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ORIGINAL ARTICLE

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The perineuronal glial tissue of spinal ganglia. Quantitative changes in the rabbit from youth to extremely advanced age

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Abstract The volumes of the nerve cell bodies and those of the enveloping satellite cell sheaths from spinal ganglia were determined by morphometric methods applied to electron micrographs in young, adult, old and very old rabbits. The mean volume of the nerve cell bodies increased progressively with age; this is probably related to the increase with age of the body size of the rabbits studied. The mean volume of the satellite cell sheaths did not differ significantly in young, adult and old animals, but was significantly smaller in very old animals. It is extremely unlikely that this marked reduction in the volume of the satellite cell sheath is the result of a pathological process. The mean value of the volume ratio between the satellite cell sheaths and the related nerve cell bodies did not differ significantly in young and adult animals, but was significantly smaller in old and very old animals. This ratio was particularly low in very old animals. Our analysis showed that in each age group the volume of the satellite cell sheath is linearly related to the volume of the related nerve cell body. This result suggests that in rabbit spinal ganglia the quantitative relations between glial and nervous tissue are tightly controlled throughout life. It is suggested that ganglionic neurons release signals to influence and control the volume of their associated glial tissue. Since satellite cells have important support roles for the neurons they surround, it is likely that the marked reduction in the volume of perineuronal sheaths in the extremely advanced age is accompanied by a reduction of those roles, with negative consequences for neuronal activity.

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Introduction

After it was shown that interactions between nerve and glial cells are reciprocal, a wealth of information on the functional and metabolic interactions between glial and nervous tissue has accumulated. By contrast, quantitative histological data on the relations between these two tissues are scarse, particularly at the level of the individual neuron. There are several reasons for this lack of information. In most regions of the nervous system glial and nerve cells are intimately and complexly intermingled, so it is not possible to determine which glial cells are related to an individual neuron. Furthermore, both glial and nerve cells are often irregular in shape, so it is difficult to determine their volume with satisfactory precision. In sensory ganglia, on the other hand, each nerve cell body is usually enveloped by a discrete group of glial cells that forms the perineuronal sheath. These cells are usually called satellite cells and will be referred to as such in this paper. The perineuronal satellite cell sheath is sharply separated from the sheaths encircling the adjacent nerve cell bodies by connective tissue. Thus, in these ganglia each nerve cell body plus its satellite cell sheath constitutes a discrete unit (for more details see Pannese 1981, 1994). Furthermore, contrary to the situation in most regions of the nervous system, each glial (= satellite) cell is associated with one neuron only. This organization together with the fairly regular shape of nerve cell bodies and their satellite cell sheaths renders sensory ganglia particularly suitable for studying the quantitative relations between glial and nervous tissue at the level of the individual neuron. Light microscope studies have shown that in spinal ganglia the number of satellite cells associated with a nerve cell body increases with increasing the volume of the latter (Pannese 1960, 1964; Humbertson et al. 1969; Ledda et al. 2004).

Electron microscope studies have shown that the volume of the satellite cell sheath increases with increasing the volume of the nerve cell body (Pannese et al. 1972, 1975).

The above studies were carried out in adult animals and little is known of the quantitative relations between glial and nervous tissue of sensory ganglia in other periods of life. As far as we are aware, only Pannese et al. (1996, 1997a) have been concerned with this topic having investigated spinal ganglia in young and old rabbits. To determine whether the quantitative relations between glial and nervous tissue in spinal ganglia remain constant throughout life we have carried out new research examining animals in four age groups ranging from young to extremely advanced age.

Materials and methods

The present study was carried out on rabbits (*Oryctolagus cuniculus*) of both sexes. Rabbits aged 1 year (three animals, 3.4–3.5 kg body weight), 3.6 years (three animals, 3.6–3.8 kg body weight), 6.7 years (three animals, 4.0–4.2 kg body weight) and 8.8 years (three animals, 4.2–4.5 kg body weight) were used. The rabbits were cared for according to the European Community Council Directive (86/609/EEC) on the use of laboratory animals. The dates of birth of all animals were documented; all had been raised by a specialist rabbit breeder with particular attention to hygiene and regular veterinary inspections and had been fed an unrestricted diet. Because the mean life span of the normal healthy *Oryctolagus* is approximately 5.6 years (Harkness and Wagner 1983) and the maximal life span is approximately 8 years (Weisbroth et al. 1974), the 1-year-old rabbits were young, the 3.6-year-old rabbits were adult, the 6.7-year-old rabbits were old and the 8.8-year-old animals were very old.

