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The neuronal structure of the red nucleus in newborn guinea pigs

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The preparations, stained according to the Nissl and Klüver-Barrera methods, were used to describe the topography and morphology of the red nucleus (RN) as well as the structure of the rubral perikarya in newborn (P0) guinea pigs. The Golgi impregnated preparations were used to distinguish types of neurons. RN is a uniform cell group and has the length from 740 to 860 µm. The Nissl stained perikarya were classified into three categories: big, medium-sized and small (A, B, C, respectively). The big perikarya, which contain a lot of tigroidal substance, were mainly observed at the caudal and ventral portions of RN. The small perikarya often have multiple nucleoli. The impregnated neurons were classified into 5 types: 1 — large, aspiny, rich-arborised multipolar cells, 2 — large and medium sized, spiny, rich-arborised fusiform or pear-shaped cells, 3 — medium-sized, spiny, rich-arborised rounded cells, 4 — medium-sized, spiny, rich-arborised bipolar cells, 5 — small and single medium-sized cells. The 5th type constitutes a heterogeneous population and also has neurons in different developmental stages. Intraspecies variations concerning both the length of RN and a number of the triangular perikarya of the red nucleus were observed in the examined guinea pigs.

key words: red nucleus, morphology, types of neurons, Nissl and Golgi studies, neonates

INTRODUCTION

The size and vigour of littermates varies widely at birth [31]. The motor abilities are different in newborn mammals of various species, ranging from opossum to man [12, 16]. It is a rule that the non-precocial (altricial) mammals have long postnatal development [12], because they are born with inadequately developed sensory and motor systems [13, 16]. The various behavioural movements depend on the development of limbs or limb-like structures [1] and are related to the development of some nervous centres, especially the cerebellum nuclei and also the red nucleus [1, 11, 17, 18]. The guinea pig belongs to the precocial mammals, which probably are less reactive to environmental differences [16], in contrast to the opossum [13, 35], some rodents, carnivores and primates [16]. The entire development of the rubrospinal tract in the opossum occurs after birth, and is probably followed by a neuroanatomical rearrangement of RN structure [12, 13, 35]. It was suggested that the precocial animals (guinea pig) are more resistant to the remodelling and plasticity concerning the rubral cells and tracts, during postnatal development, in contrast to the altricial mammals (including other rodents) [16]. It was found that significantly more rubral cells are lost in newborn than in adult rats, following spinal cord hemisection [4]. On the other

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hand, the extensive neuroanatomical remodelling occurs in rats hemicerebellectomised up to the 10th day after birth, but not in animals lesioned at later ages [5]. In young animals plasticity requires among other things: the cellular prion protein [25] and a high level of hyaluronic acid [3]. The latter was also observed in adult animals but in lower amounts. The differences between young and mature brains manifest also in other aspects: the myelination process [8, 10, 19], an axonal fluorescence of monoaminoergic neurons [2], the activity of sorbitol dehydrogenase [29], the expression of calcium-binding proteins [30] and the expression of angiotensin II in the red nucleus [15]. The latter appears in rat at early embryonic stage (at E15 and E17), i.e. the next day after the neurogenesis of the rubral cells [11]. Its level is high in RN and in other nuclei involved in motor functions and sensory integration, and persists until the maturity of the brain [15]. During brain development, the morphology of nuclei and their connections change. For example, the cortico-rubral crossed projections in cat are reduced in the postnatal period [6, 34]. The morphological structure of neurons is the last to undergo remodelling [12]. The topography, shape and subdivisions of the red nucleus, as well as the types of rubral neurons, have been described in adult guinea pigs [21] but not in younger specimens. The aim of this study is to examine this subject in newborn guinea pigs.

MATERIAL AND METHODS

The studies were carried out on the brains of 5 newborn (P0) guinea pigs (coloured or Dunkin-Hartley strain). The animals were overdosed with sodium pentobarbital and perfused transcardially with phosphate and then formaldehyde buffered solutions at pH 7.4. The paraffin preparations (10 μm-thick) were stained according to the Nissl and the Klüver-Barrera methods. The other blocks of mesencephalons were processed according to the Bagiński and Golgi-Kopsch techniques, and then cut into 60 μm--thick sections in sagittal and transversal planes. The microscopic images of selected, impregnated neurons were digitally recorded by means of a camera that was coupled with a microscope and an image processing system (VIST-Wikom, Warsaw). From 30 to 120 such digital microphotographs were taken at different focus layers of the section for each cell. On the basis of these series the computerised reconstructions of neurons were made. The neuropil was removed to clarify the picture.

