Role of progesterone in peripheral nerve repair

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Progesterone is synthesized in the peripheral nervous system in glial cells. The functions of progesterone are indicated by the findings that it stimulates neurite outgrowth from dorsal root ganglia sensory neurones in explant cultures, accelerates the maturation of the regenerating axons in cryolesioned sciatic nerve, and enhances the remyelination of regenerated nerve fibres. The formation of myelin sheaths around axons is a sexually dimorphic process, as the sheaths are thicker in female than in male regenerating nerves. The progesterone-induced myelination is probably mediated by progesterone receptors, as it is impaired by mifepristone (RU486), a progesterone antagonist. The stimulation of neurite growth in the peripheral nervous system may be mediated by a progesterone metabolite, 5α-tetrahydroprogesterone, through GABA_A receptors.

Progesterone is conventionally thought of as a female gonadal steroid hormone synthesized in the ovary. Its classical target tissues are the uterus, mammary glands and brain. There is now abundant evidence that progesterone is more than just a female sex hormone. It is also a neurosteroid synthesized in the central and peripheral nervous systems, where its non-reproductive functions are only beginning to be understood (Koenig et al., 1995; Schumacher et al., 1996; Baulieu, 1997; Jung-Testas et al., 1999). This review summarizes the evidence that progesterone has neurotrophic roles in the peripheral nervous system (PNS), that it activates the growth and maturation of axons and stimulates the repair and replacement of myelin sheaths in regenerating nerve fibres. Progesterone, as has been suggested for androgens, may be a ‘potential therapeutic agent in enhancing the reparative response of neurones to injury’ (Jones, 1993).

The possibility that steroid hormones are also involved in nerve repair was first indicated by the finding that inhibition of the synthesis of cholesterol, the precursor of steroid hormones, inhibits neurite outgrowth in retinal explants (Heacock et al., 1984), delays myelination in the sciatic nerve of postnatal mice (Rawlins and Uzman, 1970) and that the treatment of crushed rabbit nerves with steroid hormones accelerates muscle re-innervation (Vita et al., 1983). This review reports studies of previously unrecognized neurotrophic roles of progesterone in the peripheral nervous system: (1) in activating the growth of axons and their maturation, and (2) in stimulating the repair and replacement of the myelin sheaths in regenerating nerve fibres.

In vitro, [3H]pregnenolone is converted to [3H]progesterone in the PNS. First, in vitro, dorsal root (DRG) and sympathetic ganglia explants or dissociated cells, incubated in the presence of trophic factors, are used to assay ‘neurite-promoting activity’. Second, in vivo, the influence of neurotrophins and neurotrophic factors, including progesterone, is analysed mainly in the lesioned peripheral nerves of adult animals. After a nerve is wounded (cut, crushed or locally frozen), the distal part of the axons degenerate rapidly (Fig. 1).

Simultaneously, the myelin sheaths break down within the Schwann cells, which are then phagocytosed by the macrophages that invade the degenerating nerve. New Schwann cells migrate to the lesioned zone and multiply rapidly inside the basal lamina tubes. The basal lamina tubes are maintained after freezing, as they are after crushing of the nerve but are not maintained after its section (Mira, 1979, 1988). In the distal stump, the unfrozen Schwann cells divide actively while degenerating axons and myelin sheaths are removed by macrophages. These events are referred to as ‘Wallerian degeneration’ (Fig. 1). Axonal sprouts, which result from the branching of the proximal unsevered axons, appear rapidly in the frozen zone, and are enclosed in the basal lamina tubes at the external surface of the degenerating Schwann cells. The axonal sprouts surrounded by new Schwann cells constitute the ‘regenerating axonal bundles’. Next, the diameter of one or two sprouts become larger (approximately 2 μm). These sprouts segregate from the bundles and form separate ‘single axons’, surrounded by Schwann cells in the usual 1:1 relationship. During this process, myelination is initiated, either inside the bundles or in the separated ‘single axons’ (Fig. 1). This sequence of events, which mimics the developmental process, may be called ‘axonal maturation’ (Scherer and Salzer, 1996).

