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THE NEURONS OF HUMAN BED NUCLEUS OF THE STRIA TERMINALIS

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NEURONI BED NUCLEUS STRIAE TERMINALIS ČOVEKA

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ABSTRACT

The bed nucleus of the stria terminalis (BNST) is subcortical limbic nucleus which stretches among the fibers of the stria terminalis, from the amygdala to the septal region. This nucleus plays an important role in coordination of neuroendocrine, neurovegetative and somatomotor behavioral responses with obvious affective and emotional components. In spite of its significance, this nucleus wasn't completely investigated, even in animals. The study was performed on 10 adult human brains (20 hemispheres) of both genders. The Golgi impregnation, Nissl and Kluver-Barrera methods of staining, were used in a manner to describe cellular morphology of human bed nucleus of the stria terminalis. The neurons of human bed nucleus of the stria terminalis were classified into three types, based on its cellular morphology. Type I – bipolar neurons, with mainly fusiform bodies, present predominant type in human BNST, particularly in its dorsomedial part. Type II – pyramidal neurons, were numerous in central and lateral parts of dorsal BNST. Their cell bodies varied in shape (oval, triangular), had one dominant, thick, apical and two thinner dendrites. Type III – multipolar neuron, presents predominant type in ventral parts of BNST, with oval soma and dendrites radiated out in all directions. The dendritic spines of all types of neurons were higher in density as distance from cell bodies increased. These results reveal that human bed nucleus of the stria terminalis presents cytomorphologically complex limbic structure, and its complexity is consistent with its very important role in behavioural responses to stress and anxiety states.

Key words: bed nucleus of the stria terminalis, amygdala, neurons, morphology, human brain, Golgi

SAŽETAK

Bed nucleus striae terminalis (BNST) predstavlja subkortikalno limbičko jedro, koje se proteže duž vlakana striae terminalis. Stria terminalis izlazi iz amigdala, pruža se prema kaudalno i dorzalno, zatim pravi luk prema rostralno, ulazi u septalni region, tako da se granica BNST u rostrokaudalnom pravcu pruža od septuma do amigdala. Ovo jedro ima važnu ulogu u koordinaciji autonomnih, neuroendokrinih i somatomotornih bihejvioralnih odgovora koji sadrže emocionalne komponente. Ova kompleksna jedarna struktura je nedovoljno proučena čak i kod eksperimentalnih životinja. Istraživanje je izvršeno na 10 ljudskih mozgova odraslih osoba (20 hemisfera), oba pola. Golgi impregnacija je korišćena u cilju utvrđivanja morfoloških karakteristika neurona BNST čoveka. Na osnovu morfologije neurona, definisali smo tri tipa neurona humanog BNST: tip I – bipolarni neuron, tip II – piramidalni neuron, tip III – multipolarni neuron. Tip I - bipolarni tip neurona, sa somom najčešće vretenastog oblika, predstavlja najzastupljeniji tip u dorzomedijalnom delu BNST. Tip II – piramidalni neuron se u najvećem procentu nalazi u centralnom i lateralnom delu dorzalnog BNST i ima somu različitog oblika (ovalna, trouglasta). Od some neurona polaze jedan, kraći i deblji apikalni i dva, tanja i duža bazalna primarna dendrita. Tip III – multipolarni neuron dominira u ventralnom delu ovog jedra, ima najčešće ovalnu somu od koje radijalno polaze četiri do pet primarnih dendrita. Gustina dendritskih spina kod sva tri tipa neurona, povećava se udaljavanjem od some neurona. Naše istraživanje pokazuje da BNST čoveka predstavlja citomorfološki, kompleksnu limbičku strukturu, što je u skladu sa njegovom značajnom ulogom u nastanku buhejvioralnih odgovora u stanjima straha i anksioznosti.