RESULTS

Nissl studies. The red nucleus in a newborn guinea pig (Fig. 1) is a well outlined mesencephalic centre, which lies along the rostro-caudal axis of the tegmentum, from the level of the decussation of the brachium conjunctivum forwards to the mamillary region. The posterior pole of RN appears at the distance of about 200 μm in front of the posterior pole of the interpeduncular nucleus, and extends forward at the distance of 740 or 860 μm in studied animals. In front, RN ends at the level of the anterior edge of the posterior commissure, at some distance in front of the anterior pole of the oculomotor (Nu3) and interpeduncular (Ip) nuclei. On the cross-section, RN appears at mid-length between the decussation of the superior cerebellar peduncle (next to the decussation of the ventral tegmentum) and Nu3, laterally from them. The medial side of RN strictly adjoins the radicles of the oculomotor nerve, whereas the ventral side of RN adjoins the fibres of the brachium conjunctivum, and then the medial lemniscus. In newborn guinea pigs the red nucleus is a band of cells, which has no clear morphological subdivisions, although it possesses a characteristic distribution of large and small cells. On Nissl preparations, the biggest cells constitute mainly the posterior segment, but they are also observed on the ventral side of the whole RN. The posterior section of RN is composed of a few, loosely arranged, large cells. Forwards, a number of RN cells increases several times; they form an oval cell group measuring 500 x 300 μm; its long axis runs in the dorso-medial to ventro-lateral direction. RN consists mainly of multipolar, piriform and fusiform cells, measuring from 15–28 μm in long axis. Bigger cells up to 50 μm, as well as the cells smaller than 15 μm, were observed in smaller numbers. The latest have a high nucleolar/cytoplasmic ratio (large cell nucleus) and often 2 nucleoli. The rubral cells dislocate upwards, especially along radicles of the oculomotor nerve, but sometimes constitute transient isolated small groups at various places. The middle segment of RN is the best developed. Its cross-section has 500 $\times$ 500 μm. Variable small aggregations are observed on the dorsal border of RN. The red nucleus assumes a rounded shape, but then elongates horizontally and reshapes. The anterior segment of RN is an elongated, oval-shaped group, which is directed from dorsolateral to ventromedial side. The least variable in shape is the ventral portion of RN, which consists of larger neurons than the cells located above them. It was found that a number of the triangular cells vary in the studied individuals.

