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COLLATERAL AFFERENT EXCITATION OF RETICULAR FORMATION OF BRAIN STEM

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The demonstrable capacity of afferent stimulation to arouse a sleeping subject, and the obvious benefits of reducing sensory inflow in predisposing to sleep, are in seeming disharmony with recently discovered influences for wakefulness exerted by the central reticular core of the brain stem. Direct stimulation of this part of the neuraxis reproduces the electrical pattern of wakefulness in the cerebral cortex (14) while at the same time it facilitates lower motor activity (16), and so arouses the nervous system generally (9).

The ascending course of this reticular activating system is distinct from that of afferent pathways in the brain stem (19) and selective destruction of its cephalic portion is followed by the EEG synchrony and behavioral somnolence, hitherto attributed to deafferentation of the cerebrum (7,8). Such consequences do not follow selective interruption of ascending somatic and auditory paths in the midbrain and after this latter injury both somatic and auditory stimuli are still capable of awakening the sleeping animal and activating its EEG (7,8).

It seemed likely that the apparent conflict might be resolved if evidence were forthcoming that collaterals from afferent paths turned into the reticular activating system in the brain stem and exerted their admittedly important arousing and awakening influences, indirectly, by modifying its activity.

The present study has explored this possibility by probing the brain stem for alterations in electrical activity evoked by somatic and auditory stimuli. The findings establish the existence of collaterals from these sensory systems to the brain stem reticular formation, the rich wealth of which has never previously been suspected, though indications for it have been afforded by earlier anatomical investigation (2,11,13) and by study of the atypical route of conduction of the 'secondary response' to sciatic stimulation (5).

Though the results are presented here only with reference to the problem under discussion, it is felt that implications of these findings may be broad indeed, for they appear to enlarge outlooks in afferent conduction far beyond those which have been envisioned within the circumscribed limits imposed by classical sensory paths.

METHODS

Potentials evoked in the brain stem of cats by sciatic stimulation or auditory clicks were recorded with a Grass model-3 amplifier and ink-writer. B-erythroidine preparations maintained with artificial respiration were routinely used, and the findings were confirmed in

the encéphale isolé, the posterior columns being stimulated at C 1 for somatic effects. Exposure margins were infiltrated with procaine but, except for such central influences as are exerted by B-erythroidine, the brain was unanesthetized. The sciatic nerve was excited in the thigh, with a Sherrington electrode delivering condenser discharges from a Goodwin stimulator, at intensities of 3-5 volts, and with a falling phase of 2 msec. A toy cricket, manually operated, was used to evoke auditory potentials. The brain stem was explored with bipolar concentric electrodes oriented stereotaxically and histological controls obtained. Lesions were made electrolytically or surgically. Regional cortical pickups were obtained either with brass screw electrodes, 8–10 mm. apart, inserted through the calvarium until their tips rested on the underlying dura, or by silver ball cortical electrodes placed directly on the pial surface with a Grass multiple electrode carrier.

Results

Subcortical potentials evoked by sciatic stimulation were recorded from regions marked by shading in the transverse sections through the midbrain and diencephalon seen in Figure 1. Evoked potentials were routinely found in the areas occupied by the medial lemniscus (Fig. 1D–F), and ventro-posterolateral thalamic nucleus (B, C), structures which are known to mediate somatic impulses from the leg. This established pathway is well outlined by the more lateral cross-shaded regions of strong response. In addition, there was a broad involvement of medial structures from the level of the superior colliculus to the front of the thalamus.

In the midbrain, collateral* potentials were found in the entire tegmentum (Fig. 1E, F), and were best (indicated by cross-shaded areas) beside the central gray and in a paramedian position beneath it, including the region of the red nucleus. Responses were also found in the superior colliculus (F), in which the spino-tectal tract is known to terminate, presumably contributing somatic sensory impressions to reflex midbrain activities. Likewise, the lateral portion of the pretectal region also yielded effects (E)—a connection from the medial lemniscus of the dog mentioned by Rioch who used the Weigert anatomical method of study (17).

In the diencephalon, similar excellent collateral effects were found through the rostro-caudal extent of the thalamus, as well as in the subjacent sub- and hypothalamus. Hypothalamic potentials were best at the mammillary level, responses extending almost to the base of the brain (Fig. 1D). In addition, at this level the subthalamus above and the centre median of the thalamus were also completely implicated, and potentials were often found in the ventral part of the nucleus lateralis posterior (Fig. 1C). In mid-dience-phalic planes (B, C), the hypothalamus received collateral impulses in its dorsal and lateral portions only and, farther laterally, an extension into the lower part of the internal capsule occurred. At these levels, however, the most intense and reliable effects were found in the subthalamus and ventromedial thalamus. Thalamic nuclei completely involved were the ventromedial, ventralis lateralis, and the ventralis posteromedial. Marginally affected were intralaminar, reuniens, medial and lateralis posterior nuclei. At the front of the thalamus (A), the most conspicuous responsive zone included, the ventromedial part of the ventralis anterior and the underlying reticular nucleus and medial internal capsule. Collateral potentials were also found at this plane in the reuniens and anteromedial nuclei, and fringe effects were seen in the globus pallidus.

In summary, the best collateral somatic afferent potentials were found in the medial midbrain tegmentum below and beside the central gray, in the sub- and dorsal hypothalamus, and in the ventromedial part of the thalamus. These results were checked by stimulation of the posterior columns in the encephale isolé and found to be essentially the same.

*The term “collateral” is employed in a general, rather than a strict anatomical sense throughout.