Ključne reči: bed nucleus striae terminalis, amigdala, stria terminalis, neuroni, morfologija, mozak čoveka, Golgi

INTRODUCTION

The bed nucleus of the stria terminalis (BNST) is subcortical forebrain nuclear structure. This lengthy brain structure has its caudal border in the region of amygdala and stretches to the septal region, rostrally, alongside the course of the stria terminalis. The primary topographfy of BNST included intraamygdaloid, supracapsular and paraseptal sectors(1). The most significant and the largest part of BNST is its paraseptal sector, which surrounds commissura anterior. Its medial border is lateral septal area and the anterior column of fornix. The paraseptal sector of BNST flanked by septum dorsomedially, dorsaly lateral ventriculus, dosolaterally nc.caudatus and laterally capsula interna and caudoputamen. The brain structures which present its ventral border are as follows: globus pallidus (ventrolaterally), ventral pallidum and substantia innominata (ventrally) and medial preoptic and anterior hypothalamic area (ventromedially). Paraseptal sector of BNST lies caudal to nucleus accumbens and brain areas such as fornix and stria medullaris thalami while thalamus flanks it caudally.

The bed nucleus of the stria terminalis lies at the junction of different telencephalic and diencephalic systems, and its topography was the subject of numerous scientific debates. It has been considered as part of the amygdala (1-3), the septum, the hypothalamus or even the ventral striatum (4, 5), according to whether the emphasis was put upon its topography, connections, cytoarchitecture or chemoarchitecture. There have been numerous attempts to divide and subdivide the BNST, but the parcellation of BNST is still not resolved. The BNST has been divided on the basis of its cytoarchitectonic and histochemical features into medial and lateral divisions (1, 4), but also has been proposed the primary parcellation into anterior and posterior divisions on the basis of its embryological development and in the respect of the course of the stria terminalis (6-13).

Probably, the most prominent characteristic of BNST is its sexual dimorphism. This nucleus shows sexual dimorphism in the respect of its volume (14-16), number of neurons and the content of neurotransmitters (17-19). The volumes of central and posteromedial subdivisions of BNST, the brain areas that are essential in sexual behavior, are larger and these subdivisions contain more neurons

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in man than in woman (16, 20). The bed nucleus of the stria terminalis also contains many sex differences in cell density, synapse distribution and neurotransmitter receptor distribution (21). In this regard, these differences may be involved in sexually dimorphic control of reproductive function.

During the last decade, the bed nucleus of the stria terminalis has received considerable attention, because of its very important role. Due to its position, at the junction of amygdala, septal area and hypothalamus, its connections and its content of neurotransmitters, BNST is included in the numerous brain functions. The medial division of BNST is strongly connected with several brain areas that are the part of neuroendocrine control system and control system of reproductive behavior (medial nucleus of amygdala, medial preoptic area and ventromedial hypothalamus). The lateral subdivision of anterior BNST is connected with the brain areas that coordinate autonomic, neuroendocrine and ingestive behavioral responses to stress and noxious stimuli (central nucleus of amygdala, parabrachial nucleus, nucleus of the solitary tract, ventral tegmental area and the periventricular, paraventricular, dosolateral and dorsomedial nuclei of the hypothalamus) (1, 8-11, 22-25).

The bed nucleus of the stria terminalis is considered to be a part of emotional and cognitive systems and plays the key role in the integration of cognitive and neurovegetative functions. This nucleus plays an important role in coordination of neuroendocrine, neurovegetative and somatomotor behavioral responses with obvious affective and emotional component. It presents the major extrahypothalamic relay for the information from the amygdala and hippocampus to the paraventricular nucleus of hypothalamus, integrates limbic and autonomic information related to stress and in this regard it plays a very important role in the regulation of hypothalamic-pituitary-adrenal axis during stress (25, 26). Dysfunction of the BNST may cause stress-related psychiatric disorders and this subcortical limbic nucleus is considered to be a neural substrate related to anxiety states and it responds to signal more akin to anxiety than those akin to fear, whereas the central nucleus of the amygdala is involved in state of fear (27-30).

As the brain structure that integrates motivational and visceral functions, due to its inputs from the limbic areas, including amygdala, and projections to the areas that are related to reward processing such as ventral tegmental area and nc. accumbens, the BNST plays an important role in the behavioral responses related to drug and alcohol addiction (31-33). The changes in noradrenergic and dopaminergic systems in BNST, are important components in the mechanism of neuro-adaptation that is seen during the chronic exposure to cocaine (34).

