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IS THE "NONSPECIFIC" THALAMUS STILL "NONSPECIFIC"?

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INTRODUCTION

More than forty years have elapsed since Arnaldo Aduini and Giorgio Macchi delivered a presentation on the anatomical and functional organization of the thalamo-cortical system at a Meeting of the Italian Society of Anatomy (65). At that time, a basic principle of thalamic organization was considered to be represented by the distinction between "specific" and "nonspecific" thalamo-cortical connections, established under the influence of the Montreal school (42) (Fig. 1). Thus, the concept of a "specific" thalamic system was based on the organization of individual sets of projections reaching a restricted target cortical area and the electrophysiological correlate of an evoked potential upon such cortical target following thalamic stimulation. The concept of a "nonspecific" thalamic system implied instead "diffuse" projections upon the cortex (42, 88), considered to provide a basis for the "recruiting" cortical responses. These electrophysiological responses were characterized by long-latency, high voltage, repeatedly waxing and waning potentials, which were elicited from large cortical areas following low-frequency stimulation of "nonspecific" thalamic nuclei, and in particular of the intralaminar structures (35, 42, 86). Following the discovery of Moruzzi and Magoun (87) of activating connections ascending from the brain stem paramedian reticular formation, the ascending activating system was thus believed to be conveyed to the cortex via diffusely distributed thalamic projections, subserving a general regulation of cortical electrical activity, such as that involved in sleep and wake.

We wish to briefly re-examine the concept of "nonspecific" thalamus on the basis of some of the data derived from the last decades of research. It is important to recall that in experimental neuroanatomy a new era in the studies of neural connectivity was initiated in the early 1970s by the introduction of techniques based on the axonal transport of tracers (24, 54). The map of the connections in the central nervous system was thus re-designed, and enriched by circuits based on projections arising from a few and sparse neurons, whose anatomical study requires sensitive tract tracing techniques. This allowed also a re-investigation of the organization of the direct subcortico-cortical connections (see 66 for a review of early studies on this subject).

Since the first years of investigations based on the axonal transport of tracers, the studies of the mammalian thalamo-cortical connections did not confirm a clear-cut distinction between diffuse and restricted projections, but allowed instead to distinguish different categories of thalamic nuclei based on the distribution and gradient of density of their projections upon cortical targets (66). On line with the classification of the pattern of distribution of subcortico-cortical projections outlined by Divac (27a) in the rat, Macchi's laboratory forwarded a subdivision of the thalamic nuclei in the cat (Fig. 2). In this scheme of organization, the so-called "nonspecific" thalamus was thus proposed to be represented by thalamic nuclei which project preferentially upon more than one cortical area and sparsely upon other cortical fields, whereas individual thalamic nuclei giving origin to projections distributed upon the entire cortical mantle were not identified (66). In addition, in the last two decades, further data on the intrinsic organization, input-output organization, as well as functional correlates of the so-called "nonspecific" thalamus, brought about a substantial revision of thalamic "nonspecificity".

HETEROGENEITY IN THE ORGANIZATION AND CORTICAL CONNECTIVITY OF THE THALAMIC "NONSPECIFIC" NUCLEI

The "nonspecific" thalamus, as defined in the late 1950s (65) and mid-1960s (1), includes an association of nuclear masses (Fig. 1) which are now known to exhibit differences in cell composition, connectivity, functional roles and basic principles of organization. Such heterogeneity clearly emerges even from early reviews on this subject (1, 65), and the definitions of "nonspecific" thalamus, and "diffuse" thalamo-cortical projections were long considered uncertain, awaiting for further knowledge (72).

From the cytoarchitectonic point of view, two classes of relay neurons were distinguished in the thalamus since the first studies based on Golgi impregnation (114, 115). The first category of thalamic projection cells was represented by bushy "tufted" neurons, with ramified dendrites giving off a dense arborization around their cell bodies, and was considered characteristic of the primary sensory "specific" nuclei. The second type of relay cells was represented by neurons with radiating and rather regularly arranged primary dendrites, and was considered typical of the "nonspecific" thalamus. However, besides such initial dual distinction, the cytoarchitectonic arrangement of thalamic nuclei, including the "nonspe-

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Fig. 1. - *Schematic representation of the subdivision of the cat thalamus into "specific" and "nonspecific" nuclei based on Jasper's electrophysiological study (42).*

Reproduced with permission from ref. 61. Abbreviations: AM, anteromedial nucleus; AV, anteroventral nucleus; CeM, central medial nucleus; CM, centre median nucleus; GLd, dorsal lateral geniculate nucleus; GLV, ventral lateral geniculate nucleus; IAM, interanteromedial nucleus; LD, laterodorsal nucleus; LP, lateroposterior nucleus; MD, mediodorsal nucleus; MGd, dorsal medial geniculate nucleus; MGmc, magnocellular medial geniculate nucleus; MGv, ventral medial geniculate nucleus; Pf, parafascicular nucleus; POi, intermediate component of the posterior complex; POl, lateral component of the posterior complex; POm, medial component of the posterior complex; PT, paratenial nucleus; Pulv, pulvinar; PV, paraventricular nucleus; R, reticular nucleus; Re, nucleus reuniens; Rh, rhomboid nucleus; RN, red nucleus; SN, substantia nigra; VB, ventrobasal complex; VM, ventral medial nucleus; VL, ventral lateral nucleus.

