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**Novel perspectives for progesterone in hormone replacement therapy, with special reference to the nervous system.**

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The utility and safety of postmenopausal hormone replacement therapy has recently been put into question by large clinical trials. Their outcome has been extensively commented upon, but discussions have mainly been limited to the effects of estrogens. In fact, progestagens are generally only considered with respect to their usefulness in preventing estrogen stimulation of uterine hyperplasia and malignancy. In addition, various risks have been attributed to progestagens and their omission from hormone replacement therapy has been considered, but this may underestimate their potential benefits and therapeutic promises. A major reason for the controversial reputation of progestagens is that they are generally considered as a single class. Moreover, the term progesterone is often used as a generic one for the different types of both natural and synthetic progestagens. This is not appropriate because natural progesterone has properties very distinct from the synthetic progestins. Within the nervous system, the neuroprotective and promyelinating effects of progesterone are promising, not only for preventing but also for reversing age-dependent changes and dysfunctions. There is indeed strong evidence that the aging nervous system remains at least to some extent sensitive to these beneficial effects of progesterone. The actions of progesterone in peripheral target tissues including breast, blood vessels, and bones are less well understood, but there is evidence for the beneficial effects of progesterone. The variety of signaling mechanisms of progesterone offers exciting possibilities for the development of more selective, efficient, and safe progestagens. The recognition that progesterone is synthesized by neurons and glial cells requires a reevaluation of hormonal aging.