Shown in Figure 2 are representative responses from various collateral areas. In the midbrain, evoked potentials were usually sharper and more spike-like than at more rostral levels, as seen in the red nucleus (Fig. 2A) and the midbrain reticular formation (B), although the effect assumed more of a wave form in marginal regions such as the pretectal area (C). With diencephalic pickups, spikes were also frequently present, but these were almost always accompanied by a wave. Such double effects recorded from the subthalamus are illustrated in Figure 2D, in which a small spike first occurred, followed by a wave. In the ventromedial thalamic nucleus (E) a progressive decrement of voltage with each successive stimulus was seen. In this case, however, the first sharper component of the response was relatively little affected, but the secondarily occurring wave was much reduced by the time of the third stimulus. Shown also are records from the ventralis lateralis (F), and reuniens (H), in which potential complexes were little changed within a period of three stimuli. Of the recruiting nuclei, only in the centre median were spikes found (Fig. 3A–4). Potentials elsewhere in the diffusely projecting thalamic nuclei were always waves. A frequent finding in these latter nuclei was the precipitation of a spindle burst by a sciatic stimulus. Instances are shown in the ventromedial-intralaminar area (Fig. 2I) and the ventralis anterior (J), in both a reflection of the bursts occurring in the cortex (upper channel). When responses were found in the association nuclei, they were always of a wave variety, and inconstantly would exhibit a marked waxing and waning as shown in the lateralis posterior (Fig. 2G).

In all regions of collateral pickup, responses were usually equally good whether the ipsilateral or contralateral sciatic nerve was stimulated. Examples of pickup ipsilateral to sciatic stimulation are shown (Fig. 2J; Fig. 3A, B). Another frequent feature of collateral evoked potentials was a reversal of phase as the exploring electrodes were lowered through the responsive area, as seen in the centre median and subthalamus (Fig. 3A). Here the deflection was at first positive (1, 2), then biphasic (3), and finally negative (4–6).

Having outlined the regions exhibiting collateral potentials on single shock somatic afferent stimuli, attention was next directed to the effects of repetitive afferent stimulation on deep structures, with correlated cortical findings. Recorded in the subthalamus, evoked collateral potentials followed the sciatic stimulus at 6/sec. (Fig. 3B-1). Following the stimulus period, an after-effect of desynchronization was present in the deep lead, while the sensory-motor cortex was little affected, either during or after stimulation. With sciatic stimulation at 15/sec. (B-2), the subthalamic potentials, after the first one, were greatly reduced. Although large waves were still seen in the deep lead following stimulation, more low fast activity was exhibited than before, and a definite arousal of the cortex occurred during and after stimulation. With 25/sec. (B-3), the subthalamic potentials were even more reduced although the general effect differed little from that with 15/sec. With sciatic stimulation at 50 sec. (B-4), individual subthalamic potentials could no longer be distinguished, but the activity of this subcortical region was thoroughly desynchronized, as was that at the sensory-motor cortex.

In cats under B-erythroidine, the spontaneous activity of the red nucleus at times was characterized by 20–30/sec. waves, whose amplitude was capable of undergoing great variation (Figs. 2A, 3C). This region receives a large supply of somatic collaterals and, by stimulation of the sciatic nerve, its activity could be altered remarkably. With excitation of the sciatic nerve at 3/sec. (Fig. 3C-1), a background effect of 20/sec. waves occurred riding along with the evoked potentials, and with stimulation at 10/sec. (Fig. 3C-2) the same thing was noted. In both cases an after-discharge of these waves continued upon cessation of stimulation. At times single stimuli could initiate this effect. With high frequency stimulation of the sciatic nerve, the activity of this area was desynchronized, but the after-discharge remained again the same.

Through the remainder and greater part of the midbrain tegmentum, this variety of after-discharge was not seen but, rather, effects were more like those just described in the

subthalamus. Collateral potentials could follow stimuli up to 30–40/sec., and the effect of sciatic stimulation at frequencies of 10, 20, 30, and 50/sec. are illustrated (from left to right) in the midbrain tegmentum (Fig. 3D), followed in each instance by a period of increased desynchronization.

Effect of lesions on somatic afferent collaterals

Because much of the area through which the collateral somatic afferent system is distributed is traversed also by efferent cerebellar and by corticofugal connections, control exploration was conducted in these zones after bilateral extirpation of the somatic cortex and complete removal of the cerebellum. Following such dual lesions, there was no widespread alteration of collateral pickup. In the ventromedial thalamus and subthalamic areas were large responses at stimulus frequencies of 1.2/sec. (Fig. 4A-1, left), and 3/sec. (right). With repeated stimulation or with higher frequencies, there was a falling out of the wave component of the potential complex (cf. Fig. 4A-1, right, with Fig. 2D, E, from an intact brain). Responses after these lesions are also shown from the centre median (Fig. 4A-2), superior colliculus (A-3), and the red nucleus (A-4). Any variation from the picture seen in the intact brain was found deep in the tegmentum in the area of the red nucleus. Evoked collateral potentials could still be obtained, as illustrated, but they were considerably smaller than those found in the intact cat, and no 20/sec. wave after-discharge could be produced. The lesions had no effect on the bilaterality of the potentials at any level of the collateral zone. In Fig. 4A-1 and 2, stimulus was ipsilateral to the pickup and in A-4 contralateral. Even in the superior colliculus, a bilaterality of effect was noted (A-3), indicating either uncrossed spino-tectal paths or intercollicular connections.

Next, the most rostral level at which medial collateral fibers leave the classical somatic pathway was determined. To accomplish this, lesions of the medial brain stem were made, sparing only the more lateral direct somatic routes. In this way all collateral responses rostral to the lesion were attributable to fibers moving medially above that point rather than to cephalically propagated impulses that had turned in at lower levels. With this type of lesion at the intercollicular level, excellent collateral potentials were still obtainable through the front of the midbrain and in the thalamus, shown from a ventromedial-intralaminar pickup (Fig. 4B-1), in the same responsive zone as in an intact brain. With such a lesion at the tegmento-thalamic junction, 1.5 mm. behind the centre median, collateral discharge was still in evidence; large potentials were still obtainable from the centre median (Fig. 4B-2) and, more anteriorly, from the ventromedial thalamus and subthalamic (B-3). After such medial brain stem lesions, collateral responses were still found in both the contralateral (B-3), and ipsilateral (B-1, 2) thalamus. Since an ipsilateral direct somatic path exists (B-4), it is not possible at present to decide whether the ipsilateral impulses were mediated by it or were conducted by collateral connections that had crossed through the medial brain stem from the opposite side. It seems likely that both routes were involved.