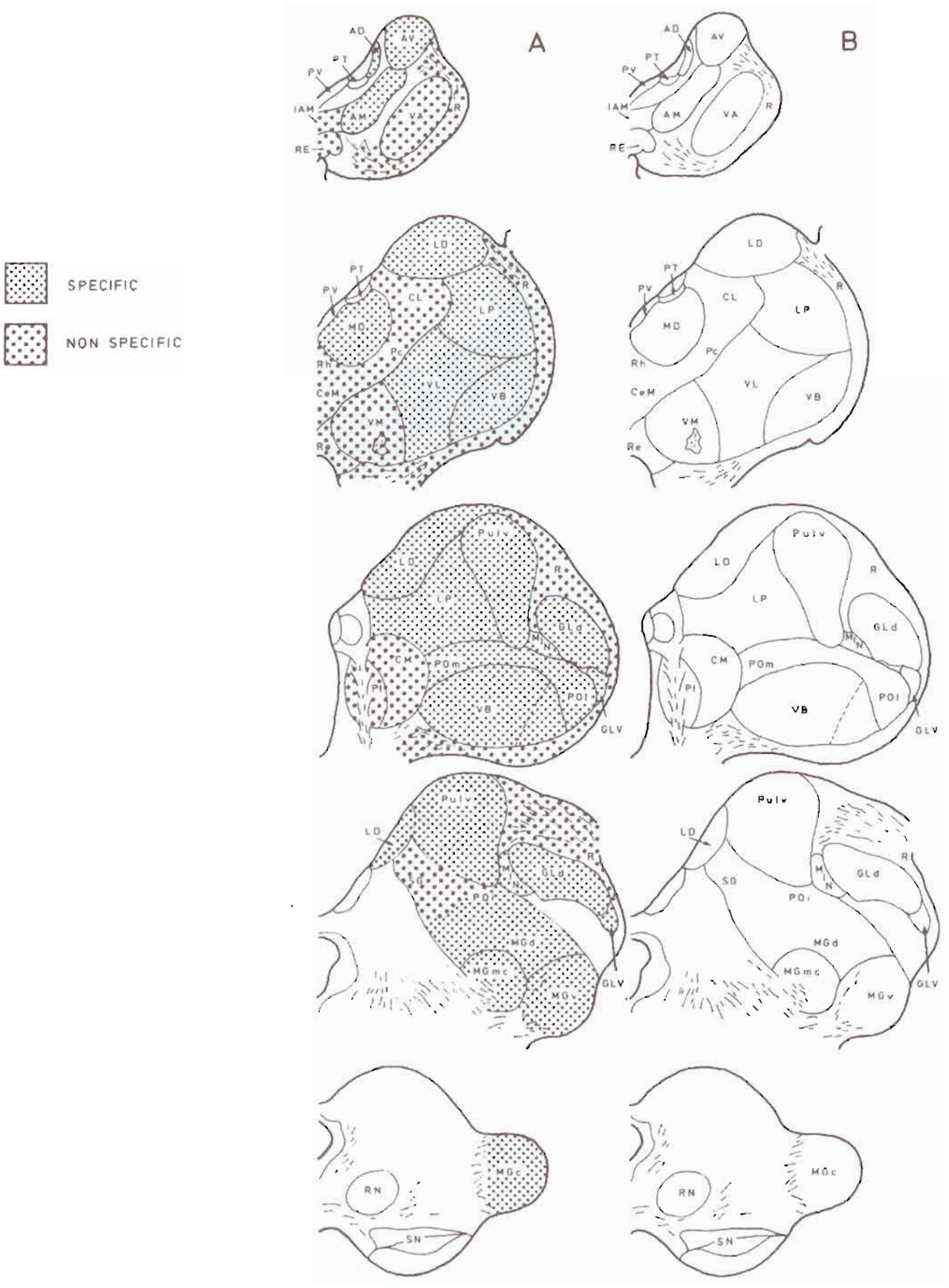
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Fig. 1.

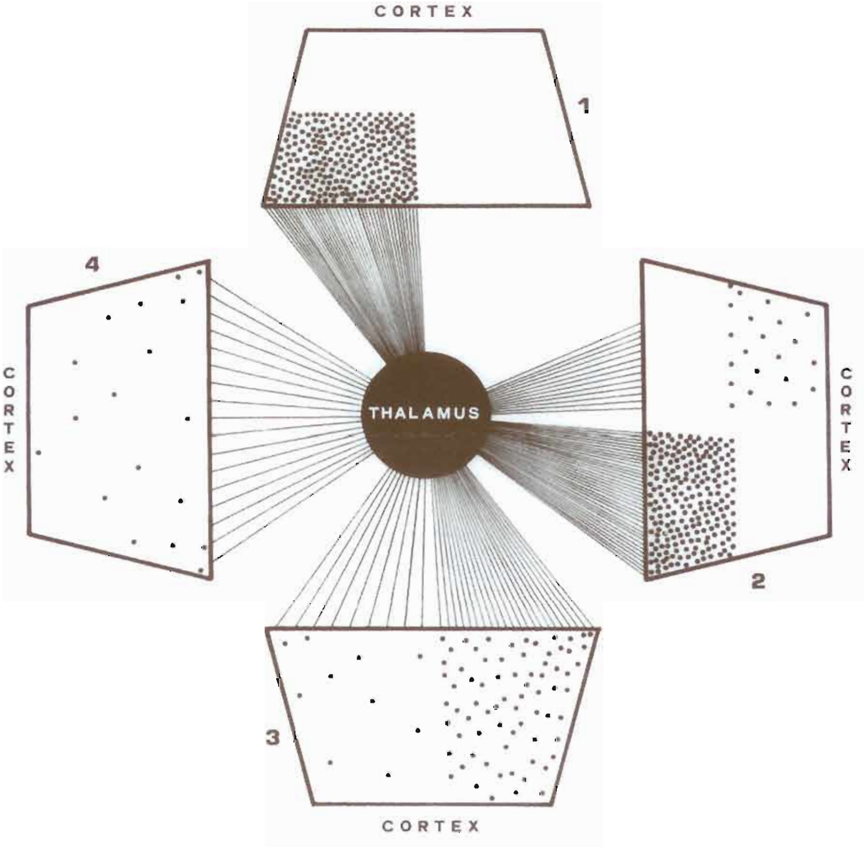

Fig. 2. - *Schematic representation of the gradients of density and distribution of thalamo-cortical projections in the cat, drawn adapting a scheme proposed by Divac (27a) for the subcortico-cortical projections in the rat.*

A first group is represented by thalamic nuclei projecting densely upon one cortical area; a second group by nuclei projecting densely upon one cortical area and less densely upon another cortical field; a third group by nuclei projecting preferentially upon more than one cortical area and sparsely upon wide cortical territories; finally, a fourth group is represented by nuclei projecting sparsely upon widespread cortical fields. Reproduced with permission from Ref. 61.

cific" ones, has been found in further studies to exhibit numerous diversities and species-related variations (reviewed in 12, 45, 47, 121). The different thalamic sectors which were originally included in the "nonspecific" system on the basis of their electrophysiological features should now be reconsidered in the light of modern studies pointing out such distinct features of organization.

The ventral anterior and ventral medial nuclei

The *ventral anterior nucleus* (VA), which is scarcely distinguishable in small mammals (45), is located at the rostral pole of the ventral group of thalamic nuclei and is part of the motor-related thalamus. VA is characterized in the cat by medium-sized cells, uniformly distributed throughout the nucleus and represented by two classes of projection neurons, i.e. cells with a relatively high number of radiating primary dendrites, and neurons with a tufted distribution of primary dendrites. An early tract tracing study showed that in the cat VA projects mostly to the prefrontal, frontal and parietal fields, and sparsely upon cingulate and temporal fields (15). Projections of the cat VA to several cortical areas have been confirmed in several studies (121). In addition, in the cat a subset of VA neurons projects to the caudate nucleus, and is therefore part of the thalamo-striatal system (68, 121).