The first evidence that progesterone is synthesized in the PNS comes from the finding that pregnenolone, the precursor of progesterone, is present in large quantities in the sciatic nerves in rats (Akwa et al, 1993) and humans (Morfin et al., 1992). In mice, both pregnenolone and progesterone accumulate in the peripheral nerve (Koenig et al., 1995).

**In vitro**, [3H]pregnenolone is converted to [3H]progesterone in Schwann cells harvested from rat embryonic dorsal root ganglia.
explants (Koenig et al., 1995). In DRG cultures, both Schwann cells (satellite cells) and neurones contain 3β-hydroxysteroid dehydrogenase (3β-HSD), which converts pregnenolone to progesterone (Guennoun et al., 1997). Neurones of DRG incubated in [3H]pregnenolone produce significant amounts of [3H]progesterone and [3H]5α-dihydroprogesterone. In similar conditions, Schwann cells isolated from DRG produce radioactive progesterone, 5α-dihydroprogesterone and 3α,5α-tetrahydroprogesterone (Guennoun et al., 1997). Rat sciatric nerve fragments were shown to contain 5α-reductase, the enzyme that converts progesterone to 5α-dihydroprogesterone (Celotti et al., 1992).

**Effect of progesterone on axonal growth and maturation in the peripheral nervous system**

*Studies in vitro*

The addition of progesterone to cultured DRG from 16-day-old rat embryos results in the growth of a halo of neurites surrounding the explants and increased myelination (Fig. 2).

Both the surface area and the apparent density of the neurites increase (compare Fig. 2 a with b). The surface area of the growing neurite increases by 60–130% after 3 days of progesterone treatment (Fig. 2e). Progesterone may stimulate neurite growth through progesterone receptors present in DRG (Jung-Testas et al., 1999). Low amounts of progesterone receptor have been detected in rat peripheral nerves (Jung-Testas et al., 1996) but not in mouse sciatic nerves (I. Jung-Testas and H. Koenig, unpublished). The addition of RU486 to control cultures of DRG containing no progesterone did not decrease the growth of neurites (W. H. Gong and H. Koenig, unpublished). Therefore, it is uncertain whether the endogenous progesterone produced within DRG plays a role in neurite outgrowth. The addition of 5α-dihydroprogesterone and 3α,5α-tetrahydroprogesterone to cultured DRG also increased neurite outgrowth (W. H. Gong and H. Koenig, unpublished). Since 3α,5α-tetrahydroprogesterone does not bind to nuclear progesterone receptors, but interacts with gamma-aminobutyric acid (GABA)A receptors (Celotti et al., 1992; Melcangi et al., 1999), it is possible that 3α,5α-tetrahydroprogesterone stimulates neurite outgrowth via this receptor subtype. This view is supported by the finding that the stimulation of neurite outgrowth from DRG explants by 3α,5α-tetrahydroprogesterone, 5α-dihydroprogesterone and progesterone is inhibited by the GABA_A antagonists: bicuculline and picrotoxin (W. H. Gong and H. Koenig, unpublished). Furthermore, progesterone-induced neurite outgrowth from DRG explants is blocked by finasteride, an inhibitor of 5α-reductase. Therefore, it appears that neurite outgrowth is stimulated by 5α-dihydroprogesterone or 3α,5α-tetrahydroprogesterone, or both, rather than by progesterone (W. H. Gong and H. Koenig, unpublished).

Sensory neurones in DRG are heterogeneous cells with different cell body sizes, functions and receptors. Small cells mediate pain and temperature, express trk A receptors and are sensitive to nerve growth factor (NGF). Medium-size cells mediate pressure sensations, express trk B receptors and respond to brain-derived neurotrophic factor (BDNF) and neurotrophin 4–5. Large cells mediate proprioception, express trk C and respond to neurotrophin 3. The question arises if all or only subpopulations of DRG neurones are progesterone- and 3α,5α-tetrahydroprogesterone-sensitive and respond to steroids.