The animals were perfused transcardially with a solution containing 2% formaldehyde and 2% glutaraldehyde in 0.1 M sodium cacodylate buffer (pH 7.3) under deep anaesthesia with Nembutal i.p. (80 mg/kg). After fixation for about 3 h, the thoracic spinal ganglia were removed, washed in cacodylate buffer (0.2 M, pH 7.3) for 2 h and then postfixed on ice for 1.5 h in 2% OsO_4, buffered with 0.1 M sodium cacodylate. The specimens were washed in distilled water, stained with 2% aqueous uranyl acetate, dehydrated in alcohol and embedded in Epon-Araldite resin.

As even during optimum fixation, dehydration and embedding there is some degree of cellular swelling or shrinkage, to study the volume ratio between the satellite cell sheaths and the related nerve cell bodies a basic assumption was that any artifactual volume changes were about the same for both in all age groups. This assumption seems justified by the fact that all the ganglia used for the study satisfied the following conditions: (a) the interval between the nerve cell body and the enveloping satellite cell sheath was of uniform width; (b) the clefts between the satellite cells were of constant width; (c) neither nerve cell bodies nor perineuronal satellite cells showed signs of swelling or shrinkage; (d) neither empty areas nor clumping were observed in the connective tissue surrounding the satellite cell sheaths. Overall, 96 ganglia (8 for each animal) were used for this study.

The volumes of the satellite cell sheath and related nerve cell body were determined by the circle-fitting method specifically devised to estimate the sizes of these structures (see Pannese et al. 1972 for a detailed description). This method provides reliable results if the following conditions are observed: (1) the sections used pass near the centre of the nerve cell body, and (2) the nerve cell bodies are indeed approximately spherical. To verify that this was the case, we carried out a preliminary light microscope study on serial semithin sections (1 μm thick). This study revealed that there was only one nucleolus in each nerve cell body and this was centrally located in 90% of the nerve cell bodies examined; therefore the nucleolus could be used to recognize equatorial sections. Relatively few profiles of the nerve cell bodies containing the nucleolus were truly circular, most being oval. However, the profiles of the nerve cell bodies whose least diameter was 75% or more of the maximum diameter could be considered nearly circular. We found that 70% of the nerve cell body profiles were circular or approximately so. On the bases of these observations and of the theoretical analysis of Hennig (1967) we felt justified in using this method to determine the volume of the satellite cell sheaths and related nerve cell bodies in rabbit spinal ganglia. The reliability of the circle-fitting method was previously assessed by comparing the results obtained in rabbit spinal ganglia by means of this method with those obtained by one of the new generation procedures (the nucleator method, Gundersen 1988) and with those obtained by serial sectioning. The latter method is the most direct and accurate procedure presently available for estimating cell size. The comparison (Pannese et al. 1997b) showed that: (1) the results obtained by the circle-fitting method are closely similar to those determined by the nucleator procedure; (2) the results obtained by the above two methods deviated by less than 2% from those obtained by serial sectioning.

For each ganglion, an isotropic uniform random (IUR) thin section was obtained following the orientator procedure (Mattfeldt et al. 1990). Thin sections parallel to the IUR section, 50 μm apart, were then cut. These sections were examined under the electron microscope. All units (of whatever size) in which the nucleolus of the nerve cell body was evident, were photographed. Photographs were taken at an initial magnification of 2,500×; the negatives were enlarged 4× to give prints with a final magnification of 10,000×. In total 190 units from young rabbits, 156 units from adults, 195 units from old rabbits and 155 units from very old rabbits were photographed using the same electron microscope. With the aid of a digitising tablet connected to a computer, the profile area of the nerve

cell body and that of its associated satellite cell sheath, nuclei excluded, were evaluated in each unit. From the values obtained, the volumes of each nerve cell body and its satellite cell sheath were calculated. The satellite cell nuclei were excluded in order to avoid overestimation of the volumes of the satellite cell sheaths which presented one or more nuclei in the photographed sections. Finally, for each unit the volume ratio between the satellite cell sheath and the related nerve cell body was evaluated.

The values obtained for the three rabbits in each age group were compared by one-way ANOVA to establish whether they differed significantly. Subsequently, the values obtained for each age group were compared by one-way ANOVA. When ANOVA revealed significant differences, the post hoc Tukey test for multiple comparisons was used to identify differences between individual age groups. Values were expressed as means ± SEM. Both for ANOVA and post hoc Tukey test, differences were considered significant for P values < 0.05. All data analyses were carried out using SPSS 11.0 software.