The homologous structure exhibits a different cytoarchitectonic organization in primates, in which different portions, and in particular a magnocellular (VAmc) and a parvicellular (VApc) divisions, can be distinguished (12, 47, 71, 98). VAmc is characterized by darkly stained, irregularly distributed and predominantly large neurons, but includes cells of different sizes, with perikaryal areas ranging from 100 to 900 μm^2. On the other hand, VApc, which has also been simply defined as VA (71), is characterized by lightly stained medium-sized cells (56). The different sectors of VA in the primate are inserted in parallel channels of transfer of motor-related information: VAmc receives nigral afferents and projects upon area 8 and the supplementary motor cortex; VApc receives pallidal afferents and projects mainly to the supplementary motor area, and sends projections also to prefrontal and premotor areas, as well as sparse efferents terminating upon the cingulate and parietal cortices (56, 71).

Another component of the ventral group of thalamic nuclei, the *ventral medial nucleus* (VM) provides an additional example of the distinct organization of a structure originally included in the "nonspecific" thalamus (Fig. 1). In contrast with other thalamic structures, VM is best defined in nonprimates (45). From the morphological point of view VM is characterized by a fairly homogeneous population of medium-sized neurons in the cat and monkey (45). In the cat and the rat VM is recipient of nigral and cerebellar afferents (12, 121). The rat VM has been found to give origin to projections very widely distributed upon the cortex, and these fibers reach layer I (38). In the cat the VM projections are also widely distributed, but less so than in the rat, and exhibit gradients of density, being preferentially distributed upon the prefrontal, premotor, and insular areas, and sparsely upon temporal, cingulate and sylvian fields (77). VM efferents reach layer I also in the cat cortex (33). As mentioned above, in primates the VM nucleus is less developed than in rodents and carnivores; in the monkey the principal part of VM (VMp) projects mainly to premotor and prefrontal areas (71).

The intralaminar nuclei

The thalamic nuclei closely associated with the internal medullary lamina are the components of the intralaminar system. The *anterior or rostral intralaminar nuclei* include the central lateral (CL) and paracentral nuclei, and the central medial nucleus which is located at the midline. Neurons of various shapes (triangular, fusiform, polygonal) and sizes are observed in the cat in the anterior intralaminar structures, and in particular in CL. In the cat CL, the projection neurons are mainly represented by relatively large densely packed cells, showing a radiating pattern of rather long primary dendrites with a fairly limited number of second and third order dendritic branches (123). The *posterior or caudal intralaminar nuclei* include two subdivisions in the cat and monkey, the centre median (CM) and the parafascicular (Pf) nuclei, whereas only Pf can be recognized in the posterior intralaminar thalamus of the rat (45, 46, 47). The CM nucleus, which is very large in primates, contains small and medium-sized neurons giving off dendrites arborizing in different directions. The Pf nucleus, which surrounds the fasciculus retroflexus or habenulo-interpeduncular tract, is formed by slightly larger and densely packed neurons. Typical bushy projection neurons have not been observed in the intralaminar nuclei with Golgi impregnation (95, 123), although a few relay cells resembling those of the "specific" nuclei have been described in the cat CM (125).

In early studies of the "nonspecific" system based on the Golgi staining (113), it was proposed that the intralaminar nuclei were lacking Golgi type II cells (i.e. local circuit neurons). Contrary to these data, it has now been established that intrinsic neurons, represented by immunocytochemically identified GABAergic cells, are distributed throughout the intralaminar structures in the cat and monkey (16, 41, 123), similarly to the findings detected in these species in the other nuclei of the dorsal thalamus (3, 121). However, the organization of the intrinsic inhibitory circuits exhibits marked species-related variations, and most of the dorsal thalamic nuclei, including the "nonspecific" ones, lack local circuit neurons in the rat thalamus (3, 16).

The intralaminar nuclei have been traditionally considered the main components of the "nonspecific" thalamo-cortical system and, as mentioned above, they were supposed to transfer to telencephalic targets the activating inputs deriving from the medial reticular core of the brain stem (73, 107). More recent data have highlighted the importance of the cholinergic and glutamatergic innervation of the intralaminar nuclei in their modulatory role of cortical activity (see 121 for review). The cholinergic fibers derive from cell bodies of the mesopontine tegmentum (17, 43, 105, 121).

The inputs deriving from the brain stem were considered to represent a distinctive "nonspecific" feature of the intralaminar nuclei, but further studies have shown that these structures receive multiple inputs and display a rather selective input-output organization. Thus, the anterior intralaminar nuclei have been found to be composed by a mosaic of relatively segregated relay entities (62), which are innervated not only by the brain stem reticular core, but also by cerebellar, spinal, pretectal and tectal fibers and convey this information to several cortical areas and to the basal ganglia (14). Anterograde-retrograde experiments based on the use of tracers have shown a certain degree of topographical arrangement in this input-output arrangement in the cat (Fig. 3): cerebellar and spinal afferents display in the anterior intralaminar nuclei a patchy distribution without intermingling; the subsets of neurons projecting to the motor cortex are recipient of cerebellar and spinal inputs, whereas the cell population projecting to the anterior parietal association cortex is segregated from the target innervated by spinal fibers and is recipient of