![Fig. 1](https://example.com/figure1.png)

**Fig. 1.** The processes involved in the regeneration of peripheral nerve fibres after damage by local freezing (cryolesion). (a) An unlesioned nerve. The myelinated Schwann cells are separated by nodes of Ranvier, but the basal lamina is continuous up to the motor end plate. Schwann cells are responsible for myelin formation. (b) A few days after the nerve is damaged, the Schwann cells, myelin sheaths and axons degenerate distally to the site of injury. Macrophages invade the lesioned area and the distal part of the nerve to phagocytose the degenerating debris. (c) New Schwann cells appear in the cryolesioned zone, and multiply in this zone and in the distal stump of the nerve. The proximal unfrozen regenerating axons end with growth cones and axonal sprouts issued from these axons, which grow inside the basal lamina tubes. (d) After approximately 1 week, the regenerated axons are re-ensheathed and remyelinated by Schwann cells in the cryolesioned nerve. The target muscle cells are also reinnervated.
Studies in vivo

Studies in vivo on the effects of progesterone on axonal maturation have been carried out in the sciatic nerve from the mutant Trembler mouse (Koenig et al., 1991). The Trembler has an autosomal dominant mutation of the myelin protein PMP22 (Suter et al., 1992). Mutant mice develop tremor, quadripareisis and transient seizures during early development (Falconer,
Fig. 3. Effect of progesterone on the maturation of regenerating axons in the hypomyelinated peripheral nerve of a Trembler male mutant mouse. Electron micrographs from a series of ultrathin transverse sections through the sciatic nerve. The sciatic nerves were cryolesioned by repeated freezing (6–8 cycles of freezing–thawing) with a 2 mm copper cryode previously frozen in liquid nitrogen. Progesterone (100 mg kg⁻¹), dissolved in sesame oil, was immediately applied onto the nerves. After 2–4 further applications, the nerves were dissected out and fixed for electron microscopy after 7, 12 and 20 days, respectively. (a) Control sham-operated nerve, 7 days after cryolesion and application of the vehicle (sesame oil). Most regenerated axons (ax) and the sprouts (s) they give rise to are grouped in dark Schwann cells. This structure forms the axonal bundles (thick arrows), which are surrounded by multilayered basal laminae, which characterize the Trembler peripheral nerve fibre (thin arrows). There were no myelinated axons in the nerves examined. (b) Progesterone-treated nerve, 7 days after cryolesion. The number of single axons in a 1:1 relationship with Schwann cells increases as a consequence of the retraction of the sprouts. Some axons (ma) are already surrounded by a thin myelin sheath (arrowhead). (c) Progesterone-treated nerve, 12 days after cryolesion. The number of axonal bundles is markedly reduced, whereas myelination is increased. (d–e) Sciatic nerves, 20 days after cryolesion: (d) control (non-treated) nerve; (e) progesterone-treated nerve. The mean thickness of Trembler regenerated myelin sheaths is approximately 15% lower in control nerves than in progesterone-treated nerves.
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1951). The mutation produces severe hypomyelination and de-myelination of the peripheral nerve fibres. The number of Schwann cells in peripheral nerve fibres is 8–10 times higher than in normal mice. Each Schwann cell is surrounded by multi-layered basal laminae (Ayers and Anderson, 1973; Koenig et al., 1991; Do Thi et al., 1993; Fig. 3a–d). The Trembler mouse has two features that make it useful for experimentation. First, 20% of the sciatic nerve axons only are thinly myelinated in cross-sections of the nerve. These axons degenerate rapidly, within 24–48 h in the areas subjected to cryolesioning (Koenig et al., 1991). Thus, the regenerating axonal sprouts and subsequent myelination are easy to see. The rate of axonal regeneration after cryolesion of