Results

The general organization of the spinal ganglia and in particular the morphological relations between the nerve cell bodies and satellite cell sheaths did not change with advancing age (Figs. 1, 2).

The quantitative results obtained for each animal are shown in Table 1; the mean results for each of the four age groups are shown in Table 2.

The mean volume of the nerve cell bodies increased progressively with age (Fig. 3a). This volume was ~ 64% larger in the very old animals than in young animals.

As shown in Fig. 3b, the mean volume of the satellite cell sheaths did not differ significantly in young, adult and old animals, but was significantly smaller in very old animals. This volume was ~ 54% lower in the very old animals than in young animals.

The mean value of the volume ratio between the satellite cell sheaths and the related nerve cell bodies

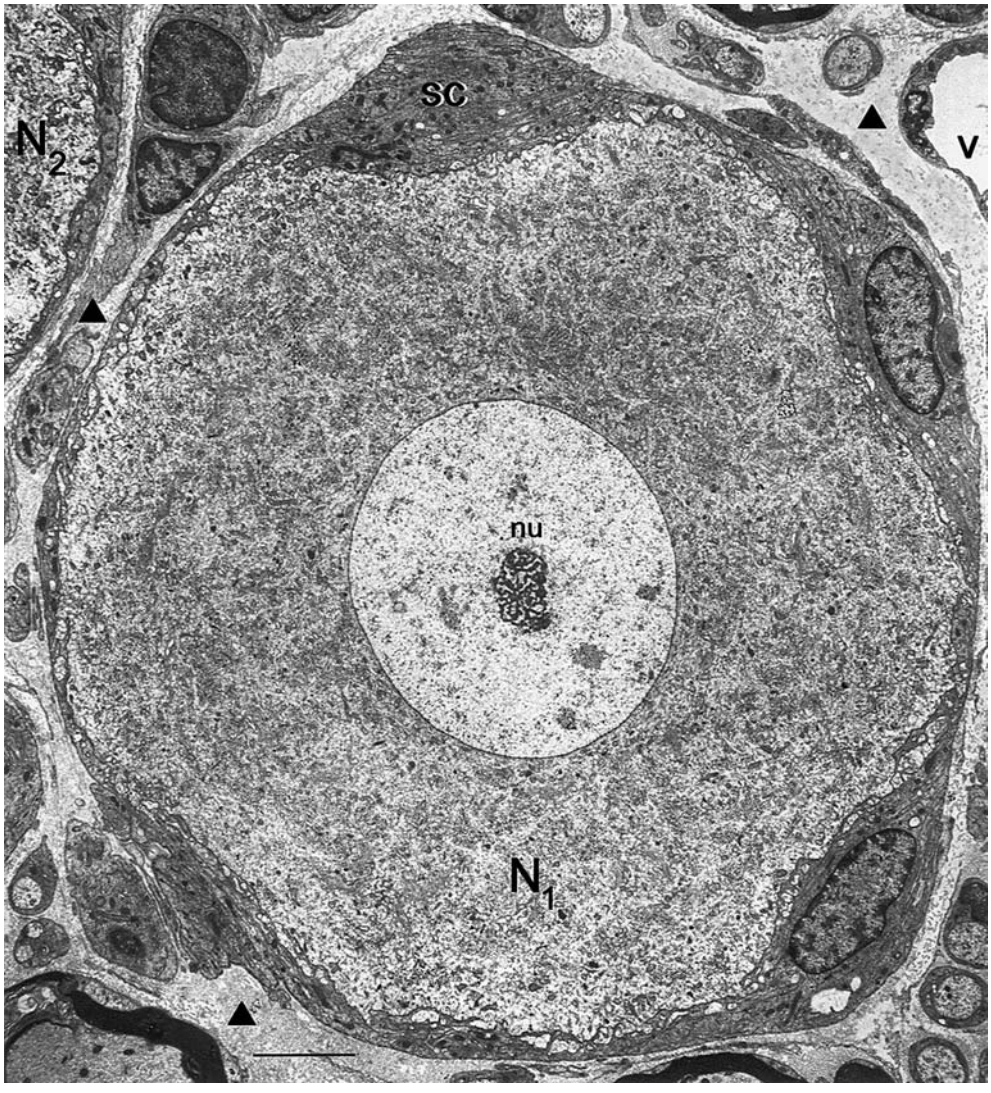

Fig. 1 Electron micrograph showing a unit consisting of a nerve cell body (N_1) and its enveloping satellite cell sheath (*sc*). The section passes through the nucleolus (*nu*) of the nerve cell body. A portion of another unit (N_2) can be seen in the upper left corner of the figure. The satellite cell sheaths of these two units are completely separated by intervening connective tissue (*filled triangle*). *v* Blood vessel. Spinal ganglion of a rabbit aged 1 year. *Scale bar* 5 μm