Finally, the medial lemniscus was destroyed bilaterally at the intercollicular level, sparing the rest of the tegmentum. From this it could be determined whether or not medial collaterals were coming in below this point and, if so, whether their potentials were being propagated cephalically through the brain stem. After this procedure, evoked potentials were still found more rostrally in the areas of collateral inflow defined in the intact brain, illustrated from the thalamic ventromedial nucleus (Fig. 4C-1) and the midbrain tegmentum (C-2). No primary potentials could be found in the ventroposterolateral nucleus, or the control sensory cortex. In the latter, however, irregular tripping of cortical bursts was seen (C-1).

Taken as a whole, the results following these lesions indicated that inflow of collateral somatic potentials occurred both below the intercollicular plane and above it, as far rostrally as the posterior thalamus, the impulses from all levels moving cephalically in the medial brain stem. Medial influx of potentials occurred bilaterally as far forward as the posterior thalamus,

although whether ipsilateral impulses were conducted from the homolateral medial lemniscus or crossings through the collateral zone is not at present known.

Distribution of subcortical potentials evoked with auditory stimulation

Responses to click stimuli were prominent in the well-known auditory pathways, the brachium of the inferior colliculus and medial geniculate nucleus, indicated by the lateral shaded areas in Figure 5. As in the somatic system, a wide distribution of collateral involvement was apparent also in the medial midbrain and thalamus. In the midbrain, collateral potentials were picked up broadly through the tegmentum and were best in its paramedial portion, beside and below the central gray (Fig. 5D–F). In the tectum, responses were seen in the superior colliculus (F), a projection previously reported (1). In the diencephalon, the dorsal and lateral hypothalamus as far forward as the tuber exhibited auditory potentials, with even stronger effects in the overlying subthalamus (B, C). At these levels, the responsive zone extended into the ventromedial thalamus as well, and included the centre median (C), and the ventromedial and ventrolateral nuclei (B). The intralaminar nuclei were involved only in the most marginal sense (B). At the front end of the thalamus (Fig. 5A), collateral effects were found in the ventralis anterior and, at this level, a small focus of spike potentials was also observed in the lateral globus pallidus. The most lateral shaded area in Figure 5B probably indicates the course of fibers from the medial geniculate on their way to the cortex, and in A the small focus in the upper right lies in the auditory cortex.

While the results shown in Figure 5 were all obtained with B-erythroidine preparations, those obtained from the encephale isole were essentially the same. A comparison of Figure 5 with Figure 1 reveals the striking similarity of distribution of the areas receiving collaterals from auditory and somatic paths; in both, collateral potentials were found widely distributed in the tegmentum of the midbrain, sub- and hypothalamus, and ventromedial part of the thalamus, including at the rostral pole the ventralis anterior.

The type of collateral potential evoked by click stimuli differed little from that induced by sciatic stimulation. The best foci in the midbrain tegmentum regularly exhibited spike potentials upon click stimulation, as seen in the reticular formation (Fig. 6A) and red nucleus (C), although responses from the superior colliculus were waves (B). At times, in the tegmentum, a duplication or triplication of potential was seen, the initial spike being followed by a much diminished second or third deflection (Fig. 6A — 4th and 5th stimuli). The subthalamic response evoked by a click stimulus was indistinguishable from that obtained with sciatic stimulation, a spike and broad wave occurring (F). With repeated clicks, the spike persisted but the wave was extinguished (F). In the hypothalamus, similar alterations were observed, the spike being the hardest component of the response complex. Illustrated is an example where only a spike occurred (Fig. 6G). Likewise, nuclei located in the ventromedial part of the thalamus, the ventralis lateralis and ventromedialis (see Fig. 7E) frequently showed response complexes of spikes and waves. Of the recruiting nuclei, only the centre median regularly manifested spike potentials upon auditory stimulation (Fig. 6D, E). Elsewhere in the diffuse thalamic nuclei, collateral impulses were waves. In these regions—whose electrothalamogram is characterized by spindle bursts, particularly under barbiturate anesthesia—collateral potentials initiated subcortical bursts, seen from the centre median (Fig. 6E) and ventralis anterior (I). In the basal ganglia, tiny spikes were sometimes seen in the globus pallidus (H) and adjacent part of the putamen.

Thus with both auditory and somatic collaterals, the responses were sharper and more spike-like, the more caudal the pickup in the collateral zone. Through diencephalic levels, complexes of initial spikes followed by broader waves were frequently seen. The literature in the nuclei of the diffuse thalamic projection system consisted no only of an evoked potential, but

frequently a rhythmic after-discharge of 7–10/sec. waves, as well, suggesting that discharge had triggered a spindle burst.

Effect of lesions on auditory collateral potentials

To be sure that excitation of the medial brain stem by auditory stimulation did not involve cerebellar circuits, complete cerebellectomy was performed and exploration of collateral zones repeated. This procedure caused no change in distribution of response either in the midbrain or diencephalon, and persisting responses are shown from the ventromedial thalamic nucleus (Fig. 7E) and midbrain tegmentum (F). To eliminate the possibility of cortico-subcortical connections being involved, the auditory receiving areas were removed bilaterally. Again no change in effect was seen, and post-topectomy pickups are illustrated between the ventromedialis and centralis medialis of the thalamus (Fig. 7A), and from the midbrain tegmentum (B).

To determine the caudal extent of collateral influx, the medial geniculate bodies were bilaterally destroyed with persistence of collateral potentials, seen in the subthalamus and red nucleus (Fig. 7C). The inferior colliculi were next completely removed bilaterally through a subtentorial approach, the cerebellum first having been sucked out. After this lesion, collateral potentials evoked by click stimuli were greatly thinned out, but were nonetheless clearly present in the midbrain tegmentum, subthalamus (Fig. 7D), and centre median. No effect was seen in the control auditory cortex (D, upper channel), but tiny potentials were still present in the medial geniculate bodies. These persisting medial geniculate potentials may be explained by the preservation of lateral lemniscal fibers bypassing the inferior colliculi (3,6), but these responses were so minute compared to the collateral effects that it seemed likely that the medial brain stem potentials recorded were being propagated rostrally through the collateral system from levels behind the inferior colliculi.