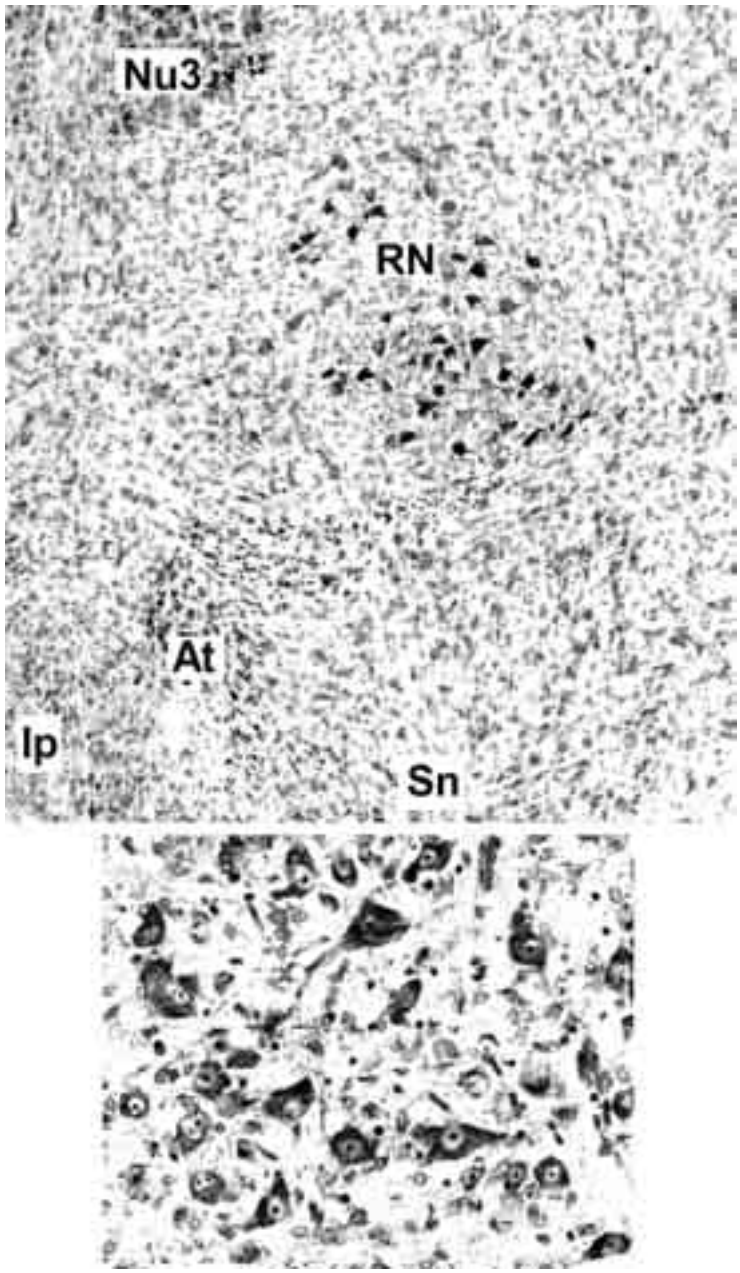

Figure 1. The cross-section at the middle segment of the newborn guinea pig RN (above); higher magnification of the rubral cells (at the bottom); RN — red nucleus, Nu3 — oculomotor nucleus, Ip — interpeduncular nucleus, At — ventral tegmental area, Sn — substantia nigra; Nissl method.

In one of the two examined animals the triangular cells appear in great number, whereas in the other they are rarely observed. On the basis of common cytological features of RN in newborn guinea pigs, the rubral perikarya were classified into three categories:

A (Fig. 1, 2[a]) — big perikarya (30–50 μm), especially characteristic for posterior and ventral portions of RN. They are typical multipolar, or take shapes from irregular oval to fusiform. Their perikarya contain a large and light cell nucleus, mainly located centrally, with 1 or rarely 2 intensively stained nucleoli. In some cells, the intensity of staining of their nucleus and cytoplasm are almost the same. The neuroplasm contains numerous rough granules of the tigroidal substance, which are irregularly distributed. They often penetrate into the dendrites. The thickness of primary dendrites may be varied even in one cell.

B (Fig. 1, 3[a]–6[a]) — medium-sized perikarya (18––28 μm), oval or rounded and, in smaller numbers,

multipolar and fusiform. They are distributed throughout the whole nucleus. Within this cell population there are two kinds of neurons. The first kind has cell bodies similar to the big perikarya. The second kind are lightly stained neurons. They contain small amounts of cytoplasm and also tigroidal substance, which penetrates into dendritic trunks only at a short proximal distance, or does not enter at all. Their cell nuclei are large and possess often 2 or 3 nucleoli.

C (Fig. 1, 6[a]) — small perikarya (5–16 μm); the majority of them have rounded or multipolar, seldom fusiform cell bodies. They are similar to the lightly stained perikarya B. Some cells have a narrow rim of cytoplasm located only on one side of a cell, forming a cap over the cell nucleus. The cells without visible tigroidal substance cause the impression of "neglected" nuclei. There are also intensively stained perikarya with plenty of the tigroidal substance, which does not enter deeply into dendritic trunks. The number of small perikarya with multiple nucleoli is greater on the dorsal side of the red nucleus and increases towards its anterior pole.

Golgi studies. On the basis of the shape and size of perikarya, number and arborisation of dendrites, the presence of dendritic spines and pattern of axon, in the red nucleus of a newborn guinea pig the following types of neurons were distinguished:

1. Large, aspiny, rich-arborised multipolar cells (Fig. 2). These neurons have various shapes of perikarya measuring from 40 to 60 μm in long axis. They usually possess 4 or 5 thick dendritic trunks, which divide near the soma, and further branch at relatively short distances up to quaternary order dendrites. The thinner, daughter branches are varicose and have irregular contours. Generally, these neurons are devoid of typical knob-like spines, but various dendritic processes are observed. The dendrites run in all directions and form an oval-shaped dendritic field. The thick axon emerges from a soma. These cells in Golgi methods correspond to perikarya A in Nissl preparations.