The bed nucleus of the stria terminalis is also the very important brain area for the central neural regulation of cardiovascular functions, especially during the state of stress (35-37). This nucleus plays important role in reproductive physiology and express the high level of receptors for steroid hormones (38).

The aim of our research was defined in manner to describe cellular morphology of human BNST using the Golgi impregnation, and to define types of neurons of BNST, disregarding its parcellation, since the complex parcellation of this nucleus is still not clear and resolved. Nissl and Kluver-Barrera stained sections of human BNST were also used in our study, for the precise orientation and visualisation of fibers of the stria terminalis.

MATERIAL AND METHODS

The present study included 10 postmortem human brains (20 hemispheres), taken of patients of both genders, 25 to 75 years old. The brains were with no visible pathological changes and without neuropsychiatric history. The brains were fixed in phosphate buffered solution of 10% formalin (3,7% formaldehyde) over a period of at least three months. After fixation, the slices of brain tissue were stained alternatively with Golgi-Kopsch impregnation, Nissl and Kluver-Barrera methods of staining. The blocks of tissue dimensions of 2x2x1 cm were used for Golgi impregnation method and were cut on microtome into sections, 80 to 100 μm thick. For Nissl and Kluver-Barrera methods of staining paraffin blocks were cut into sections 8-10 μm, thick. After that, sections were deparaffinized and led to the solution of the lowest concentration of alcohol by successive changing of the solution. Sections were stained in 1% of water solution of Cresyl violet for 60 min for the Nissl method of staining. For the Kluver-Barrera method, sections were stained in 0,05 % solution of Luxol fast blue and after rinsing in Li2CO3 these sections were stained in water solution of Cresyl violet. After rinsing and differentiation by acetic acid and mounting with DPX, sections were covered with cover glasses.

Neurons of the human BNST were drawn using Camera Lucida Leica DMBL 2 and photographed under different magnification. The drawings of the neuronal types were first recorded by scanning, to be subsequently digitalized, and finally exposed to the measurements.

In the present study, maximal length (Dmax) and maximal width (Dmin) of the cell body, as the total dendrite length (TDL), were measured using the Zeiss Axiovision 3.0.6.

The classification of neurons was performed according to the following criteria: a) shape and size of the cell bodies; b) dendritic organization - the position, number, length and its branching patterns; c) density of the spines covering dendrites; and d) axonal branching patterns.

RESULTS

The neurons of human BNST were classified into three types, with the respect to its cellular morphology: type I – bipolar neuron, type II – pyramidal neuron, type III – multipolar neuron (figure 1).

Type I - bipolar neuron (figure 2) presents the most common cell type of BNST, especially in its medial dorsal parts, although these bipolar neurons are visible in central and lateral parts of dorsal BNST. We also found this type of neurons in the ventral BNST, scattered among

the multipolar cells. Bodies of bipolar neurons were mainly fusiform in shape, and there were oval-shaped and elongated fusiforme neurons, too.