In an effort to learn the rostral extent of collateral auditory inflow, electrolytic lesions were next placed in medial brain stem areas sparing only the more lateral through sensory paths. With such a lesion at the level of the superior colliculus, medial potentials were still obtained above the lesion, from the midbrain and diencephalon. Shown are such effects from the subthalamus (Fig. 7G) and the red nucleus (H). In the latter instance, further evidence is provided that at least part of the collateral firing of the red nucleus is not referable to its cerebellar connections, for these had here been eliminated. Finally, a similar lesion was placed at the tegmento-thalamic junction. This procedure reduced medial diencephalic collateral potentials to a minimum, but some effects were still present, shown in the ventromedial thalamic nucleus (I).

As a group, these experiments indicate a medial collateral system into which auditory impulses feed from below the level of the inferior colliculus as far forward as the posterior part of the thalamus. Potentials entering this zone at caudal levels are propagated forward through the medial brain stem. Conduction through the cerebellum does not play an essential role in this system, and corticifugal contributions are insignificant.

Discussion

Using anatomical techniques, numerous indications of brain stem collaterals from the somatic pathways have been reported. With lesions of the anterolateral white column of the monkey's cord, spino-reticular fibers have been traced with the Marchi method to the reticular formation at the level of the inferior olive (13). After lesions of the gracile and cuneate nuclei in the guinea pig, Marchi degeneration has been traced to the medial midbrain tegmentum in the red nucleus area and to the subthalamus (2). Recently, in cats with destruction of the gracile and cuneate nuclei, degeneration has been found with the Marchi stain in the subthalamus and

hypothalamus, the collaterals in this case forming a perceptible bundle splitting off the medial lemniscus at the rostral end of the midbrain (11). Similarly, many investigators have reported lemniscal fibers running to the internal medullary lamina of the thalamus, particularly to the centre median, and a review of this literature has been given by Walker (20).

With physiological methods, indications have also been obtained for collateral afferent connections with the medial part of the brain stem. In the auditory system, some evidence for discharge from the superior olivary complex into the reticular formation and medial longitudinal fasciculus has been reported (6,15). In the case of the somatic system, reticular potentials from trigeminal stimulation have been described (12) and, with sciatic stimulation (4), such widespread bulbar excitation occurred that in order to map the course of the medial lemniscus it was necessary to use the saphenous nerve. In the midbrain, evoked potentials have occasionally been seen medial to the medial lemniscus (10) and, in the diencephalon, impulses were recorded from the centre median (4,10) and occasionally from the subthalamic (10). Upon stimulation of the sciatic nerve or injection of hypertonic saline solution into the gastrocnemius muscle, a desynchronization of hypothalamic electrical activity was observed by Gellhorn and Ballin (5a) and was attributed to afferent excitation of this region. The failure of these earlier investigations to detect the presently observed profusion of afferent connections with the reticular formation of the brain stem may have been the result of the fact that the experiments were usually performed under full barbiturate anesthesia, a possibility with interesting suggestions for the manner in which anesthesia prevents arousal by afferent stimulation.

The present study, then, indicates a much broader afferent collateral system in the brain stem than has previously been recognized, into which such an extensive influx of sensory data pass that it must have important functional implications. It has been shown that collaterals leave the main sensory paths and move medially at least as far rostrally as the posterior thalamus in the case of both the auditory and somatic sensory systems. The caudal limit has not been accurately delimited for either modality. With sciatic stimulation, however, it is clear that collaterals split off from the medial lemniscus below the intercollicular plane. Moreover, both electrical (4) and anatomical (13) studies have demonstrated the presence of somatic afferent collaterals entering the reticular formation at the bulbar level. It seems justifiable, then, to conclude that almost the entire length of the reticular formation of the brain stem, from the medulla to the posterior thalamus, receives contributions from ascending somatic paths.

Auditory collateral inflow has been shown in the present study to occur behind the level of the inferior colliculus. Although it is impossible from present information to mark the caudal limit of these contributions surely, the second order auditory neurones of the superior olive and trapezoid nuclei lie in most intimate contact with the pontobulbar reticular formation, and some indication exists that auditory impulses leave the main pathway here (6,15). Thus the auditory system also gives off an extensive brush of collaterals to the reticular formation through most of its brain stem course and the distribution of its collateral influx is almost identical with that from somatic afferents.

From this work it is also clear that the influences of afferent collaterals entering the caudal part of the reticular formation are propagated rostrally through the medial brain stem, for, after lesions destroying the through sensory pathways, evoked potentials could still be recorded medially above the level of the lesion. Similar cephalic transmission of evoked potentials has recently been studied by direct single-shock stimulation of the ascending reticular activating system at various levels of the brain stem (19). Through the midbrain and thalamus the distribution of these evoked potentials was almost identical with the afferent collateral zones here outlined and at present it seems likely that we are dealing with the same system. Further knowledge must, however, await study of interaction of potentials evoked by various afferent and reticular stimulation.

The long extent of collateral inflow, coupled with the fact that caudal potentials are ultimately relayed to the upper brain stem, may help explain the complexity of responses obtained, for a given response may represent at once impulses which have entered the caudal limit of the collateral zone and passed forward in the medial brain stem—possibly across several synapses—and discharge of a collateral which has split off the main sensory path at a more cephalic level. In this case one might expect to find a spike coupled with a wave, and this has been a frequent finding. In such complex recordings the wave was invariably unable to follow stimulus frequencies that had little or no effect on the spike, again suggesting multi-synaptic conduction of the wave component.