did not differ significantly in young and adult rabbits, but was significantly smaller in old and very old animals (Fig. 3c). The ratio was particularly low in the very old animals, being ~ 76% lower than in young animals.

The relations between the volume of the satellite cell sheath and the volume of the related nerve cell body in each unit are shown in Fig. 4 for young, adult and old animals, and in Fig. 5a for very old animals. The regression lines are

Young animals: Vs = 0.1819Vn + 371.19
Adult animals: Vs = 0.1705Vn + 26.12
Old animals: Vs = 0.1149Vn + 733.63
Very old animals: Vs = 0.0419Vn + 508.23

The data presented in these figures show that in all age groups the volume of the perineuronal satellite cell sheath is linearly related to the volume of the nerve cell body.

The linear regression lines for the four age groups are presented together in Fig. 5b. It can be seen that, for a given nerve cell body volume, the volume of the satellite cell sheath is in all cases much smaller in the very old animals than in young, adult and old animals.

Discussion

We found that the mean volume of the nerve cell bodies increased progressively with advancing age. Studies on neurons innervating the periphery have revealed that the volume of the nerve cell body correlates with the size of its peripheral field of innervation (Levi 1906, 1908; Hahn 1912; Terni 1914; Donaldson and Nagasaka 1918; Netto 1951). In turn, the size of the peripheral field innervated by a given type of neuron usually correlates with the body size of the animal. The body size of the animals we studied increased with age, providing an explanation for the progressive increase in the mean volume of the body of the neurons.

We also found that the mean volume of the satellite cell sheaths was significantly smaller in the very old animals. This reduction in volume could be a physiological or a