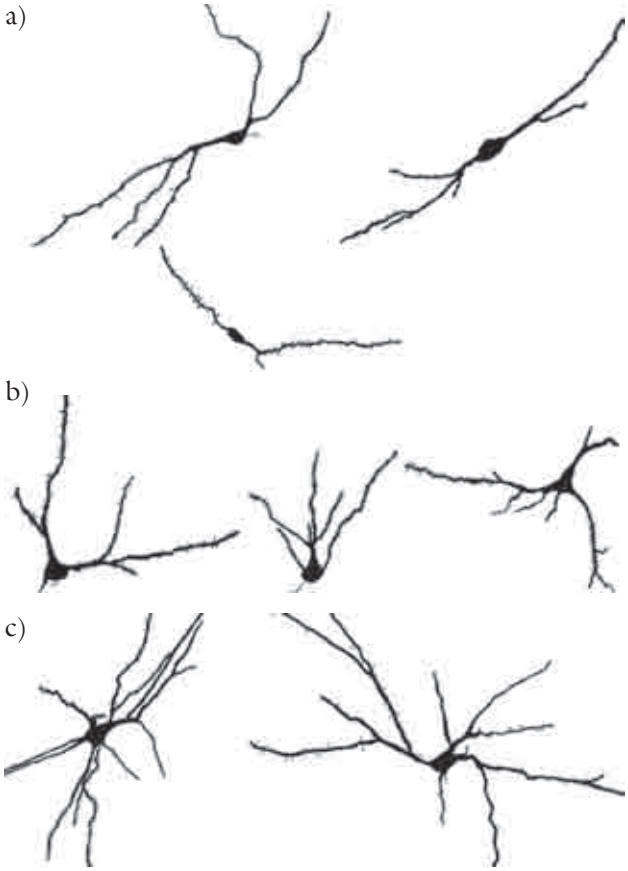

Figure 1. Drawings of Golgi impregnated bipolar (Type I), pyramidal (Type II) and multipolar (Type III) cells of the human bed nucleus of the stria terminalis. Scale = 50 μm. A: Bipolar neuron; B: Pyramidal neuron; C: Multipolar neuron

The primary dendrites of this type of neurons, which extend from the opposite poles of the cell body, were usually aspiny, or covered by very moderate number of pedunculated dendritic spines, while a few primary dendrites were covered with the numerous pedunculated and stubby spines. The more spinous primary dendrites were mostly found in the ventral half of dorsal BNST. The primary dendrites also exhibit varicosities. The orientation of primary dendrites was from dorsolateral to ventromedial. The secondary and tertiary dendrites exhibit a dense covering with spines, and dendritic spines were higher in density as distance from the cell body increased. These spines were mostly pedunculated, although there were also stubby spines. The maximum length (Dmax) of cell body of bipolar neuron was 30.46 μm ± SD 4.1. The maximum width (Dmin) of cell body of bipolar neuron was 19.64 μm ± SD 2.32. The total dendritic length of bipolar cells was 500.74 μm ± SD 63.7 (table 1). According to our results, neurons of the lateral BNST had orientation from dorsal to ventral, while the ones from medial BNST were mostly oriented from dorsolateral to ventromedial. However, the bipolar oval-shaped neurons of medial BNST were oriented from dorsomedial to ventrolateral. The axon, difficult to impregnate satisfactorily, was given off from the soma or from the root of the one of the dendrites and was mainly aspiny. Axons of bipolar neurons from the ventral half of dorsal BNST had ventromedial orientation, while the axons of neurons of the same type from the dorsal half of dorsal BNST were directed dorsolaterally.

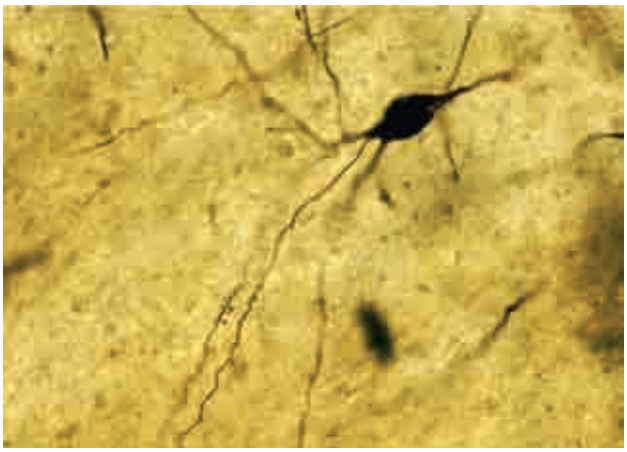

Figure 2. Microphotograph of Golgi impregnated bipolar (Type I) neuron of the human bed nucleus of the stria terminalis (x 400)

Type II – pyramidal neuron (figure 3), presents the less numerous type of neurons of BNST in comparison with bipolar neurons. This type was mostly found in central and lateral parts of dorsal BNST, although scattered pyramidal neurons were clearly visible in dorsomedial and ventral parts of BNST. Their cell bodies varied in their shape and size. We differentiated pyramidal neurons with oval, round, piriform and triangular cell bodies. According to the maximum length of their soma, round neurons of type II, were the smallest (19.42 μm ± SD 0.08), while the triangular ones were the largest (32.91 μm ± SD 3.59). This type of neurons had one dominant, thick, apical and two thinner basal dendrites. Apical dendrites of these neurons from the greatest part of dorsal BNST and from the ventral BNST were oriented dorsally (dorsolaterally or dorsomedially), while apical dendrites of the most dorsal neurons of BNST were oriented ventrally (ventolaterally or ventromedially). The primary apical dendrites of this type of neurons were mostly aspiny, or covered with sparse pedunculated spines. Only few primary apical dendrites also exhibit varicosities.