2. Large and medium-sized, spiny, rich-arborised cells (Fig. 3). They measure from 40 to 55 μm and possess mainly fusiform or pear-shaped perikarya. They are somewhat similar to the multipolar cell, but their dendritic trunks are thinner and "polarised". The trunks (3–4) run from a soma approximately in one direction and create a fan-shaped dendritic field only on one side of the cell. From the opposite side of the perikaryon a rather thick axon emerges, which is observed only for a short distance. Relatively thin

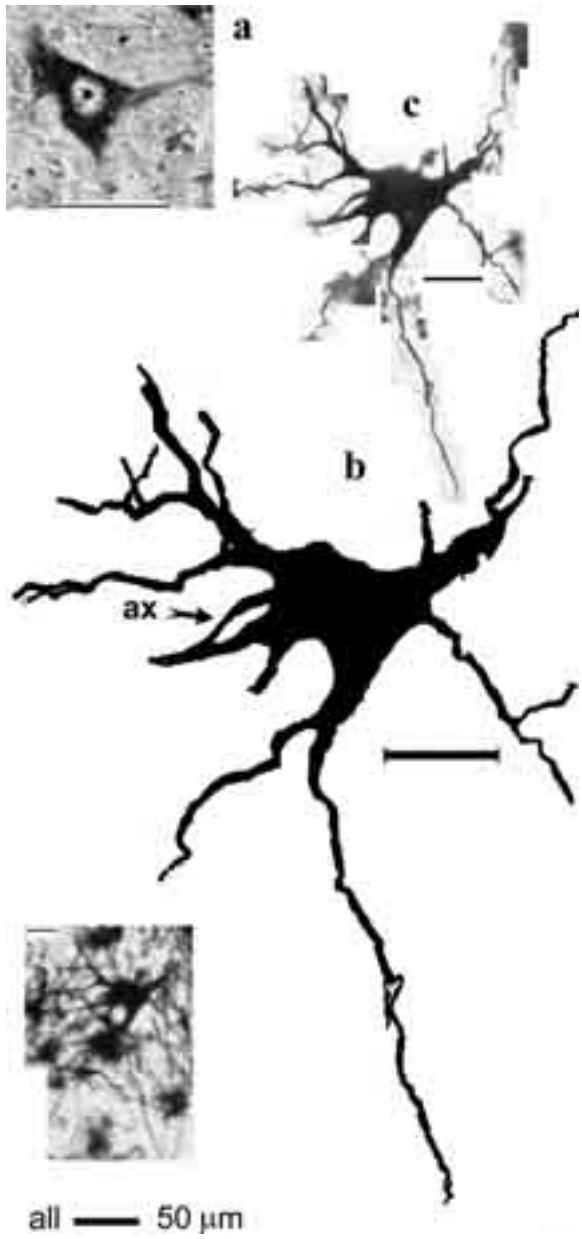

Figure 2. Large, aspiny, richly arborised, multipolar cell of type 1; **a.** Klüver-Barrera stained perikaryon; **b.** Clarified computerised reconstruction of impregnated neuron; ax — axon; **c.** Non-clarified microscopic image; Golgi impregnation; additionally: in the bottom left corner — the microphotograph of the neuron in the light microscope; Golgi-Kopsch technique.

dendrites usually divide into quaternary order branches. They possess clearly visible, mainly rose-thorn appendages. The cells of the second type correspond also to perikarya A in Nissl picture.

3. Medium-sized, spiny, rich-arborised cells with rounded perikarya (Fig. 4). They measure from 20 to 45 μm. They have 3 or 4 dendritic trunks, which at the distance of 10–30 μm from the soma divide into secondary and finally up to 5 order branches. Some