The relationship of the afferent collateral zones to the reticular activating system is an important one. The regions outlined in the present study are also those through which the EEG arousal reaction is mediated, judged both from direct stimulation and recording techniques (19). It is well known that the cortex is widely activated by afferent stimuli, although the direct sensory path goes only to a discrete cortical area. Moreover, in cats with chronic lesions of the direct sensory pathways immediately below the thalamus, the animals are easily aroused both behaviorally and electro-encephalographically by sensory stimulation (8) and in this case the cortex is apparently being influenced entirely by collateral routes. In the present experiments, it was shown that a desynchronization of subcortical activity through this collateral system occurred with repetitive sciatic stimulation, and that this effect preceded or was concomitant with cortical desynchronization.

In cats with large central lesions at the tegmento-thalamic junction, sparing main sensory paths, it was observed that generalized arousal of the electrocorticogram could be produced by intense nociceptive and auditory stimuli (8). Such arousal was evidently due to the direct arrival of afferent impulses somewhere above the midbrain. In addition to the possibility of desynchronization by the arrival of afferent impulses at the cortex, the present findings allow an alternative interpretation of these results, for it has been seen that collateral potentials are still turning from the main sensory paths into the ventromedial diencephalon above the level of such a lesion.

Within the thalamus, the present study has also shown a relation of afferent collaterals to the nuclei of the diffuse thalamic projection system, for evoked potentials could be recorded from them, and always occurred as waves except in the centre median. These discharges followed only very low frequencies, seldom greater than 1–2/sec., and when stimuli were delivered at sufficient intervals subcortical bursts could be initiated. It is known that the recruiting nuclei are functionally interconnected with one another and project to the association nuclei of the thalamus (18). Therefore it is possible that collateral impulses entering the centre median may be responsible for effects observed in the more rostral recruiting constituents, the intralaminar and ventralis anterior nuclei. By the same token, responses from the association nuclei, which frequently waxed and waned, may have represented dispersion from the same fountainhead.

The topographical features of these findings are depicted in Figure 8, in which the course of the ascending reticular activating system is indicated by cross-lining and the collateral afferent influx into it is shown occurring through the length of the brain stem. The wide distribution of this system of afferent collaterals appears to offer new avenues of investigation in subcortical mechanisms. It seems clear that with sensory stimulation—at least with somatic and auditory modalities—there is not merely excitation of through afferent pathways but functional mobilization of the entire brain stem from the medulla to the thalamus. This carries obvious implications for subcortical motor activity, and for the generalized behavioral and electrocortical arousal which may be provoked by afferent stimulation. In addition, it has long been thought that there existed a subcortical component of sensory perception. If such be the

case, the collateral system offers for subcortical integration a substratum of great range and diffuse connections.

Summary

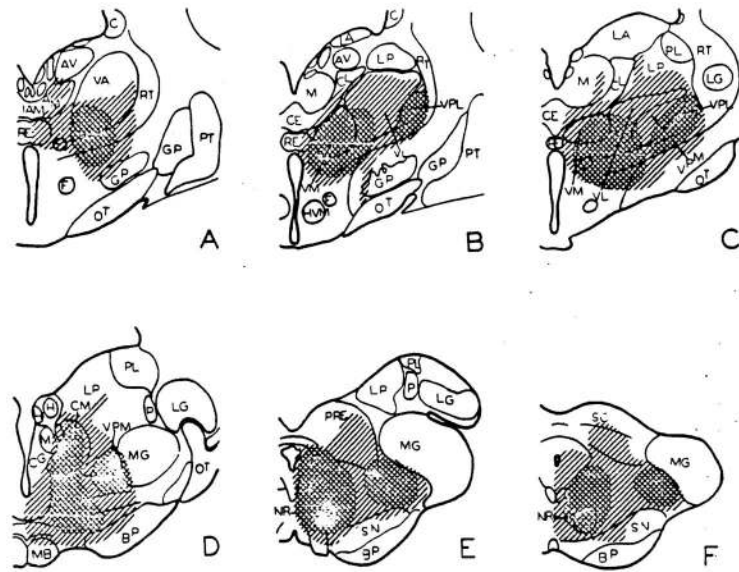
The distribution of afferent collaterals to the reticular formation of the brain stem has been investigated in the cat by probing for potential changes evoked by somatic and auditory stimulation.

In the case of each modality, a rich supply of collateral connections to the midbrain tegmentum, sub- and hypothalamus and ventromedial thalamus was encountered. These findings offer an explanation for a number of the generalized consequences of afferent stimulation which have been difficult to understand in terms of conduction within classical sensory paths. Specifically, they indicate that the arousing and awakening influences of sensory stimulation may be exerted indirectly, and at a subcortical level, by collateral excitation of the reticular activating system in the brain stem.

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**Fig. 1.**

Transverse sections through hemisphere with shading indicating areas from which evoked potentials are recorded upon single-shock stimulation of sciatic nerve. Cross-hatched zones are regions of greatest response potentiality, and are seen to be in medial brain stem areas as well as along through sensory path. Only B-erythroidine preparations included. Abbreviations for Figs. 1 and 5 are as follows: A—amygdala, AM—anteromedial nuc., AV—anteroventral nuc., BIC—brachium inferior colliculus, BP—basis pedunculi, C—caudate nuc., CE—nuc. centralis medialis, CG—central gray, CL—nuc. centralis lateralis, CM—centre median, F—fornix, GMES—middle ectosylvian gyrus, GP—globus pallidus, H—habenular nuclei, HP—habenulo-peduncular tract, HVM—ventromedial nuc. of hypothalamus, IAM—intermediate anteromedial nuc., LA—nuc. lateral anterior, LG—lateral geniculate nuc., LP—nuc. lateralis posterior, M—medial nuc., MB—mammillary body, MG—medial geniculate nuc., ML—medial lemniscus, NR—red nuc., OT—optic tract, P—posterior nuc., PL—pulvinar, PRE—pretectal region, PT—putamen, RE—nuc. reuniens, RT—reticular nuc., SC—superior colliculus, SN—substantia nigra, SU—subthalamic nuc., VA—nuc. ventralis anterior, VL—nuc. ventralis lateralis, VM—ventromedial nuc., VPL—ventroposterolateral nuc., VPM—ventroposteromedial nuc.