Fig. 4. Effect of progesterone applications to cryolesioned sciatic nerve on axonal regeneration and myelination in Trembler mutant mice. The sciatic nerve was exposed and a portion subjected to local freezing. Progesterone and control vehicle (sesame oil) were then applied several times for 7, 12 and 20 days. Measurements were made directly on the electron microscope screen or on the electron micrographs. The Trembler mice used in these experiments were heterozygous adult mice (homozygous mutants do not survive in our strain). (a) Number of axonal bundles present after 7 and 12 days after cryolesion in progesterone-treated (■, n = 8) and sesame oil-treated (control; □, n = 5) regenerating nerves. (b) Number of axonal sprouts per axon bundle. (c) Number of myelinated fibres. (d) Number of myelin lamellae. *** P < 0.001; ** P < 0.01; * P < 0.05; ++ P > 0.01 (ANOVA Student’s t test). (a–d) The results were obtained in the same groups of animals (7, 12 and 20 day old mice.)
the sciatic nerve in *Trembler* nerves is double that in normal mice (Ferzaz et al., 1989). Second, cryolesioned axons in *Trembler* mice have robust regenerative capabilities (Ferzaz et al., 1989). Axonal sprouts first appear 6–12 h after cryolesion and remain enclosed in the Schwann cell sheath, surrounded by the basal lamina tube, for more than 12 days. Local application of exogenous progesterone to the cryolesioned sciatic nerve of the *Trembler* mouse accelerates the process of regeneration. The number of clusters of regenerating fibres (Fig. 4a) and the number of axons per cluster decreases in the bundles of treated nerves (Fig. 4b). Twelve days after cryolesion, the axonal bundles and the number of their sprouts are still lower in progesterone-treated nerves than in the untreated control nerves (Fig. 4a,b). As a consequence of the loss of redundant sprouts and bundles, the number of individualized ‘single axons’ doubles in 7 days in progesterone-treated nerves (Fig. 3c).

It is not known whether the progesterone produced in the *Trembler* sciatic nerve is involved in axonal growth and maturation, since the concentrations of progesterone and its precursor, pregnenolone, are very low (Koenig et al., 1995). Axonal maturation promoted by exogenous progesterone is probably the result of an acceleration of the natural regenerative processes. It is not known whether 5α-dihydroprogesterone and 3α,5α-tetrahydroprogesterone accelerate axonal maturation in vivo. The mechanism by which axonal growth is stimulated by progesterone or its 5α-derivatives probably involves several neuronal genes expressed in neurofilaments, microtubules and in the axolemma. The expression of these genes may be regulated either at transcription or at translation level by progesterone or its 5α-metabolites. The progestagen target cells may be neurones or Schwann cells. In regenerating nerves, Schwann cells synthesize and secrete several neurotrophic factors that contribute to axonal growth (Terenghi, 1999). Progestagens may enhance the synthesis of neurotrophins or other factors that induce an axonal signal for growth. The signal molecule may act either locally on the axonal membrane or the growth cones or be transported in a retrograde direction to the neurone cell bodies to stimulate the genes of proteins associated with and necessary to the growth of the axons (Fig. 5).

Fig. 5. Hypothetical mechanisms explaining the direct stimulatory effect of progesterone on myelination in the Schwann cells of regenerating peripheral nerve fibres. PR: progesterone receptor; DHP: dihydroprogesterone; THP: tetrahydroprogesterone; GABA\(_A\)-R: GABA\(_A\) receptor.