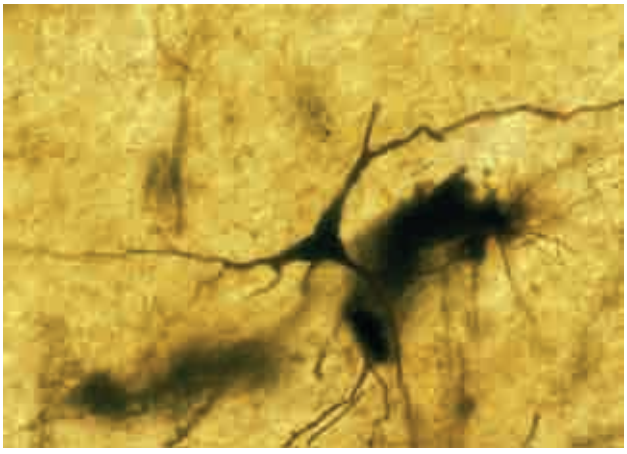

Figure 3. Microphotograph of Golgi impregnated pyramidal (Type II) neuron of the human bed nucleus of the stria terminalis (x 400)

The primary basal dendrites were mostly aspiny, too, although we found pyramidal neurons that had primary basal dendrites covered by moderate number of pedunculated and stubby spines spines. The varicosities were rare and visible on dendrites without spine. Dendritic spines were higher in density as distance from the cell body increased, so the secondary and tertiary dendrites were covered with the great number of pedunculated and stubby spines spines. The maximum length (Dmax) of cell body of pyramidal neuron was 30.55 μm ± 3.52. The maximum width (Dmin) of cell body of pyramidal neuron was 21.52 μm ± 1.53. The total dendritic length of pyramidal cells was 715.98 μm ± 72.70 (table 1). The axon of pyramidal neurons arose from the base of the cell body and usually was oriented dorsolaterally. Axons of pyramydal neurons exhibit sparse spines.

Table 1. Neurons of the human bed nucleus of the stria terminalis. The measured diameters of cell bodies (±SD) - the maximum length (Dmax), the maximum width (Dmin) and the total dendritic length (TDL). Results are in micrometers (μm).

Type	Dmax	Dmin	TDL
I - Bipolar	30.46 ± 4.1	19.64 ± 2.32	500.74 ± 63.7
II - Pyramidal	30.55 ± 3.52	21.52 ± 1.53	715.98 ± 72.70
III – Multipolar	27.36 ± 2.86	22.13 ± 2.37	1303.51 ± 140.09

Type III – multipolar neuron (figure 4) is predominant cell type in the ventral part of BNST, although this type is rare, but also visible in dorsal parts of BNST. Multipolar cells had oval cell bodies, with primary dendrites which arose from any part of cell body and radiated out in all directions. Among these primary dendrites of one cell, we distinguished the primary dendrite that had the greatest length or width. These, the longest or the widest primary dendrites of multipolar neurons of ventral BNST, were oriented dorsally, while those from the dorsal part of BNST were oriented ventrally. The primary dendrites were covered with sparse dendritic spines, and these dendrites branched to form two or three secondary dendrites.

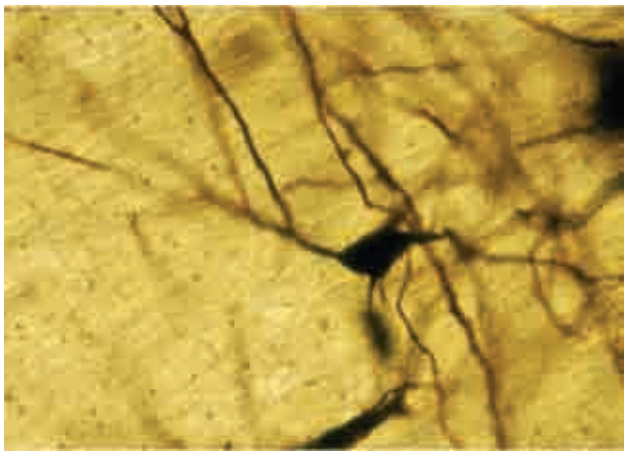

Figure 4. Microphotograph of Golgi impregnated multipolar (Type III) neuron of the human bed nucleus of the stria terminalis (x 400)

