density of dopamine neurons around the electrode tip; the highest rates and lowest thresholds are in areas containing the highest number of dopamine-containing cell bodies. The caudal pole of the midbrain dopamine neuronal population was found negative for ICSS. This finding may indicate a potentially important functional differentiation within the midbrain dopamine groups.

While these results and those of other studies have suggested dopaminergic involvement in ICSS at hypothalamic and midbrain sites, these data are largely correlational. Moreover it is the case that ICSS has been reported from sites that are near no known dopamine elements; this includes sites in the pons[48], hippocampus[37], medulla[5], and cerebellum[3] in addition to the two positive regions dorsal to the dopamine cell groups which were seen in the present study. It may be that ICSS from these regions is due to the indirect, trans-synaptic activation of dopamine neurons[51], but other possibilities cannot be ignored. The fact that ICSS is still observed at some sites following near-total depletions of brain dopamine stores raises the possibility that there are reward pathways that do not involve any dopamine system[28,41]. The anatomical and neurochemical characterization of non-dopamine elements that play a role in reward phenomena seems to be a promising direction for future research.

ACKNOWLEDGEMENTS

This research was supported by a fellowship from the Province of Quebec and by a grant from the National Institute on Drug Abuse of the United States (DA 01720).

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