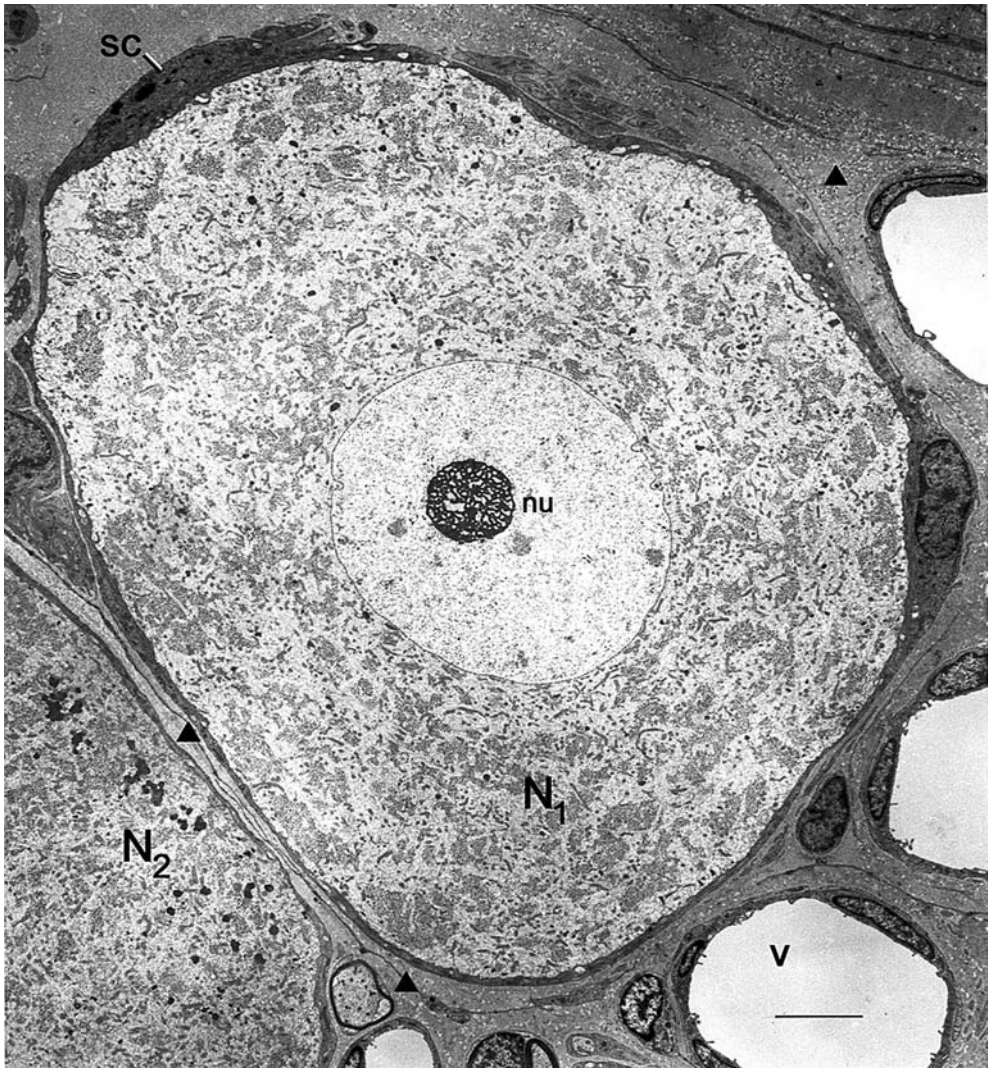

Fig. 2 Electron micrograph showing a unit consisting of a nerve cell body (N_1) and its enveloping satellite cell sheath (*sc*). The section passes through the nucleolus (*nu*) of the nerve cell body. A portion of another unit (N_2) can be seen in the lower left corner of the figure. The satellite cell sheaths of these two units are completely separated by intervening connective tissue (*filled triangle*). *v* Blood vessel. Spinal ganglion of a rabbit aged 8.8 years. *Scale bar* 5 μm

Table 1 Volumes of the satellite cell sheaths and of the nerve cell bodies: mean values for each rabbit

Rabbit	Age (years)	Number of ganglia examined	Total number of units[a] examined	Mean volume of the satellite cell sheaths (μm^3)	Mean volume of the nerve cell bodies (μm^3)	Mean volume ratio between satellite cell sheaths and related nerve cell bodies
1	1	8	64	4,166	15,668	0.221
2	1	8	65	3,864	15,936	0.211
3	1	8	61	3,795	15,879	0.249
4	3.6	8	49	3,693	20,785	0.228
5	3.6	8	54	3,868	20,658	0.220
6	3.6	8	53	3,892	19,671	0.230
7	6.7	8	71	3,382	23,554	0.154
8	6.7	8	58	3,594	23,740	0.171
9	6.7	8	66	3,482	23,805	0.176
10	8.8	8	44	1,545	27,682	0.056
11	8.8	8	55	1,674	25,395	0.053
12	8.8	8	56	1,660	25,632	0.053

[a]Each unit consists of a nerve cell body and its own satellite cell sheath

Table 2 Volumes of the satellite cell sheaths and of the nerve cell bodies: mean values for each age group

Age group	Age (years)	Number of ganglia examined	Total number of units[o] examined	Mean volume of the satellite cell sheaths (μm^3)	Mean volume of the nerve cell bodies (μm^3)	Mean volume ratio between satellite cell sheaths and related nerve cell bodies
Young	1	24	190	3,940[a]	15,829[e]	0.227[i]
Adult	3.6	24	156	3,801[b]	20,480[f]	0.226[l]
Old	6.7	24	195	3,479[c]	23,695[g]	0.167[m]
Very old	8.8	24	155	1,640[d]	26,000[h]	0.054[n]

There are no significant differences between [a] and [b], between [b] and [c] and between [a] and [c], whereas the differences between [c] and [d], between [b] and [d] and between [a] and [d] are significant ($P < 0.05$)
There are no significant differences between [e] and [f], between [f] and [g], between [g] and [h] and between [f] and [h], whereas the differences between [e] and [g] and between [e] and [h] are significant ($P < 0.05$)
There is no significant difference between [i] and [l], whereas the differences between [l] and [m], between [m] and [n], between [i] and [m], between [l] and [n] and between [i] and [n] are significant ($P < 0.05$)
[o]Each unit consists of a nerve cell body and its own satellite cell sheath