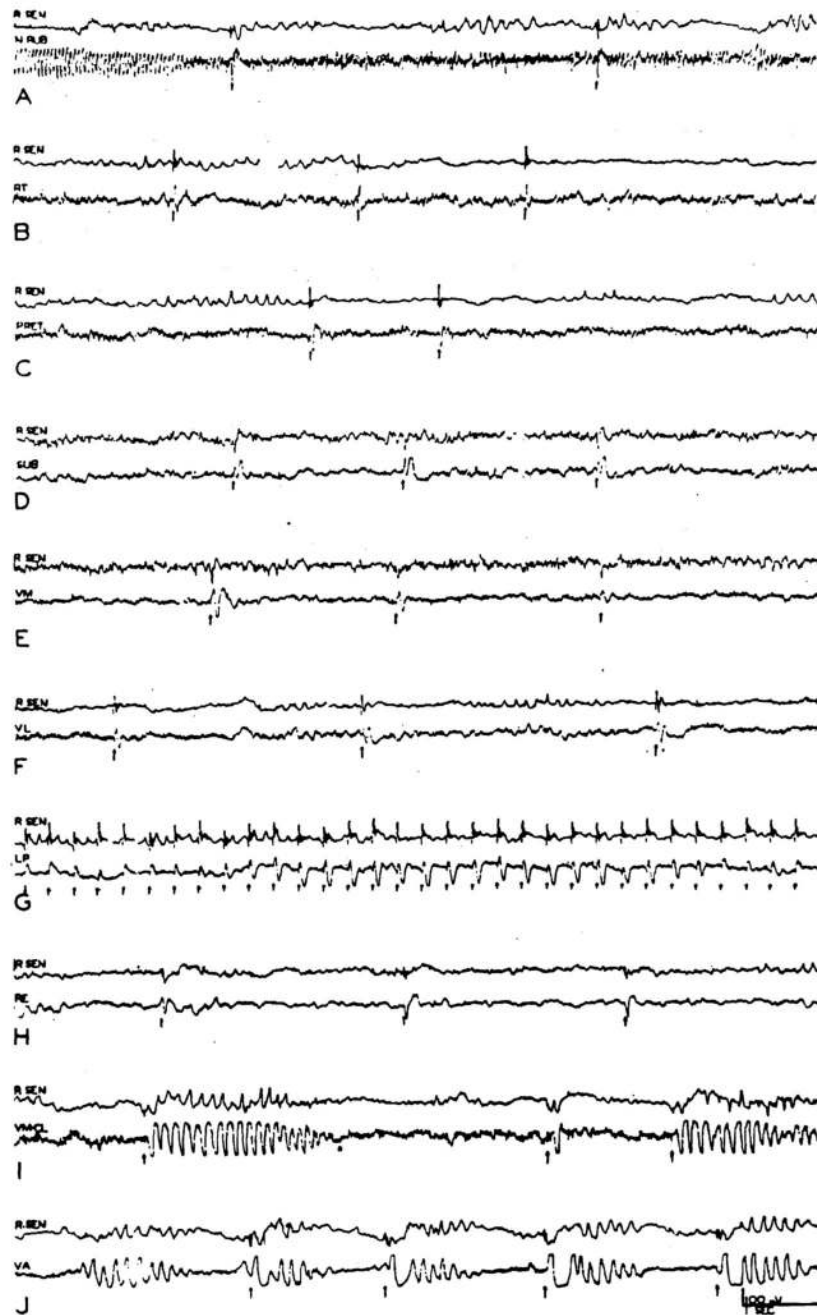


Fig. 2. Records of collateral afferent somatic potentials evoked by stimulation of left sciatic nerve with 3–5 volts. Responses illustrated are from red nucleus (A), tegmentum of midbrain (B), pretectal region (C), subthalamus (D), ventromedial thalamic nucleus (E), ventralis lateralis (F), lateralis posterior (G), reuniens (H), ventromedial to centralis lateralis (I), and ventralis anterior (J). All deep pickups are on right side, contralateral to stimulus, except J which is ipsilaterally located. In each case, activity of right sensory cortex (R SEN) is recorded in upper channel. Notice waxing and waning of evoked potentials in G, and tripping of spindles in I and J. Individual stimuli are marked with arrows. All under B-erythroidine.