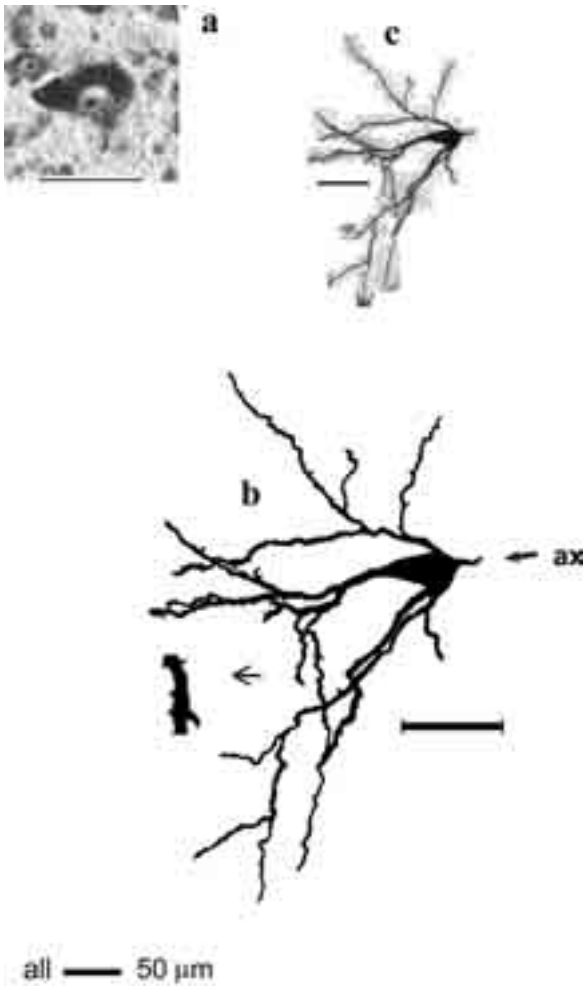

Figure 3. Medium-sized, spiny, richly arborised cell of type 2; **a.** Klüver-Barrera stained perikaryon; **b.** Clarified computerised reconstruction of impregnated neuron; ax — axon; the thin straight arrow indicates an enlargement of the dendrite with the rose-thorn spines; **c.** Non-clarified microscopic image, Golgi impregnation.

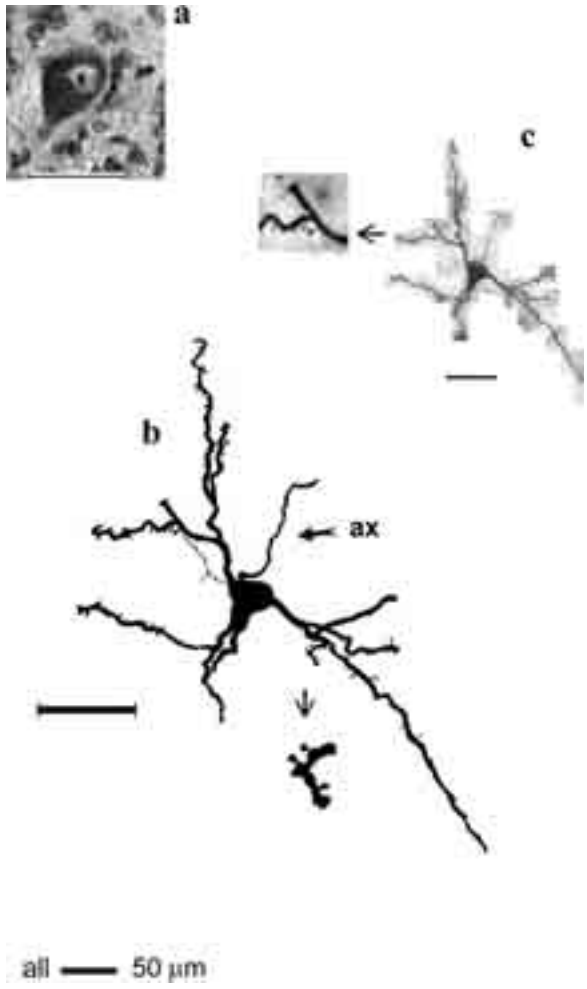

Figure 4. Medium-sized, spiny, richly arborised cell of type 3; **a.** Klüver-Barrera stained perikaryon; **b.** Clarified computerised reconstruction of impregnated neuron; ax — axon; **c.** Non-clarified microscopic image, Golgi impregnation; the thin straight arrow (also in b) indicates an enlargement of the dendrite with the knob-like spines.

primary dendrites are undivided and run for the distance of about 250 μm. The dendritic field is oval-shaped. The distal portion of dendrites or their branches are covered with numerous, irregularly arranged, but prominent typical knob-like spines. The relatively thick axon arises from the soma, and is impregnated for about 100 μm. These neurons correspond to the light stained perikarya B in the Nissl preparations.