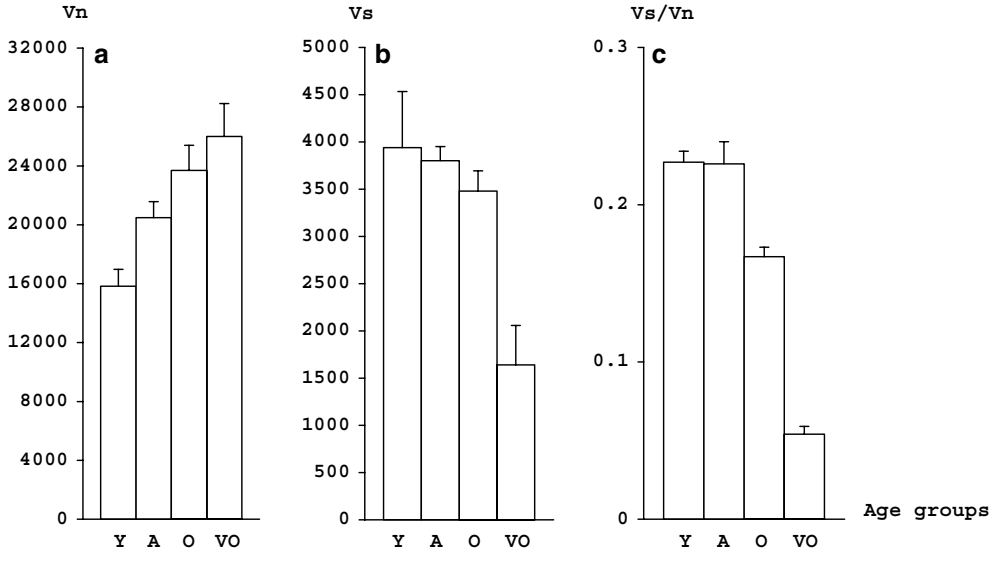

Fig. 3 **a** Mean volumes of nerve cell bodies (Vn), **b** mean volumes of satellite cell sheaths (Vs), **c** mean values of the volume ratio between the satellite cell sheaths and the related nerve cell bodies (Vs/Vn) in spinal ganglia of rabbits aged 1 year (young, *Y*), 3.6 years (adult, *A*), 6.7 years (old, *O*) and 8.8 years (very old, *VO*). *Vertical bars* indicate the standard errors of the mean