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**Table**

<table>
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<td>Retrograde signal to neurone soma</td>
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<tr>
<td>Myelin initiation</td>
<td>Myelin wrapping</td>
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**Diagram**

- **Axonal growth**
  - **Axonal maturation**
    - **Myelin initiation**
      - **Myelin wrapping**

**Signal to axon** (axon membrane)

**Retrograde signal to neurone soma**

**Gene activity**

**Axonal growth**

**Axonal maturation**

**Neuronal gene activity**

**Signal to axon**

**Retrograde signal to neurone soma**

**Gene activity**

**Axonal growth**

**Axonal maturation**

**Progestagene target cells** may be neurones or Schwann cells. In regenerating nerves, Schwann cells synthesize and secrete several neurotrophic factors that contribute to axonal growth (Terenghi, 1999). Progestagens may enhance the synthesis of neurotrophins or other factors that induce an axonal signal for growth. The signal molecule may act either locally on the axonal membrane or the growth cones or be transported in a retrograde direction to the neurone cell bodies to stimulate the genes of proteins associated with and necessary to the growth of the axons (Fig. 5).
Effects of progesterone on myelination of injured axons in the peripheral nervous system

Myelin originates from the Schwann cell surface membrane, which forms a mesaxon that elongates and wraps spirally around the axon. Further growth leads to a compact sheath composed of concentrically arranged lamellae. The stimulatory effect of progesterone on the remyelination (1) of regenerating sciatic nerves in wild-type male mice, indicating that decreased myelination is not due to the toxicity of trilostane. (d) Nerve from a female ovariectomized mouse 10 days before cryolesion, treated with progesterone after the lesion. The myelin sheaths are thicker than in male mice treated with progesterone. (e) Quantification of the effects of pregnenolone, progesterone, and inhibitors (mifepristone, RU486; trilostane; and trilostane plus progesterone) on thickness of myelin sheaths in male nerves, classified in increments of five lamellae. The inset shows the average width of the myelin sheaths (that is, the number of lamellae). The data are obtained from the same animals as used for data in Fig. 4, and are expressed as percentages of control (baseline). From 300 to 500 myelin sheaths were counted per nerve. Progesterone-treated nerves were surrounded by thicker myelin sheaths than nerves from vehicle-treated mice. The action of progesterone on myelination was inhibited by drugs that inhibit the action of progesterone (modified from Koenig et al., 1995). During the process of peripheral nerve regeneration, the thickness of the myelin sheaths is not related to the diameter of the axons. This absence of relationship is maintained for life in Trembler hypomyelinated mice, both in regenerated and non-operated nerves.
Sexual dimorphism in the effects of progesterone on peripheral nerve remyelination. (a) Thickness of sciatic nerve myelin sheaths (that is, number of lamellae) from intact and gonadectomized male and female mice, processed simultaneously for electron microscopy after cryolesion and local treatment with the vehicle (control) or progesterone. (b) Thickness of sciatic nerve myelin sheaths from ovariectomized females treated with progesterone, an inhibitor of progesterone synthesis (trilostane) or a progesterone receptor blocker (mifepristone, RU486). Six to ten mice were analysed 15 days after they received four local applications of progesterone or progesterone blockers.