4. Medium-sized, spiny, rich arborised bipolar cells (Fig. 5). They have oval or fusiform perikarya (mainly B in Nissl study), which measure from 20 to 35 μm in long axis. These cells have 2 or 3 dendritic trunks (in that case two of them emanate from one pole of the soma). Their dendritic field has the form of an hourglass. The primary dendrites branch dichotomously close to the cell body or at the distance up to 25 μm. The daughter distal branches may run for about 300 μm. The dendrites are covered with knob-like and rose-thorn spines, which are sparsely and irregularly distributed. Only rarely are they grouped on a short sector. The axon leaves the soma close to the dendritic trunk and possesses an irregular contour with buttons.

5. Small cells (10–20 μm) and single medium-sized, up to 22 μm (Fig. 6). They are a heterogeneous cell population, and the majority of them possess dendritic spines. These neurons have various perikarya: rounded, fusiform, triangular and quadrangular in shape, which corresponds to categories B and C in Nissl picture. The dendritic trunks (2–3) vary in their thickness and number, usually are thin and divide once. Their dendritic field has a stream-like form. Sometimes 1 or 2 dendritic trunks are relatively thick and send secondary branches usually

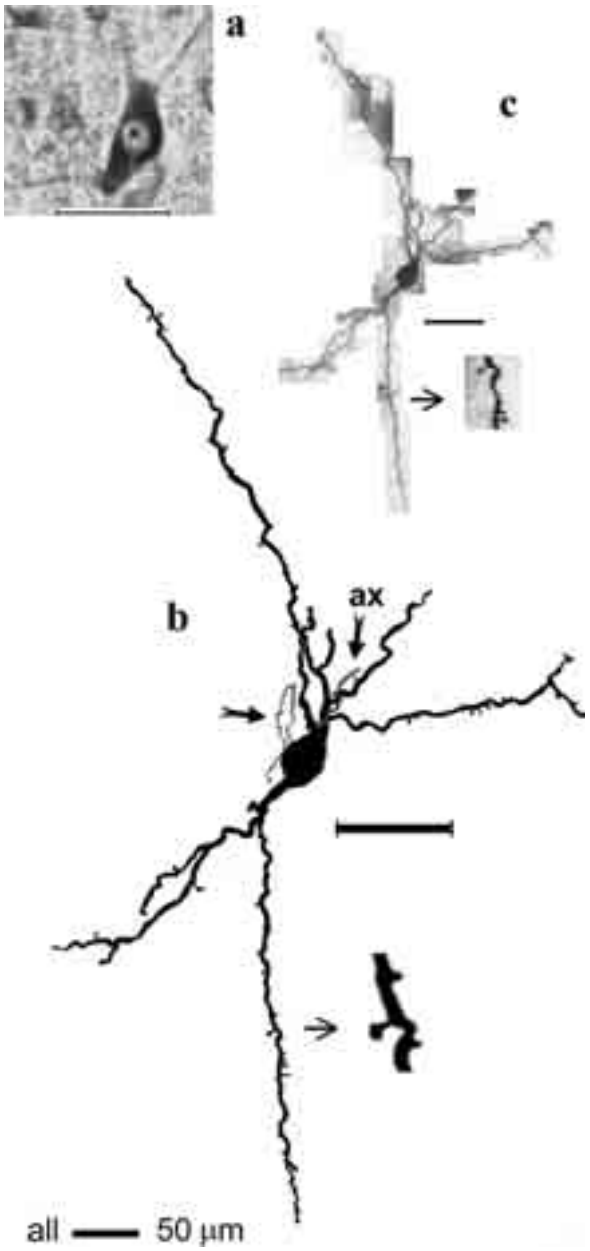

Figure 5. Medium-sized, spiny, richly arborised cell of type 4; **a.** Klüver-Barrera stained perikaryon; **b.** Clarified computerised reconstruction of impregnated neuron; ax — axon; **c.** Non-clarified montage of neuron; the thin straight arrow (also in b) indicates an enlargement of the dendrite with the knob-like and rose-thorn spines.