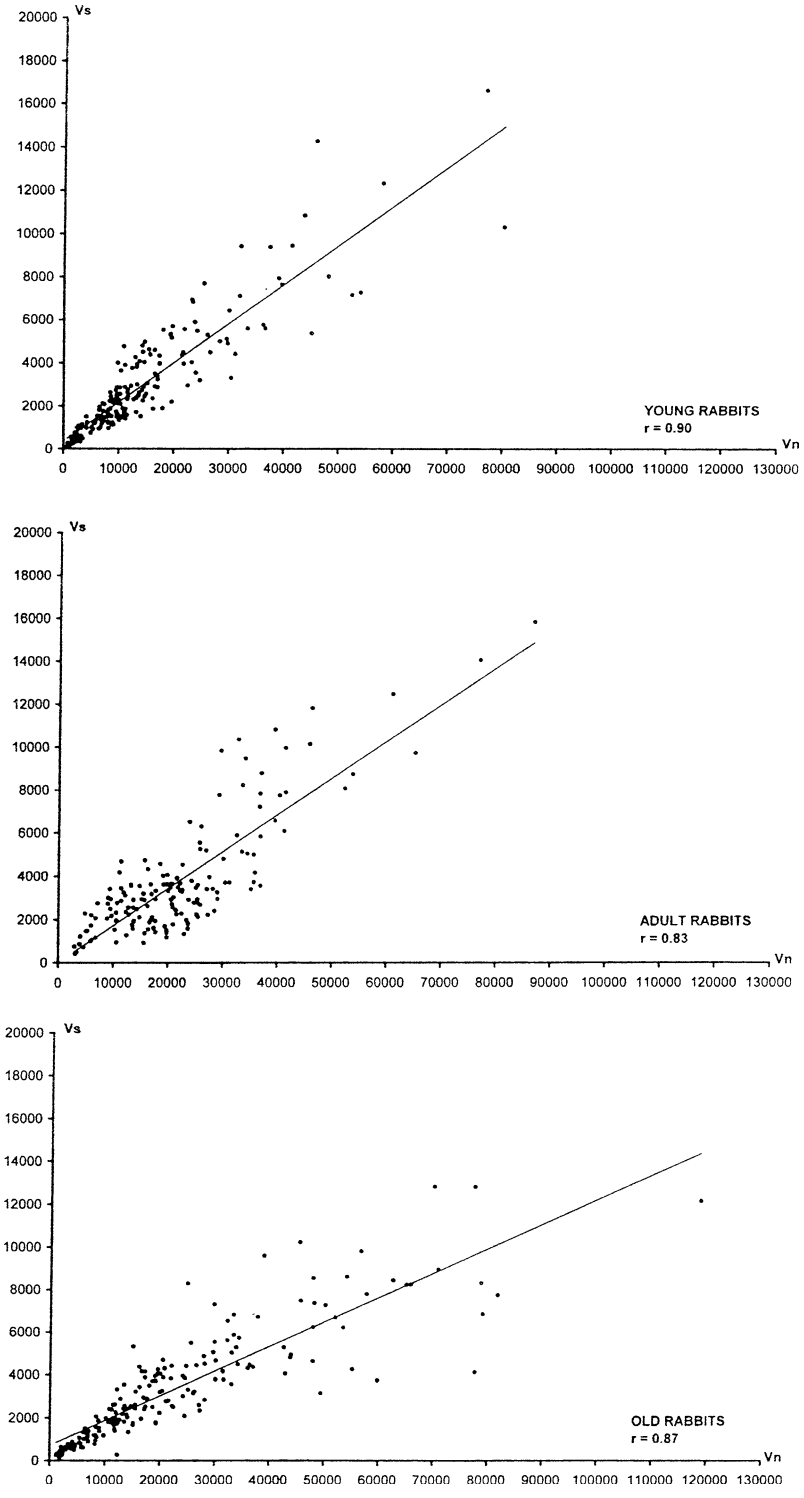

Fig. 4 Relations between the volume of the satellite cell sheath (Vs, ordinate) and the volume of the nerve cell body (Vn, abscissa) in young, adult and old rabbits. Each *dot* represents the value obtained from a single unit. The regression lines for these values are also shown

pathological process. To address this issue we note firstly that, in spite of a careful search, none of the structural features that usually accompany pathological processes (nerve cell degeneration, myelin fragmentation, evidence of satellite or Schwann cell proliferation, presence of residual nodules, and presence of leucocytes or macrophages) was found in the ganglia we examined. Furthermore, the reduction in the mean volume of the satellite cell sheaths was of the same amount in all three very old animals. These facts make it extremely unlikely that the decrease in the mean volume of the satellite cell sheath is the result of a pathological process.

The mean value of the volume ratio between the satellite cell sheaths and the related nerve cell bodies was much lower in very old animals. It is difficult to compare the changes in the volume ratio between glial and ner-