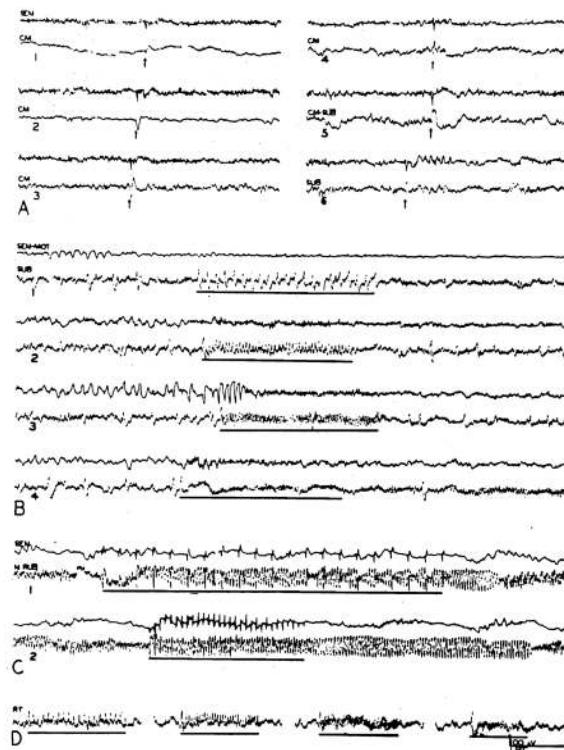


Fig. 3. Records illustrating various characteristics of collateral somatic afferent potentials upon stimulation of sciatic nerve with 3–5 volts. In A is shown phase reversal of response on passing through centre median-subthalamic region, electrode having been lowered by 1 mm. steps (1–6). In B is illustrated the differing effects, in both subthalamic and cortical leads, with different frequencies of sciatic stimulation. Frequencies used were 6/sec. (1), 15/sec. (2), 25/sec. (5), and 50/sec. (4). In C are seen the large collateral potentials in red nucleus area with sciatic stimulation at 3/sec. (1), or 10/sec. (2). Notice increase in background activity produced by stimulation and its persistence as an after-discharge in both cases. D illustrates effects of frequency variation on collateral potentials recorded from midbrain tegmentum; sciatic nerve was stimulated (from left to right) at 10, 20, 30, and 50/sec. Deep pickups are on side of sciatic stimulation in A and B, and contralateral in C and D. In each strip, upper channel records the activity of sensory cortex contralateral to side of stimulus, except B which is ipsilateral. Arrows indicate single stimuli, and dark lines mark periods of repetitive excitation. Cortical abbreviations are: SEN—sensory, SEN-MOT—sensory motor. All under B-erythroidine.

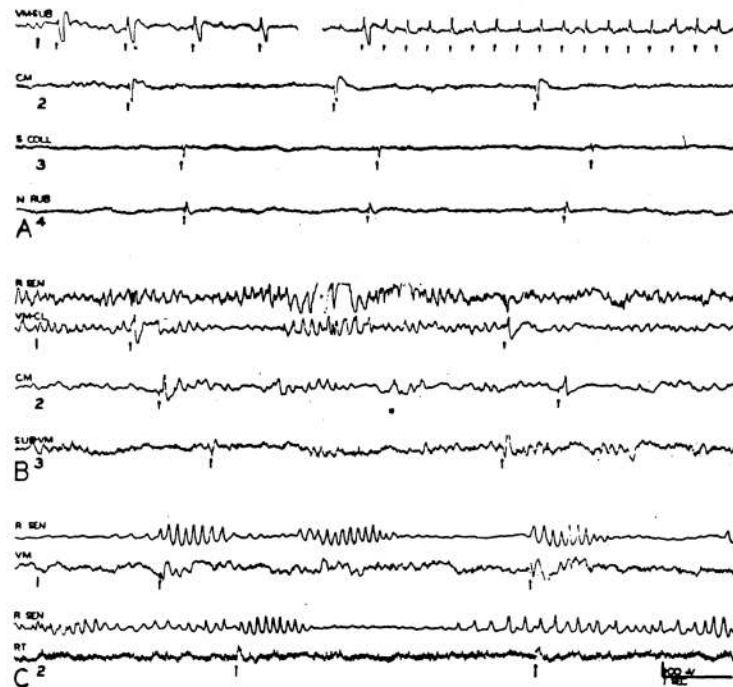


Fig. 4.

Records showing collateral somatic afferent potentials evoked by sciatic stimulation (3–5 volts), after various lesions. After complete cerebellectomy plus bilateral extirpation of somatic cortex (A), responses are evoked by sciatic stimulation in region of ventromedial nucleus and subthalamus (1), centre median (2), superior colliculus (3), and from red nucleus (4). In recording between subthalamus and ventromedial nucleus, the full response is seen with stimuli at 1.2/sec. (A, 1—left), but with 3/sec, the wave component falls out leaving a spike (1—right). After lesions of medial midbrain tegmentum (B), collateral responses are still found at more rostral levels. In B, 1, such a medial lesion was placed at intercollicular level leaving only lateral sensory pathways intact, and collateral potentials were recorded between centralis lateralis and ventromedial nuclei of thalamus. In B, 2 and 3, a lesion was placed at tegmento-thalamic junction, sparing only laterally located sensory pathways. Electrodes placed in centre median (B, 2), and between subthalamus and ventromedial nucleus (B, 3), revealed continued presence of medially located collateral potentials. Complete bilateral destruction of medial lemnisci at intercollicular level, sparing medial tegmentum, does not abolish collateral responses at more rostral levels (C) as shown from ventromedial nucleus (C, 1), and upper midbrain tegmentum (C, 2). With lemnisci eliminated, sensory cortex does not exhibit a primary spike, but sciatic stimulation still appears to have an initiating effect on bursts (C, 1). Subcortical pickups were ipsilateral to side of sciatic stimulation (A, 1–3; B, 1–2), and contralateral (A, 4; B, 3; C, 1–2). All sensory cortical pickups (R. SEN) were contralateral to stimulus. Shocks are marked by arrows. All under B-erythroidine.

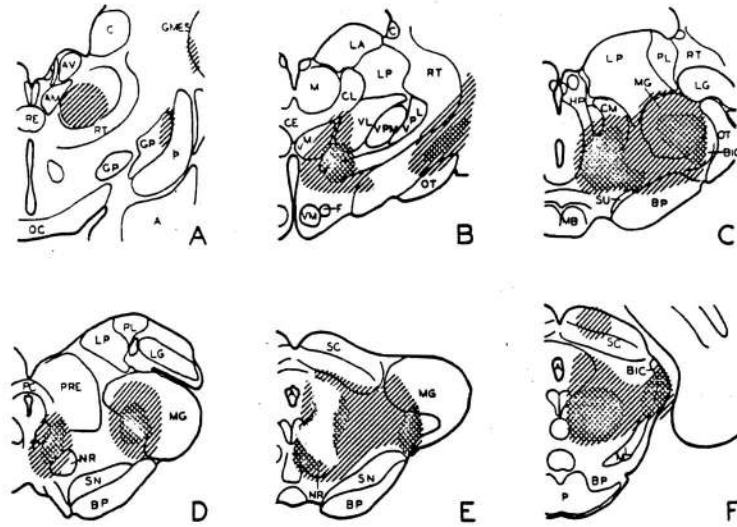


Fig. 5. Transverse sections through hemisphere, with shading indicating areas from which evoked potentials are recorded upon click stimulation. Cross-hatching areas indicate regions of best response. As with somatic system, large medial area of brain stem is implicated, as well as through auditory pathway. Only B-erythroidine preparations included. In D and E, lateral part of medial geniculate was not explored.