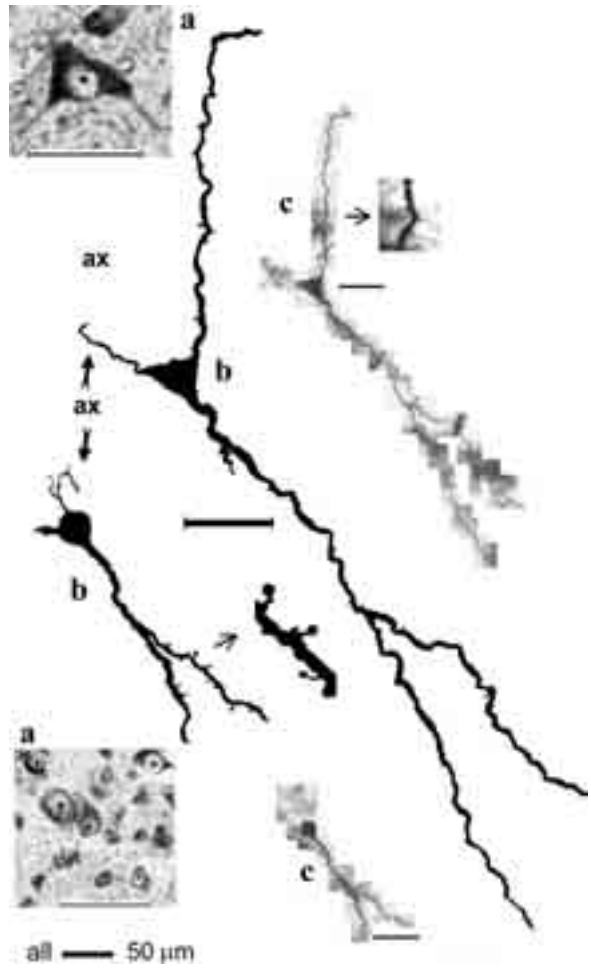

Figure 6. Medium-sized and small cells of type 5; **a.** The Klüver-Barrera stained perikarya; **b.** Clarified computerised reconstructions of impregnated neurons; ax — axon; **c.** Non-clarified microscopic images; Golgi impregnation; the thin straight arrows (also in b) indicate enlargements of the dendrites with the knob-like and rose-thorn spines.

for a distance of about 100 μm. In some neurons, the daughter branches are shorter than the parent ones. Their dendrites are covered with spines, which vary in their density and shapes. The dendrites without spines were also observed, but occasionally rose-thorn spines may be observed on the soma. The axons arise from the perikarya. In the smallest neurons, axons usually have irregular contours, give off collaterals and possess swellings like a button. The single spines on the dendritic trunks are also observed. Probably these cells represent the neurons in different developmental stages, because they possess the processes like a growth cone.

DISCUSSION

In mature mammals the red nucleus histologically consists of parvicellular (RNp) and magnocellular (RNm) parts, but their anatomical delineation differs in various species. The posterior segment of the red nucleus in monkey is considered as a separate entity [17], whereas in man [30] and many other mammals, the posterior segment is a subdivision of RN. This was discussed in a previous paper dealing with the red nucleus of adult guinea pig [21]. In newborn guinea pigs, the red nucleus is a uniform cell band and the three morphological groups