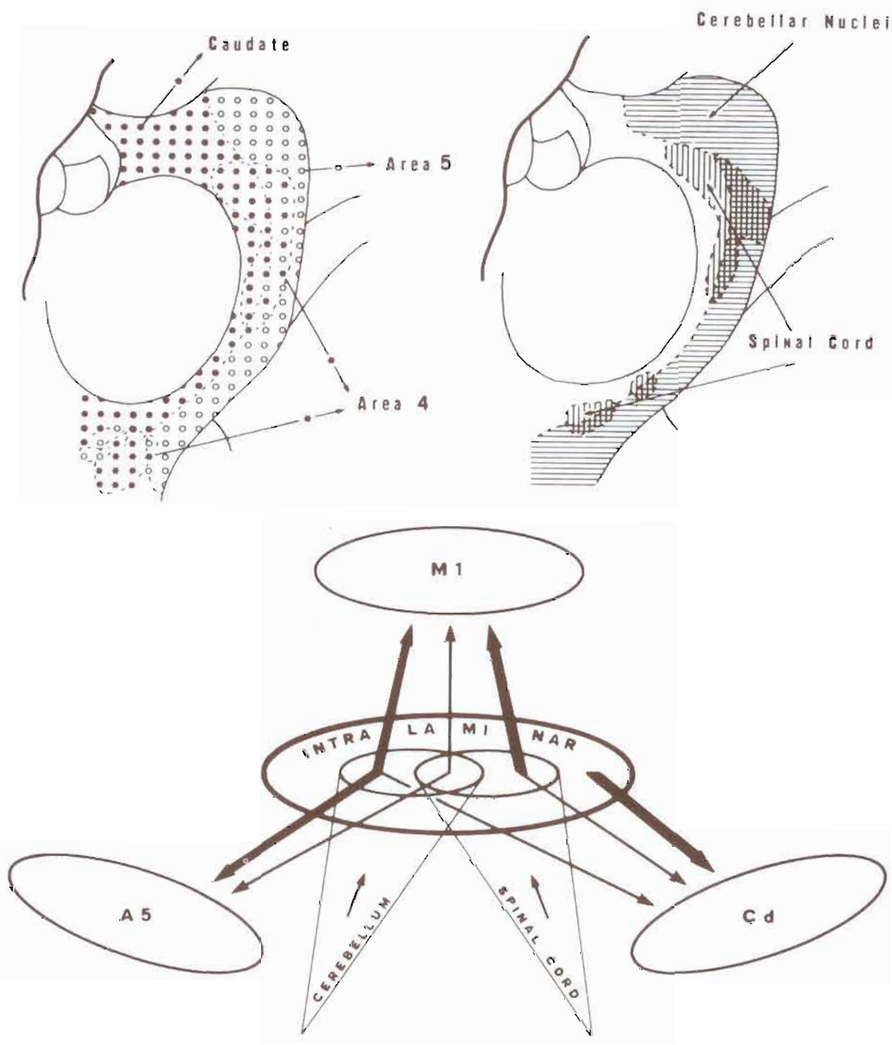

Fig. 3. - *Summary diagram of the organization of efferents (upper left) and afferents (upper right) of the anterior intralaminar nuclei, which is also schematically outlined in the lower part of the diagram.*

Thick arrows indicate quantitatively dense sets of efferents. Abbreviations: A5, cortical area 5 (anterior parietal cortex); Cd, caudate nucleus; M1, primary motor cortex. Reproduced with permission from Ref. 14.

cerebellar afferents (14). The cell population of the anterior intralaminar nuclei projecting to the caudate nucleus, and in particular the thalamo-striatal sector located in the dorsal portion of CL, is reached by spinal and cerebellar afferents (14).

The anatomical and functional "specificity" of the connections of the anterior intralaminar nuclei is also supported by the somatotopic and retinotopic arrangement of the intralaminar sectors projecting to visual and somatosensory cortical areas, respectively, in the cat (79). A discrete termination of the intralaminar-cortical projections has been detected in the rat (19).

The components of the posterior intralaminar group, i.e. the CM and Pf nuclei, are recipient of afferents from the medial portion of the globus pallidus in the monkey (and of the homologous structures, the entopeduncular nucleus, in the cat) and project densely upon the striatum and sparsely upon the somatosensory, motor and premotor areas of the neocortex in the cat and monkey (see 67 and 121 for review).

Thus, the anterior intralaminar nuclei seem to be principally involved in mechanisms of sensory-motor integration, linking multiple and heterogeneous sets of information (deriving from the deep cerebellar nuclei, spino-thalamic tract, tectal and pretectal structures, basal ganglia) with discrete cortical areas and with the striatum. Through the pallidal input to the posterior intralaminar structures (see 91 and 98 for review), whose interruption may be responsible for abnormal (such as dystonic) movements (see 63 for review), the intralaminar system also establishes a subcortical loop with the extrapyramidal system.

Altogether these features of organization suggest that the intralaminar system includes a variety of relay entities (62), which convey "supplementary" channels of neural information, integrating the principal (i.e. "specific") thalamic output channels. In addition, the intralaminar system serves a more global role in the modulation of cortical activity. This is also demonstrated by the clinical features of thalamic lesions in humans. Cerebellar syndromes (32), impairment of vigilance and unilateral neglect have been observed after thalamic paramedian lesions involving the intralaminar nuclei (see 63 and 67 for reviews). Experimentally, disturbances of gaze orientation have been reported after stimulation or lesion of the intralaminar domain (57, 116). It has also been suggested that the intralaminar nuclei play a role in attention and stimulus selection (119), and a recent study based on positron emission tomographic imaging in humans has emphasized the role played by the upper midbrain reticular formation and anterior intralaminar nuclei in attentive processes (52).

The midline nuclei

In its original definition the "nonspecific" system also included components of the thalamic midline nuclei (Fig. 1). The main nuclear structures of this group are represented along the dorsoventral axis by the paratenial (Pt), thalamic paraventricular (PVT), rhomboid (Rh) and reuniens (Re) nuclei. PVT and Rh contain small and densely packed neurons, whereas Pt exhibits cytoarchitectonic similarities with the medial portion of the mediodorsal nucleus and in Re medium-sized and small cells are loosely arranged (12). The PVT nucleus has also been considered part of the epithalamus on the basis of its embryological origin (45).

Afferents from hypothalamic structures and brain stem, as well as fibers belonging to the spino-thalamic tract, reach the midline group of thalamic nuclei (10, 12). These nuclei are in turn composed by a mosaic of projection cell populations: thalamic midline cell groups projects to limbic and limbic-related areas of the cerebral cortex, the amygdaloid complex and the nucleus accumbens in the rat, cat and monkey (see 10 and 12 for reviews; see also 18 and 19). In particular, the Re nucleus is a thalamo-hippocampal relay (37) and modulates the activity of neurons in the CA1 field of the hippocampus (28). On the other hand, some neurons of the thalamic midline nuclei send collaterals to subcortical forebrain targets and to the viscero-sensory division of the nucleus of the solitary tract (89). In addition, PVT is connected with relays of the circadian timing system, and in particular with the suprachiasmatic nucleus (81, 129), which plays a role of circadian pacemaker in the mammalian brain.

The limbic circuits in which the thalamic midline nuclei are inserted make these structures a functionally distinct sector of the "nonspecific" thalamus, which may be involved in the regulation of emotions and may take part in some aspects of memory formation (9). In addition, through their connections with hypothalamic and brain stem structures, the midline nuclei may be involved in visceral regulation and/or in visceral responses to emotional stimuli, as well as in the transfer of circadian information to the limbic system. Such putative functional roles delineate a sharp distinction with the intralaminar system, which, as mentioned above, can instead serve a dual function, being part of sensorimotor integration mechanisms and of a system regulating the synchronization and desynchronization of cortical activity.

Immediate early gene expression in the midline and intralaminar nuclei in basal conditions

The data reviewed above point out a selectivity in the organization of "nonspecific" thalamic nuclei, and in particular a differential organization of the midline and intralaminar nuclei. However, it is of interest that data in support of distinctive features of these latter groups of nuclei in respect to the principal thalamic relay nuclei have derived in the last years from the study of gene expression in the diencephalon during sleep and wake.