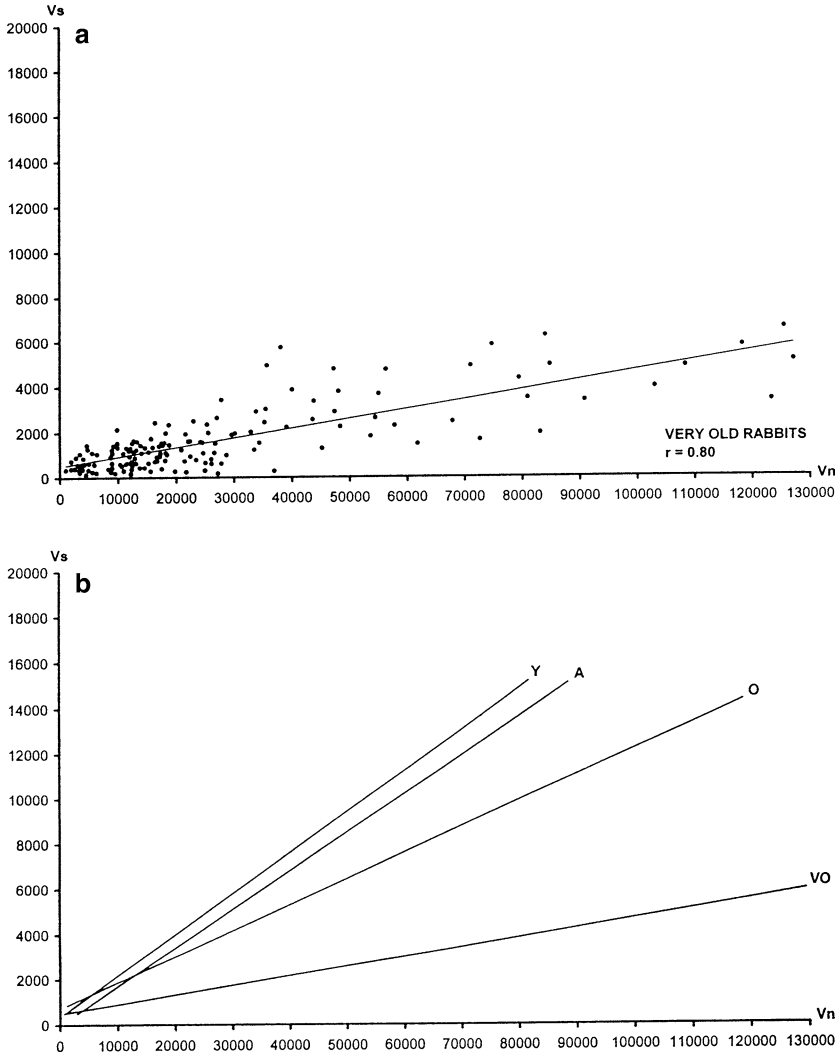

Fig. 5 **a** Relation between the volume of the satellite cell sheath (Vs, ordinate) and the volume of the nerve cell body (Vn, abscissa) in very old rabbits. Each *dot* represents the value obtained from a single unit. The regression line for these values is also shown, **b** the regression lines of Figs. 4 and **a** are shown together in order to compare the data for young (*Y*), adult (*A*), old (*O*) and very old (*VO*) animals

vous tissue we observed with those found in other regions of the nervous system, mainly because the published results are discordant. With regard to the peripheral nervous system, Carney and Lyon (1990) found no age-related changes in the volume fraction of perisomatic satellite cell cytoplasm in the rat vestibular ganglion. In the grey matter of the central nervous system, some authors have reported an increase in the number ratio of glial cells to neurons with age (Brizzee et al. 1968, 1976; Brizzee 1975; Terry et al. 1987; Sturrock 1989c; Peters 1991), others have reported that the volume fraction occupied by glial cells increased with age (Geinisman et al. 1978). By contrast, other authors found that the number of glial cells did not change with age (Vaughan and Peters 1974; Tomlinson and Henderson 1976; Diamond et al. 1977; Diamond and Connor 1981; Sturrock 1988, 1989a, b; Peters et al. 1991). The discrepancies between these results may be due to the different species studied, to the different age studied or to the variety of quantification methods employed. Furthermore, most studies on the grey matter of the central nervous system used light microscope preparations in which it is often difficult to distinguish small neuronal nuclei from glial nuclei. At present, therefore, it is not possible to determine whether the differences between the results obtained in the various regions of the nervous system are due to the above factors or to the various regions of the nervous system being differentially affected by the aging process.

Our analysis also showed that in each age group the volume of the perineuronal satellite cell sheath is linearly related to the volume of the nerve cell body. This result suggests that in rabbit spinal ganglia the quantitative relations between glial and nervous tissue are tightly controlled throughout the life of the animal. This conclusion is in agreement with the results obtained studying adult geckos, lizards and cats (Pannese et al. 1972, 1975). Only hypotheses can be advanced at present regarding the mechanisms by which this tight control is achieved. For example, it is possible that ganglionic neurons release signals influencing and controlling the volume of their associated glial tissue. In the extremely advanced age, the reduced increase (compared to younger ages) in the volume of the satellite cell sheath with increase in the volume

of the nerve cell body could be due to a reduced release by neurons of the signals to the satellite cells. Alternatively, glial tissue may have reduced ability to respond to signals in extremely advanced age.

That neuronal metabolism reduces in old age has been documented by various studies (e.g. see Meier-Ruge et al. 1976; Mann et al. 1978; van den Bosch de Aguilar and Vanneste 1980; Finch and Morgan 1990). There is evidence suggesting that satellite cells of sensory ganglia perform the following roles (for more details see Pannese 1981, 1994; Martinelli et al. 2005; Thippeswamy et al. 2005): (1) metabolic support of ganglionic neurons; (2) spatial buffering of ions in the perineuronal microenvironment of the ganglion; (3) control over the traffic of materials to and from the ganglionic neurons; (4) neuroprotection. It is likely that the marked reduction in the volume of the perineuronal satellite cell sheath in very old animals is accompanied by a reduction in these functions with negative consequences for neuronal metabolism.

Finally, it can be noted that the results of this study may constitute a useful reference point for estimating the quantitative changes in the glial tissue, the nervous tissue and their ratios which may occur under experimental and pathological conditions.

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