A and PMP22; 3α,5α-tetrahydroprogesterone is more potent in this respect than 5α-dihydroprogesterone and progesterone (Melcangi et al., 1998). Therefore, the progesterone synthesized in Schwann cells or the exogenous progesterone synthesized in the sciatic nerve may serve as the parent molecule for several potentially active steroids and steroid derivatives. Exogenous progesterone also enhances the concentrations of 5α- and 3α-pregnane 3β,5α-diol, and 3α,5α-dihydroprogesterone in co-cultures of DRG neurones and Schwann cells (Notterpek et al., 1999) and stimulates the expression of their gene promoters in cultured rat Schwann cells (Desarnaud et al., 1998). These observations imply that progesterone binds to progesterone receptors in the Schwann cell cytoplasm or nucleus, although further investigation is required since progesterone receptor was not detected in mouse sciatic nerves (I. Jung-Testas and H. Koenig, unpublished). Furthermore, in progesterone receptor knock-out adult mice, the myelin sheaths around sciatic nerve axons are the same as in wild-type mice (Jung-Testas et al., 1999). Endogenous progesterone may activate the process of myelination through autocrine-paracrine actions involving a limited number of progesterone receptors (Koenig et al., 1995; Baulieu et al., 1996; Baulieu and Schumacher, 1997). An alternative possibility is that the effect of progesterone on myelination is mediated through GABA_A receptors (Melcangi et al., 1999). Finally, progesterone may increase the transfer of axonally orthograde transported phospholipids from axons to myelin (Droz et al., 1981; Toews et al., 1988). Such a transfer would increase the rate of spiral wrapping of the Schwann cell membrane, which constitutes the myelin lamellae. This interpretation is sustained by two observations. First, remyelination begins 1 week or more after nerve damage, when regenerating axons have already matured. Second, in nerves treated for 7 days during the second week after cryolesion, the thickness of myelin sheaths is similar to that in nerves treated with progesterone for 15 days immediately after the lesion (P. Pelissier and H. Koenig, unpublished). These observations indicate that progesterone is less, or not, effective in stimulating myelination in axons while they are regenerating. It remains to be determined whether progesterone acts directly on Schwann cells or if its myelin-stimulating effect is mediated through an axonal signal. An axonal signal is known to be necessary for the initiation of the myelination process (for review, see Salzer, 1995). The hypothetical mechanisms of the stimulatory effect of progesterone on remyelination in lesioned nerves are shown (Fig. 5).

### Progesterone in sexual dimorphism in peripheral nerve myelination

Sexual dimorphism of reproductive steroid hormones is generally associated with sexual dimorphism in behaviour and reproductive functions. Therefore, it is relevant to ask whether the production of progesterone in peripheral nerves is also sexually dimorphic. In rodents, the progesterone content of the peripheral nerve is higher in females than that found in males. In female mice, the concentrations of endogenous progesterone and pregnenolone differ among groups of nerves, but are higher in male sciatic nerves (M. Schumacher and H. Koenig, unpublished). In female rats, the concentration of progesterone in the sciatic nerves is higher in pro-oestrous (× 5) than it is in oestrous (× 10), as compared with that in males (Pelissier et al., 1996; M. Schumacher, unpublished). These observations prompt several questions. Does the higher progesterone content in female nerves result in a faster rate of formation of myelin in damaged nerve fibres in females than in males? Does the administration of progesterone increase myelination in lesioned nerves in males but not in females? As progesterone

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<tr>
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<tr>
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Fig. 7. Sexual dimorphism in the effects of progesterone on peripheral nerve remyelination. (a) Thickness of sciatic nerve myelin sheaths (that is, number of lamellae) from intact and gonadectomized male and female mice, processed simultaneously for electron microscopy after cryolesion and local treatment with the vehicle (control) or progesterone. (b) Thickness of sciatic nerve myelin sheaths from ovariectomized females treated with progesterone, an inhibitor of progesterone synthesis (trilostane) or a progesterone receptor blocker (mifepristone, RU486). Six to ten mice were analysed 15 days after they received four local applications of progesterone or progesterone blockers.
is mainly synthesized in the gonads, does castration influence the myelination process of damaged peripheral nerve fibres in a different way in males and in females?

In intact female mice, the mean number of myelin lamellae formed around regenerating nerve fibres after cryolesion is significantly higher (> 22%) than in regenerating nerves from intact males (Fig. 7a). A similar difference is observed in ovariectomized females (> 20%) as compared with castrated males (Fig. 7a). In both genders, progesterone treatment enhanced myelin width by approximately 22% and, in gonadectomized animals, by > 11% in males and > 14% in females. These findings indicate that the presence of gonadal hormones in the peripheral nerve and in the peripheral circulation stimulates myelination in damaged nerves. In intact and castrated progesterone-treated animals of both sexes, the increase in mean thickness of myelin is due to the increased number of thick myelin sheaths made up of more than 20 lamellae. This increase of thick regenerated myelin sheaths was identical in intact males and females (> 125%), whereas it was different in gonadectomized males (> 60%) and females (> 38%). However, in both intact and ovariectomized females, the number of thick myelin sheaths is higher than in males (intact and castrated). The faster rate of remyelination in females is probably associated with the high content of progesterone in female nerves (Pelissier et al., 1996) and the higher concentrations of residual progesterone remaining after cryolesion (M. Schumacher and H. Koenig, unpublished). A similar difference is described in the rat hypoglossal nerve (Yu, 1982) and in the male hamster facial nerve, in which the axonal regeneration is 20% slower than in females (Kujawa et al., 1991).