The cellular immediate early genes (IEGs), also defined as early response genes, are proto-oncogenes which play a major role in the transduction of extracellular signals into short- term and long-term changes in neurons (85). Thus, the IEGs are characterized by their rapid and transient inducibility in response to different stimuli, and encode for proteins whose combinatorial interactions constitute transcription factors. Besides the induction by external stimuli, the expression of IEGs, such as *fos*, *jun* and *krox* and their protein products, has been reported to undergo an oscillation during spontaneous wakefulness and sleep in neuronal populations of the rat brain (see 11 for review). In this respect, it is interesting to note that during spontaneous wakefulness Fos (the protein encoded by the c-*fos*, the IEG prototype in the nervous system) immunoreactivity was found in the thalamus to represent a selective feature of neurons of the midline nuclei, and in particular of PVT, as well as of the intralaminar nuclei (23, 99). As in other brain structures, the number of Fos-mmunostained cells after a period of sleep was found to be remarkably lower than during wake, thus indicating an oscillation of genomic expression in these neurons in relation to the animal's physiological state. Although the factors which underlie IEG induction in basal conditions have not been hitherto clarified, it is remarkable that such induction occurred in the structures which historically have been considered crucial in wakefulness and arousal as targets of the ascending activating reticular system.

The targets of the neurons of the thalamic midline in which Fos is induced during spontaneous wakefulness have been investigated by means of retrograde tracing combined with Fos immunohistochemistry (96). These data showed that such neurons include cells projecting to the amygdala as well as cells projecting to the nucleus accumbens, thus indicating that information on genomic changes occurring in the alternation between sleep and wake could be transferred to limbic and limbic-related targets through the thalamic midline.

The discrete organization of thalamo-striatal fibers

The bulk of efferents to the caudate and putamen derives from the intralaminar system (45, 46), but thalamo-striatal neurons are also located in "nonspecific" territories outside the boundaries of the intralaminar nuclei, and in particular in cell populations of the midline, VA and VM nuclei (121). An overview of the thalamo-striatal system goes beyond the scope of the present article, but we wish to point out that the different sets of thalamic efferents destined to the striatum exhibit a rather selective organization. The projections of the intralaminar and midline nuclei to the striatal complex are topographically arranged in mammals, including primates, and the main target of midline fibers is the nucleus accumbens (18, 30, 91, 111, 113). The efferents arising from PVT and Re are part of a medial thalamo-striatal system and are concentrated within the striosomes of the ventral striatum (Fig. 4). On the other hand, projections arising from the anterior intralaminar, VA and VM nuclei are part of a lateral thalamo-striatal system, which mainly terminates in the striatal matrix in the cat and monkey (Fig. 4) (100, 101).

The phylogenetic development of the posterior intralaminar CM-Pf complex parallels that of the caudate-putamen; the posterior intralaminar nuclei are recipient of collateral projections of the pallido-thalamic fibers arising from the entopeduncular nucleus in the cat and from the medial pallidum in the monkey, thus representing a relay of the pallido-thalamo-striatal system (91, 92, 93). CM efferents arborize within the striatal matrix (30, 113). The topographic organization of the thalamo-striatal projections arising from the posterior intralaminar complex in primates defines different cortico-striatal and thalamo-striatal circuits: CM efferents are concentrated in a sector of the putamen recipient mainly of cortical input arising from the sensorimotor cortex, whereas Pf projections are concentrated in a region of the caudate nucleus which receives inputs mainly from the prefrontal cortex (93).

The cortical control

As a general rule the cortico-thalamic fibers are much more abundant than the thalamo-cortical ones, and this quantitative discrepancy guarantees a highly discriminative control of thalamic information processing and transfer (45, 53, 121).

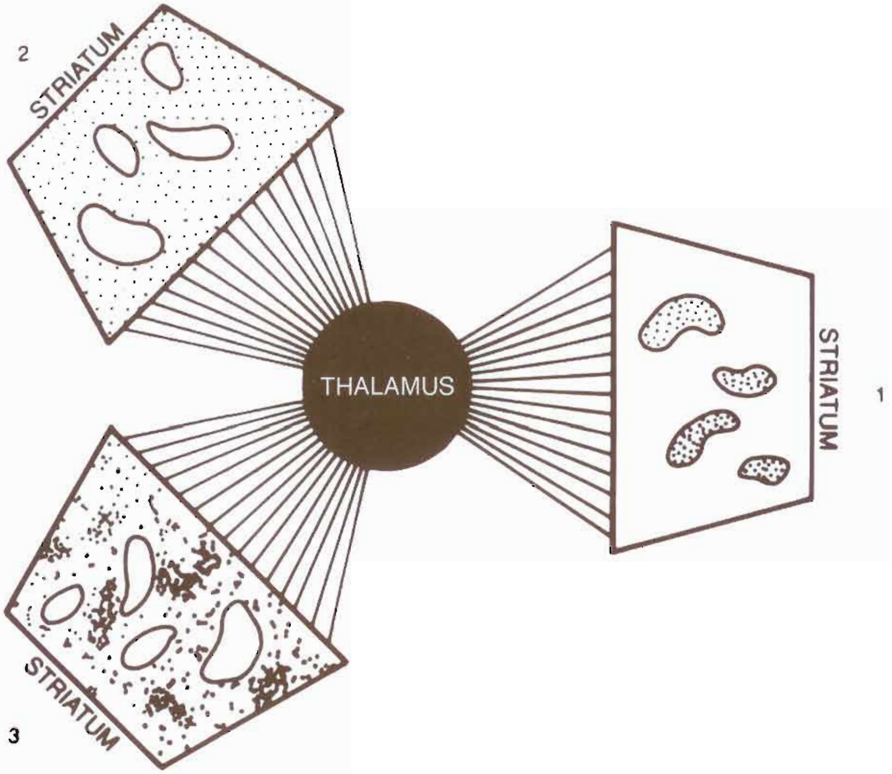

Fig. 4. - *Schematic representation of the compartmental organization of thalamo-striatal projections in the cat.*

The medial thalamo-striatal system (1), which originates from the midline thalamus, distributes terminals concentrated in the striosomes; 2 and 3 depict the pattern of two of the matrix-projecting lateral thalamostriatal system: the anterior intralaminar nuclei project diffusely to the matrix (2); the posterior intralaminar nuclei project mainly to the matrix in a more heterogeneous manner and with a patchy distribution (3). Reproduced with permission from Ref. 101.