Dendritic spines were higher in density as distance from the cell body increased, so the secondary and tertiary dendrites were covered with the great number of pedunculated and stubby spines spines. The maximum length (Dmax) of cell body of multipolar neuron was 27.36 μm ± 2.86. The maximum width (Dmin) of cell body of multipolar neuron was 22.13 μm ± 2.37. The total dendritic length (TDL) of pyramidal cells was 1303.51 μm ± 140.09 (table 1). Axon of the multipolar neuron that arose from the cell body, was oriented ventrally and mostly without dendritic spine.

DISCUSSION

Although the numerous studies were performed, in the last two decades, in order to describe the cytoarchitecture of BNST, basic morphology of neurons of human BNST is still not known enough, instead of its important function as relay nucleus of limbic system which connects amygdala and hippocampus with the paraventricular nucleus of hypothalamus. Those earlier studies that were performed on the brains of the rats and monkeys, gave us the important data about morphology of BNST, but there were only few research articles about morphological characteristics of human BNST.

After intensive cytoarchitectonic and chemoarchitectonic studies of rat BNST, Ju and Swanson (7) gave the very detailed description of morphological characteristics and proposed the parcellation of BNST. They described neurons of BNST as smaller or larger, oval, spindle-shaped, round, triangular and multipolar neurons, but their descriptions did not include average measurements of the size of neurons or of the length of dendrites and they did not classified neurons. De Olmos (1) studied BNST of rat, monkey, but also, of the human brain and on the basis of these investigations he proposed the parcellation of BNST, that is the most useful in literature, clearly defined the borders of each division or subdivision, and gave detailed description of neuronal orientation, density, intensity of staining, and presence of glial cells. The shape of cell bodies of BNST neurons, in his descriptions, was defined as oval, round, spindle-shaped, triangular and angular-shaped and his description of the size of neurons was limited to the terms such as larger or smaller neurons. Our study of Golgi-impregnated sections confirmed the presence of morphological heterogeneous neurons in the BNST, but also provided quantitative measures of the cell bodies, dendrites, dendritic spines and axons.

Moga et al. (23), on the basis of their research of the rat brain, proposed the parcellation of BNST. The special emphasis had been given to studding the connections between BNST and nc. parabrachialis and in this regard, their conclusion was that neurons of BNST that projected to nc. parabrachialis contained the same neuropeptides as neurons of central nucleus of amygdala that had the same target area. This conclusion once more confirmed morphological similarity between neurons of BNST and central nucleus of amygdala. These researchers also gave more detailed description of topography and parcellation of BNST, than of morphology of its neurons. They differentiated oval, round, tear-shaped and angular cell body of neurons which were described as smaller, medium sized and larger ones. According to their findings, the most numerous neurons in medial division of BNST were ones with oval shaped cell bodies,

but they also described spindle-shaped and round neurons. These neurons were mostly small-sized, but there also were found medium-sized and large neurons, scattered among the small ones. These neuronal types exhibit resemblance to our bipolar neurons of type I, which are predominant in medial half of BNST. The smallest neurons were found in medial half of BNST, just dorsal to the commissura anterior. In lateral division of BNST, they found neurons very heterogeneous in the respect to the shape of cell body. Our study confirmed this heterogeneity and suggested that the most common neurons of lateral half of BNST were pyramidal ones of type II, but in this sector we also found neurons of type I and III. The predominant neurons of their ventral division of BNST were multipolar, large neurons and these data are in remarkable resemblance to our findings (type III – multipolar neurons).