distinguished in RN of adults [21] were not observed. Two parts (RNm and RNp) are distinguishable in twenty-day-old guinea pigs (unpublished data). In the human red nucleus [30] these parts are clearly outlined, both in postnatal and prenatal periods, however as regards the dominance of RNm over RNp, the reverse situation is found in the two mentioned periods. In the pig, the red nucleus develops as other motor nuclei [32], whereas in prenatal cats, the red nucleus grows at a different, slower pace than, for example, the caudate nucleus and substantia nigra [33]. During the postnatal period, the cat's RN comes within range of adulthood size by P60 [33]. In young rats, RN reaches the length of the adult by P40 [11]. In newborn guinea pigs the length of RN varies from 740 to 860 μm and reaches about 950 μm by P20 (unpublished data). In the following period, from P20 to adulthood, RN increases to 1.2 mm in its length [21]. The present studies show that the arrangement of the large and small perikarya within RN in general resembles the distribution of these perikarya of adult guinea pigs [21], but in newborns there is no anatomical delineation of the cell groups. A large number of perikarya with multiple nucleoli as well as the varied number of triangular perikarya in RN at birth are the main differences between the rubral cells of newborns and adults. Owing to the fact that the multiple nucleoli are the rule in developing neurons [8], it may be supposed that the posterior sector of RN develops before the anterior part. The experimental studies show that in the cat small cells of anterior part of RN receive the corticorubral projections [22]. The common view is that the rubrospinal and cerebellorubral connections develop before the corticorubral ones [11, 12, 27], and that the RNm projections are somatotopically arranged [14, 22, 26, 28]. In the newborn guinea pig the cells dislocating along the fibres of the oculomotor nucleus may partly correspond to the cells somatotopically responsible for forelimbs or mouth [22]. Our Golgi studies show that the red nucleus at birth consists of five neuronal types, which constitute three populations: I) aspiny (large, multipolar cells of type 1); II) spiny (mainly medium-sized cells varying in shapes of perikarya; types from 2–4), and III) mixed population (spiny or aspiny, mainly small cells of type 5). The neurons of the 5th type are poorly arborised, in contrast to the cells of the remaining types (1–4). In the newborn guinea pigs the population of the 5th cell type contains triangular cells, which are absent in corresponding type IV in adult individuals [21]. Moreover, type 5 contains developing cells. The axons of the small cells send collaterals and create an axonal arborisation in the vicinity of the soma. These cells often possess perikarya with 2 or 3 nucleoli. They may give rise to interneurons or Golgi II cell type [8]. The interneurons are a very varied population [20] and they are probably the last cells which develop in the nervous centres [8]. Taking into consideration the reasons mentioned above, we assume that the neurons of the 5th type may be a source for the rubral interneurons in guinea pig. During the cell development, the axons are covered with a myelin sheet. The myelination process occurs segmentally with no proximodistal order and it does not depend on the type of neuron [10]. In a newborn guinea pig, the impregnated axons were observed for longer distances, in contrast to adult animals [21]. During myelination, the branches that are not at a node of Ranvier are eliminated [8], thus collaterals may be present in smaller numbers. An interesting case is represented by the development of the large, multipolar, aspiny neurons (type 1 at P0), which correspond to the large neurons of type I in adults [21]. During the postnatal period, the dendrites of large neurons acquire spines. Moreover, the dendrites take a more linear course and divide at longer distances from a soma, thus the dendritic tree becomes more regular in adult than in newborn individuals. These cells are partly the source of the rubro-spinal projections in mammals [4, 14, 22, 26]. It may be deduced that the number of rubral afferents (synapsing on large neurons) increases throughout the postnatal period. During this period, a preferential termination and a synaptic site segregation for various afferent fibres on the rubral cells in cat were noted [23, 24, 27]. Jacobson [8] stated that in the absence of normal axodendritic connections, the dendrites remain stunted and the dendritic tree becomes malformed. In newborn guinea pigs, apart from cells of the 5th type, all other neurons possess a richly arborised dendritic tree. During postnatal life, from birth to mature stage, the process of the pauperisation of the dendritic tree is noted. The loss of distal dendrites affects the neurons of the 4th type (at P0), which corresponds to the cells of type II in adult guinea pig [21]. It was found that the length of the dendritic branches was shortened from 300 to 180 μm and the dendritic field changed from hourglass to streamlike, in the two comparative stages, respectively. Additionally, the number of dendritic spines was diminished, whereas the

spine-like protrusions have a tendency to increase throughout postnatal life to adulthood. In the red nucleus of an adult guinea pig there were triangular, medium-sized and small cells, with a rather poor dendritic tree. They were aspiny, and only varicosities were observed [21]. The cells of type 2 in a newborn are absent in adults [21]. Similar cells (multipolar, mainly medium-sized) were present only in a transitional period in gibbons [17]. Some of the multipolar cell bodies may act as integrative junctions [7]. Their dendroarchitectonic patterns may change [20], but probably conform to the orientation of the cell body [8]. They may come from the heterogeneous population of cells of the 5th type in newborns.

Concluding, the red nucleus is a part of a long feedback loop assisting the ongoing movement [18], however RNp and RNm are involved in different loops in rat [9], monkey [11], and probably other mammals, including guinea pig. Other studies indicate that among developing brain structures the projections are formed earlier, before the nervous centres, which acquire their adult morphology at the latest [6, 33]. Comparing our results with data of other studies, we may suppose that: 1) different RN length in newborn guinea pigs is compensated by P20; 2) during this period the rubral cells are segregated into magnocellular and parvocellular parts; 3) RN grows faster from P0 to P20 than from P20 to adulthood [21]; 4) the spiny, richly arborised mainly medium-sized cells (types 2–4 at P0) lose the dendritic spines and distal dendrites during postnatal development; 5) the reverse situation is noted for the large, multipolar, aspiny cells (type 1 at P0), which postnatally acquire dendritic spines and have a dendritic tree which is more regular than at birth; 6) the interneurons may come from a heterogeneous population of the small cells (type 5 at P0).

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