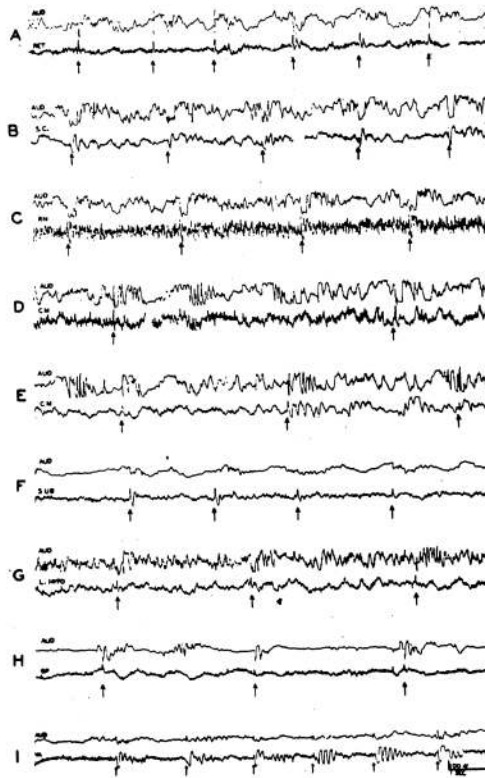


Fig. 6. Records of collateral auditory potentials, evoked by click stimuli, in midbrain tegmentum (A), superior colliculus (B), red nucleus (C), centre median (D, E), subthalamus (F), lateral hypothalamus (G), globus pallidus at its junction with putamen (H), and ventralis anterior nucleus (I). Note occasional tripping of spindles in centre median (E) and regular tripping in ventralis anterior (I). Record from auditory cortex (AUD), on same side as deep pickup, is shown in upper channel in each case. Click stimuli are marked by arrows. All under B-erythroidine except I, from an encephale isolé.

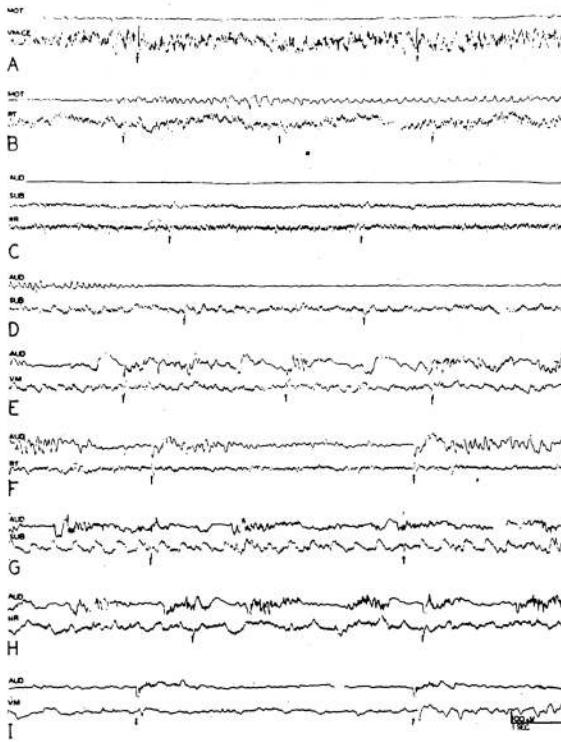


Fig. 7.

Records of collateral auditory potentials after various lesions. After bilateral removal of auditory cortex, responses are shown in region of centralis medialis and ventromedial nuclei (A) and midbrain tegmentum (B). After complete bilateral destruction of medial geniculate bodies, collateral potentials are seen in subthalamus and red nucleus (C), former in this case being a broad wave. With complete bilateral destruction of inferior colliculi, responses are shown in subthalamus (D). After complete cerebellectomy, collateral potentials are illustrated in ventromedial thalamic nucleus (E) and midbrain tegmentum (F). After destruction of medial midbrain tegmentum at level of superior colliculus, leaving only lateral sensory pathways intact, collateral auditory responses are shown in subthalamus (G) and red nucleus (H). With such a medial lesion at tegmento-thalamic junction, sparing only lateral sensory paths, a collateral auditory response is seen in ventromedial nucleus (I). Click stimuli are marked with arrows. Abbreviations for cortical leads are: AUD—auditory, MOT—motor. All under B-erythroidine.

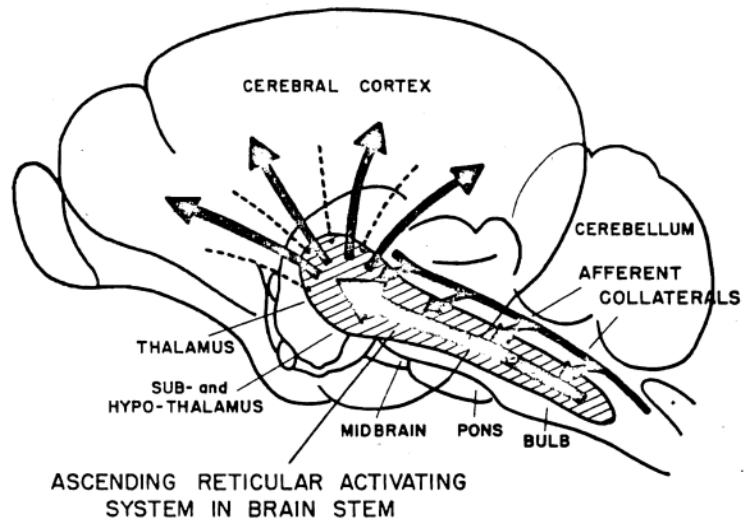


Fig. 8.
Outline of brain of cat, showing distribution of afferent collaterals to ascending reticular activating system in brain stem.