Lesur et al. (4), in contrast to majority of the scientists, studied the BNST of human brain. They used immunocytochemical techniques in their research in order to classify BNST into functional systems, together with morphologically or/and functionally similar brain structures. They divided BNST into lateral, central and medial sector. In the lateral sector, adjacent to capsula interna, they found small to medium-sized neurons (10-16 μm diameter) and in addition, along its lateral border they found a few larger-sized neurons (25-30 μm diameter) with dark Nissl staining. Our results clearly indicate presence of the neurons with a wide range of diameters in this region of BNST, which are, in general, larger (Dmax=19.36-35.69 μm) than those in description of Lesur and his research fellows. Central sector, according to their parcellation, is composed of fusiform or triangular medium-sized cells (15-25 μm diameter) with homogenous pale staining. The presence of fusiform and triangular shaped cell bodies in the central sector of BNST was confirmed in our study, but in this region we also found oval, multipolar and piriform neuronal soma. The maximum length (Dmax) of cell body of neurons of this region of BNST was 24.23-35.72 μm, but we also found the neurons with elongated fusiform bodies and diameter which was approximately 60 μm. According to their findings, the medial sector is made up of small neurons (10-14 μm diameter). The presence of small neurons in the medial sector of BNST was confirmed in our research, but only in the parts of BNST just dorsal to the commissura anterior, where we found the cell bodies with the minimum Dmax which was approximately about 15 μm (14.72 μm). In our study, in the dorsal parts of medial sector of BNST, we found large neurons with Dmax from 25.96 μm up to 43.83 μm.

Previous Golgi studies of McDonald (39) gave detailed descriptions of neuronal morphology of BNST, but he made his conclusions by observing the Golgi sections of rat brain. In the lateral subdivision of BNST, he found neurons with oval cell bodies, and 4-5 dendrites which arose from the cell body, branched several times and were covered with dense dendritic spines. In juxtacapsular subdivision he found small-sized neurons with dense dendritic spines. Our findings of neuronal morphology in the lateral third of BNST correspond to these descriptions, in respect of neurons with oval cell bodies, especially in the ventral part, but in this region of BNST, we also found neurons with round, fusiform and triangular shaped soma. According to our study, the predominant neurons in the lateral part of BNST were ones that we classified into type II. These neurons had 2 or 3 mostly aspiny primary dendrites and the secondary and tertiary dendrites, covered with the numerous pedunculated and stubby spines. In the medial subdivision of BNST, he found oval shaped neurons, with 2 or 3 primary dendrites, which ramified considerably, and which were covered by sparse to moderate number of spines. Our findings were similar in comparison with these.

Our findings, in some way, match with the findings of Larriva-Sahd (40, 41). In very detailed morphological analysis of juxtacapsular and oval nucleus of BNST, he clasiffied the neurons into six and eleven types, respectively. These studies were performed not on the human brain, but on the brains of adult rats. In the of juxtacapsular nucleus of BNST, we also found neurons with oval, round and triangular soma, and classified them into type I (bipolar neurons) and type II (pyramidal neurons). In regard to oval nucleus, in this part of BNST we found neurons of all three types (in our classification), but the most frequent neurons were with oval cell bodies and with two or three primary dendrites, that match with the results of recent studies (41). In general, the human neurons of BNST, from our study, are larger than in rats.

In spite of many morphological similarities, it is evident that a number of histochemical and morphological features, characterized in human BNST, are different or lacking in the rodent BNST. Lateral and ventral parts of human BNST are more developed than in the rat and also in comparison with medial and intermediate parts. Lateral and ventral parts of BNST receive inputs from entorhinal and infralimbic cortex, agranular insula and from central and basolateral amygdala. The latter two structures are also more developed in the human brain. Previous studies reported that medial division of BNST appears to be less developed in human brain. It is the similarity with the reported relative regression of human medial amygdala and accessory olfactory system, which are the place of origin of massive inputs of medial BNST (4). These facts are exceptionally significant for the supposed functions of BNST divisions.

The interest for the BNST, the structure morphologically and functionally closely related to the amygdala, increased in the last decade, mostly because of their key role in the states of fear and anxiety. Mental disorders with a symptoms of anxiety and dysfunction of fear are very common and in progress. In this respect, the future detailed studies of these significant limbic nuclei are necessary. The results of this study provide evidence for distinguishing between various cell types in the BNST and a reasonable framework for more detailed studies, because the knowledge of role of such brain structure can not be complete, without full knowing of its basic morphology. Disproportion between their great significance and the incomplete knowledge is still very obvious.

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