The question of the role of 5α-reduced metabolites of progesterone in remyelination of damaged peripheral nerves remains to be analysed. In these nerves, activities of 5α-reductase (an enzyme involved in the conversion of progesterone to 5α-dihydroprogesterone) are high (Celotti et al., 1992). Furthermore, small quantities of 3α,5α-tetrahydroprogesterone increase the myelin protein Po expression in rat Schwann cell cultures (Melcangi et al., 1998).

Initiation of myelination by progesterone in Trembler mutant mice

In Trembler mice, the treatment of regenerating nerves with progesterone results in the appearance of myelin lamellae at
day 7, after axonal maturation is nearly completed (Figs 3b and 4c). In Trembler cryolesioned untreated (control) nerves, myelin is formed after day 10. Thus, it is likely that the accelerated formation of the myelin sheaths in nerves of Trembler mice induced by progesterone is a consequence of the faster maturation of the lesioned axons. At later time intervals (after 12 and 20 days), the increased number of myelinated fibres (Fig. 4c) and the increased myelin width (Fig. 4d) in progesterone-treated nerves may be the result of an increased rate of myelin synthesis or an increase in the rate at which lamellae wrap around the axons.

Concluding remarks and future perspectives

The dual function of progesterone and its metabolites in the regeneration of PNS nerves is well established. One function of progestagens is to stimulate axonal growth, which entails, sequentially, the maturation of the axons, their covering by Schwann cells, the initiation of myelin formation from mesaxon, and the elongation and spiral wrapping of Schwann cell membranes inside the cytoplasm. A second function of progestagens is to accelerate the myelinating process directly. Several intracellular pathways may be involved in the effects of progesterone or its 5α-metabolites on axonal growth and maturation and on the remyelination processes (Fig. 8).

In fact, nothing is known of the mechanisms involved in progestagen-dependent PNS nerve regeneration. The mechanisms must involve progestagen-dependent functions in both the damaged neurones and their associated Schwann cells, possibly including changes in the gene transcription or protein translation of proteins required for repair of the whole injured system. Progesterone, or its derivatives, may act either directly on the cells responsible for axonal regeneration or contribute to the release of growth or myelin regulatory molecules at the site of peripheral nerve injury. For both axonal growth and myelination, two questions arise: does progesterone act through its receptor or through the GABA_A receptors (Figs 5 and 8); and what are the subsequent signalling pathways? In addition to a study of myelin proteins and steroid enzymes stimulated during nerve regeneration, research is needed on the effect of progesterone on the enzymes involved in lipid synthesis in both axon and Schwann cells. Axon membranes and myelin contain high concentrations of lipids, the synthesis of which may be stimulated by progesterone. Cholesterol transport mechanisms are probably also important, since apolipoprotein E is involved in axonal growth (Handelmann et al., 1992; Nathan et al., 1994; Mahley et al., 1996) and apolipoprotein A–I gene expression is increased in myelinating nerves (LeBlanc et al., 1989). Other cells, such as macrophages and fibroblasts, also secrete trophic substances, which might contribute to PNS nerve regeneration, but to a lesser extent than steroids. If motoneurones and their axons are shown to be sensitive to progesterone or to its 5α-reduced metabolites, better understanding of the molecular control of steroid modulation on axonal growth and myelination is likely to lead to the development of therapies for PNS diseases and spinal cord diseases.

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