Cortico-thalamic neurons are excitatory and utilize the amino acids glutamate or aspartate as neurotransmitters (see 112 for review). The cortical fibers excite directly the thalamic relay cells, and also dysinhibit them reducing the strength of thalamic intrinsic inhibition (102).

Cortico-thalamic fibers originate from the deep cortical layers, and mainly from layer VI. However, layer V pyramidal neurons also contribute to the cortico-thalamic system, as it was described in the motor thalamus of primates: the cortical afferents to CMoriginate in primates primarily from layer V of area 4, and the cortical input to Pf from layer V of area 6 (21). A wider areal distribution of cortical cells projecting to the CM-Pf complex was described in the cat (109).

Interest in the cortico-thalamic fibers originating from layer V has been raised by findings pointing out that cortico-thalamic terminals, represented by a vast majority of small boutons, also include a minor proportion of very large cortical endings in various species, including primates (see for example 40, 117). Such giant endings of cortical fibers, which were also found in the intralaminar nuclei (108), derive from layer V cortico-thalamic neurons and may subserve a distinct modulation of thalamic structures (see 118 for review).

The anterior intralaminar and midline nuclei, as well as VA and VM, receive cortical inputs deriving from the deep layers (layers V and VI), which in general reciprocate the thalamo-cortical connections in mammals (69, 121, 126). However, some discrepancies in this scheme of organization have been reported. For example, in the cat the primary somatosensory cortex (SI) and the primary visual cortex (VI) project weakly upon the intralaminar nuclei (48, 51), whereas the intralaminar projections to these areas are relatively conspicuous (25, 78, 79). Several other examples could be quoted, and a mismatch was also recently found in the thalamo-cortical and cortico-thalamic projections of the motor areas in the monkey (108); such discrepancy also involved the intralaminar nuclei (108). It is also worth mentioning that contralateral cortical projections to the intralaminar and VM nuclei have been reported in the rat and the cat (84, 127), whereas these thalamo-cortical efferents are unilateral in adulthood.

CELL POPULATIONS OF THE "NONSPECIFIC" THALAMUS BRANCHING UPON CORTICAL AND SUBCORTICAL STRUCTURES

A widely divergent axonal collateralization of the efferents arising from the "nonspecific" thalamic nuclei has been historically considered a prominent structural substrate of the "diffuse" thalamo-cortical projection system and of the recruiting cortical potentials. However, studies based on methods exploiting the simultaneous use of multiple retrograde tracers have contradicted the view of a widely divergent collateralization of thalamic cells upon their targets. For instance, experimental data in the cat have shown that the projections of the different components of the intralaminar system to the cortex arise from distinct cell populations, with a low proportion of neurons (ranging from 5% to 10% according to the considered areas) branching upon distant cortical areas (13). The studies performed on VM efferents in the cat support a selectivity in the distribution of this set of thalamo-cortical axonal branches, since VM-cortical branched connections were found to link only the insular and fronto-prefrontal cortices (77).

Functional correlates of branched thalamo-cortical neurons originating from the anterior intralaminar nuclei have been investigated in the cat by means of fluorescent tracers injected in the somatosensory and visual cortical areas (78, 79). In these experiments, a considerable degree of axonal collateralization was found in the intralaminar projections distributed within different sectors of representation of the peripheral maps in SI and VI, but a very low degree of branching of the intralaminar neurons was found to link SI and VI (78, 79).

In the investigation of neurons branching upon the cerebral cortex and striatum in the cat (68), based on retrograde double labeling, the highest proportion of branched cells was found to reach both the caudate nucleus and the motor cortex, in contrast with a very limited collateralization of thalamo-caudate cells upon the posterior parietal cortex. Even the intralaminar and VA cells branching upon the motor cortex and the caudate nucleus were found to represent a minority of these projection neurons: for example, 10-20% of CL neurons labeled from the motor cortex and 3-10% of those labeled from the caudate nucleus were found to be double labeled from both targets, and only a few posterior intralaminar neurons were double labeled in the same experiments (68).

A complete review of the branched circuits involving the thalamo-striatal neurons cannot be presented here. However, it is worth mentioning that in the monkey the projections of the anterior intralaminar nuclei and of the CM and Pf nuclei to the caudate nucleus and to the putamen were found to derive mainly from separate cell populations (94). A discrete organization of thalamo-striatal neurons was also reported in the Pf projections to the subthalamic nucleus and to the striatum, which were found to originate from separate neurons in the rat (29).

In the rat, the projections of the thalamic midline nuclei upon the amygdaloid complex, the hippocampal formation and the nucleus accumbens were found to display a low degree of axonal collateralization upon these targets (122).

Altogether these data point out that axon collaterals arising from branched thalamic "nonspecific" neurons are selectively distributed on the basis of functional needs. In addition, the findings based on multiple retrograde tract tracing indicate that subsets of thalamic projections upon the cortex, as well as subsets of thalamic efferents reaching subcortical structures, derive from diverse cell groups and are therefore organized in parallel channels.

IS THERE A NEUROCHEMICAL FINGERPRINT OF THE "NONSPECIFIC" THALAMUS?

Given the heterogeneity of the domains that had originally been included in the "nonspecific" thalamus, there is no univocal answer to the above question. However, in the growing body of information available on the neurochemical organization of the thalamus, some distinct chemical features have been pointed out in the intralaminar and midline nuclei.

The cholinergic fibers, which are distributed throughout the thalamus, are especially dense in the intralaminar nuclei, and acetylcholinesterase staining outlines distinct compartments in the intralaminar nuclei (see 121 for review). Peptidergic afferents, which derive from the brain stem and the hypothalamus, are also very dense in the midline and intralaminar domains, both in rodents and in primates (see, for example, 9 and 82). Nitric oxide synthase (NOS), the enzyme of synthesis of the free radical nitric oxide, is co-localized with acetylcholine in neurons of the mesopontine tegmentum (128), and is expressed by cholinergic fibers innervating the thalamus. Thus, NOS-containing fibers have been found to terminate densely in intralaminar and midline domains of the rat and cat thalamus (20, 76). Cell bodies expressing NOS have also been described to exhibit a selective distribution in some of the thalamic midline nuclei in the rat (20).

Thalamo-cortical neurons utilize an excitatory amino acid (glutamate or aspartate) as neurotransmitter (see 130 for review), and glutamate-immunoreactive neurons have been detected throughout the thalamus since the initial studies performed using anti-glutamate antibodies (90). In addition, aspartate-immunoreactive neurons have been found to be numerous in the rat thalamic midline, and especially in PVT, in which glutamate and aspartate did not display a co-localization, and aspartate-positive cells were found to prevail over the glutamate-positive ones (31).

It should also be noted that cholinergic neurons have been recently detected in the dorsal region of the anterior intralaminar paracentral nucleus of the monkey by means of a sensitive marker of cholinergic elements (106). These cells exhibited the features of projections neurons. The portion of the anterior intralaminar structures in which these cells are located projects to the dorsal striatum and visual association cortical areas, thus suggesting that intralaminar neurons can represent an extrinsic source of cholinergic innervation of these targets (106).

The calcium binding proteins of the EF-hand family calbindin-D28k, parvalbumin and calretinin are expressed by cell populations of the thalamus, and provide sensitive markers of these neuronal subsets (2, 22). Parvalbumin coexists with GABA in the cells of the thalamic reticular nucleus (Rt) in the rat as well as in other species, but the expression of both calbindin and parvalbumin displays marked species-related variations in neurons of the dorsal thalamic nuclei. In the rat, calbindin is a marker of subsets of medial thalamic cell populations, including intralaminar, midline and VM neurons (2, 22). In neurons of the rat thalamic midline, calbindin frequently coexists with aspartate (31). Parvalbumin and calbindin are expressed in the monkey intralaminar system, where either protein provides a marker of different districts: calbindin-immunoreactive cells predominate in the anterior intralaminar nuclei, whereas only parvalbumin immunostaining can be detected in the posterior intralaminar CM-Pf complex, which does not contain calbindin (49). In the cat and the monkey, these two calcium binding proteins have been found to define not only different compartments, but also thalamic neurons projecting to different cortical layers (83, 104): the anterior intralaminar neurons projecting to the superficial cortical layers express calbindin, and those projecting to the deep layers express parvalbumin (83).

The expression of glutamate, GABA and amine receptors in the thalamus has been investigated in last years in many laboratories. A summary of these findings goes beyond the scope of the present overview, and the reader is referred to the handbook of Steriade et al (121) for the state of the art on this subject. It is however worth mentioning that such data are opening new avenues in the chemical and functional anatomy of the thalamus.

FEATURES OF SYNAPTIC ORGANIZATION

The synaptic organization of the "nonspecific" thalamic nuclei has been subjected to less investigation than that of the primary sensory relay nuclei, in which different types of complex synaptic arrangements, and in particular the so-called thalamic glomeruli, are known to represent a basic feature of organization (45, 118, 121). The data hitherto collected pointed out diversities in the synaptic organization of the "nonspecific" nuclei, not only in respect to the primary sensory relay nuclei, but also among the "nonspecific" nuclei themselves.

The synaptic organization of VAmc has been investigated in detail in the monkey (56), where the ratio of afferent terminals on projection neurons versus interneurons was found to be 10:1. Nigro-thalamic afferents provide an extrinsic GABAergic input (see also 98), and these boutons were found to establish symmetric contacts on the somata and primary dendrites of projection neurons (56). Asymmetric contacts (small and medium-sized cortico-thalamic terminals) were detected on the distal dendrites of VAmc projection neurons, whereas medium and large-sized boutons with round vesicles and establishing asymmetric contacts (probably deriving from superior colliculus afferents) were seen on secondary and tertiary dendrites. In addition, no glomerular arrangement was found in the monkey VAmc (56).

The ultrastructural organization of the CM nucleus was also investigated in the monkey (7). The distribution of different types of synapses were found to be considerably different in CM from those of VAmc, since in CM a uniform synaptic coverage of projection neurons at different levels of dendritic arborizations was detected, indicating a very limited segregation of afferent domains of different origins (7).

In the VA and VM nuclei of the cat, GABAergic afferents deriving from the globus pallidus and substantia nigra, as well as from interneurons, were found to establish symmetric synaptic contacts mainly on the somata and primary dendrites of projection neurons (55).

Complex synaptic arrangements resembling those detected in the somatosensory primary relay nuclei have been detected in the rat CL, in which they involved spino-thalamic terminals (60), but these synaptic features were not detected in the rat midline nuclei (10). It is also worth mentioning in this respect that the ultrastructural investigation of the PVT nucleus of the rat thalamic midline (6) has revealed that the distal dendrites of relay neurons projecting to the amygdala reach the basal portion of the ependymal cells lining the third ventricle, thus suggesting that these thalamo-limbic relay neurons could be influenced by molecules circulating in the cerebrospinal fluid.

As mentioned above, a dual morphology of cortico-thalamic endings, represented by small endings and a minority of giant terminals, has been detected across modalities (i.e. deriving from various sensory and motor cortical areas), across species (rodents, cat, monkey), and they occur not only in the principal thalamic nuclei, but also in the "nonspecific" ones, such as the intralaminar nuclei (108).

LAMINAR CORTICAL DISTRIBUTION OF "NONSPECIFIC" THALAMIC FIBERS

The old concept, based on the Lorente de Nó's (59) description of two different types of thalamo-cortical projections, i.e. "nonspecific", diffuse fibers reaching layer I and "specific", localized fibers terminating in layers III and IV, requires at present a substantial revision. From the electrophysiological point of view, the thalamic projections to layer I may account for the recruiting cortical responses (33) elicited after low frequency stimulation of the "nonspecific" thalamus (86).

Overall it can be stated that the existence of a thalamic diffuse projection to layer I is still debated and the available data on the laminar distribution of individual sets of thalamic fibers have pointed out diversities in the same species, as well as considerable species-related variations.

Thus, as mentioned above, in the rat the VM nucleus has been found to project to the most superficial layer of the cerebral cortex, whereas the intralaminar nuclei have been found instead to project scarcely upon layer I and more densely to the deep cortical layers (39). In the cat and monkey, no retrogradely labeled neurons were found in the intralaminar nuclei after superficial tracer deposition in the cortex (5, 103), whereas intralaminar efferents to layer I have been detected by means of anterograde tracing in studies based on autoradiography in the cat and monkey (25, 50, 110, 124).

By means of fluorescent tracers two populations of intralaminar-cortical relay neurons have been identified in the cat: small cells were found to project to the superficial layers and larger neurons to the deep layers of the parietal cortex (83).

The different sets of midline efferents seem to exhibit a distinct pattern of laminar distribution upon their cortical targets. For example, the projections of the Re nucleus reach the superficial and deep layers of the entorhinal cortex and layer 1 of the pre and parasubiculum (37, 39).

Last but not least, it should also be considered that the axonal transport methods have allowed to establish that also the "specific" nuclei (such as the primary sensory relay nuclei) project to different layers of the cerebral cortex, including layer I (see for example 27). In particular, the thalamic fibers projecting to layer I and to the middle layers originate from two distinct populations of thalamo-cortical neurons, characterized by different soma sizes and chemical features (80, 97, 103, 104). Thus, thalamic fibers terminating in layer I were seen to derive also from cell subsets of the "specific" thalamic nuclei and do not represent a unique feature of "nonspecific" thalamic fibers.

THE STRATEGIC POSITION OF THE THALAMIC RETICULAR NUCLEUS

Historically, Rt was long regarded as a component of the "nonspecific" diffuse projection system, in which this nucleus was believed to represent the last relay to the cerebral cortex. As it is well known, this concept has been since a long time rejected, first on the basis of retrograde degeneration findings (64, 70), and then on the basis of the unequivocal demonstration provided by the Scheibels (115) and Jones (44) that Rt does not project upon the cerebral cortex and is connected instead with the nuclei of the dorsal thalamus. Thus, it has now been firmly established (see 121 for a recent overview of Rt organization) that: *i*) the Rt nucleus is composed by GABAergic neurons; *ii*) the Rt axons terminate with flattened vesicles and symmetric synapses on thalamic projection neurons as well as on interneurons; *iii*) *in vitro* and *in vivo* intrinsic properties of thalamic cells firing rhythmically (58) can be modulated by the Rt inhibitory activity which shows a spontaneous oscillatory activity *in vivo* also after deafferentation from the dorsal thalamus (120); *iv*) fibers traverse Rt either way between thalamus and cortex, leaving within this nucleus collateral branches of thalamo-cortical axons (36) and cortico-thalamic fibers. On the basis of this latter feature, Rt is constantly informed about the crosstalk between thalamus and cortex.

The cortico-Rt-thalamic and thalamo-Rt-cortical circuits are topographically organized, so that each set of cortico-thalamic projections sends collateral branches to the Rt sectors that project to the same thalamic target, and vice versa in the reciprocal loop. The topographical arrangement of the cortical input to Rt and the Rt output to dorsal thalamic nuclei may provide an anatomical substrate to a role of "filter" of thalamic information played by the different sectors of Rt (34, 118, 121). In addition, disynaptic intrathalamic pathways through Rt provide the substrate for functional interactions between dorsal thalamic nuclei relaying the same sensory modality (26).

The spindling activity is regulated by Rt, which can be considered the pacemaker or servomechanism of thalamic synchronized firing (see 121 for review). Such activity increases after stimulation of Rt and is abolished when the Rt input is disconnected from the dorsal thalamus (75, 120).

The balance between cholinergic and glutamatergic inputs to Rt ensures the alternation of activating and deactivating functions of thalamic activity (Fig. 5). The cholinergic input inhibits the Rt inhibitory action on thalamo-cortical neurons, and thus decreases the spindling activity corresponding to sleep and increases the desynchronization of thalamo-cortical neurons corresponding to REM sleep and wakefulness. On the contrary, the glutamatergic cortical input excites the Rt inhibitory function and increases the spindling activity corresponding to slow wave sleep (120, 121). The connections of Rt with the central "nonspecific" core of the thalamus, which mostly derive from the Rt rostral pole (126), play a key role in the modulation of the activity of thalamo-cortical neurons in the normal brain (121), as well as in the pathological modulation of the parossistic activity during epilepsy (4, 74, 121).

CONCLUDING REMARKS

The so-called "nonspecific" thalamic system should be considered as a modulatory system exerting a dual function. First, these structures play a global modu-

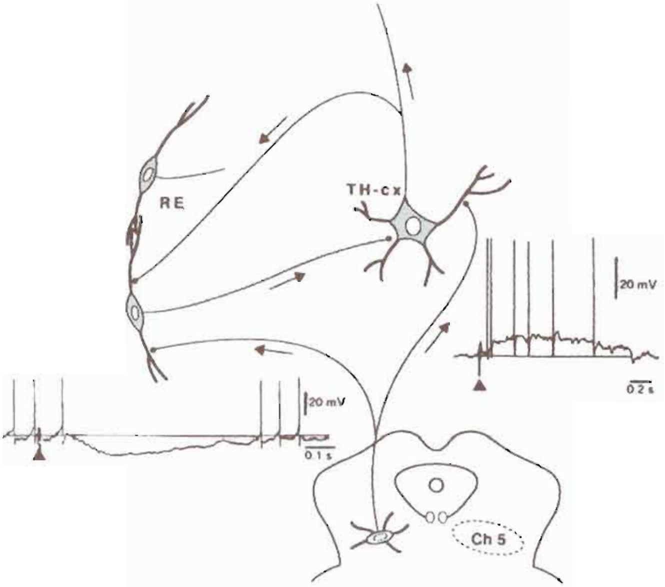

Fig. 5. - *Recurrent inhibitory loop of thalamo-cortical (TH-cx) and reticular thalamic neurons, and modulation of thalamo-cortical and reticular nucleus (RE) neurons by mesopontine cholinergic afferents (only the Ch5 group of peduncolopontine tegmental neurons is depicted).*

In insets, Ch5 stimulation (brief pulse train, arrowhead) induces a depolarization of thalamocortical neurons and a hyperpolarization of reticular nucleus neurons. The direct excitation of thalamocortical cells is accompanied by their dysinhibition through inhibition of reticular nucleus cells. These effects disrupt synchronized spindle oscillation in the thalamocortical system. Reproduced with permission from Ref. 120.

latory role, to which the Rt nucleus highly contributes, in the transfer to cortical and subcortical structures of activating and deactivating inputs deriving from the brain stem reticular formation, hypothalamus and basal forebrain. Such modulation may be involved in attention, consciousness, general alertness, sleep and wakefulness. In addition, the complex and heterogeneous structures composing the so-called "nonspecific" thalamic system are involved in the transfer of information to cortical and subcortical targets through channels parallel to the "primary" pathways. Thus, the "nonspecific" thalamic neurons also exert "specific" functions in the modulation and integration of sensorimotor activities and, through connections with the limbic system, may contribute to emotional behavior and memory formation.

SUMMARY

The classical concept of "nonspecific" thalamus, as distinguished from the principal thalamic nuclei (i.e. the primary sensory, motor and limbic relays) is here briefly revisited in the light of anatomical investigations performed in the last

decades, and primarily those based on tract tracing techniques. Altogether these data pointed out that the so-called "nonspecific" thalamus is composed by a heterogeneous collection of nuclear masses, which display not only species differences, but also marked internuclear variations in their cytological and neurochemical features, connections, areal and laminar distribution upon the cortex, and functional properties. Thus, the "nonspecific" thalamus exerts a modulatory role on cortical activity, chiefly regulated at the intrathalamic level by the interplay between the thalamic reticular nucleus and the interneurons and projection neurons of the dorsal thalamus. However, each of the components that have been traditionally considered as "nonspecific" also subserves selective roles in the transfer of different kinds of information from the thalamus to the cerebral cortex and basal ganglia.

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