flashes",[112] which have been observed at elevated rates under oxidative stress, had been suspected to induce apoptosis *via* breakdown of the mitochondrial membrane potential ($\Delta\Psi_{mt}$). However, it turned out that the duration of the mtPTP opening is decisive and that short permeability transitions are more than phenomena of superoxide release and serve the elimination of unfavourable quantities of Ca^{2+} from the mitochondrial matrix.[11] In astrocytes, melatonin was shown to inhibit a prolonged permeability transition, but still allowed short-term openings of the mtPTP.[113] Autophagy and, in particular, mitophagy have been considered as an alternative to apoptosis, although autophagy can also lead to cell death, whereas it also offers the possibility of survival. Again, beneficial effects of melatonin have been described in allowing cell survival.[114] A critical point of progressing mitophagy concerns peripheral mitochondrial depletion, especially in neurons, where it is associated with changes in the fission/fusion balance and causes impairments in transmitter release. Increases in the number of mtDNA copies, numerical density of mitochondria and total mitochondrial mass by melatonin may be indicative of a counter-action of peripheral depletion, as summarized elsewhere.[11] A further effect by melatonin in favour of mitochondrial protection and cell survival concerns the inhibition of cardiolipin peroxidation.[115–117] This process that is crucial to respirasomal dysfunction, cytochrome C release, and apoptosis induction differs from other lipid peroxidation mechanisms because it is catalysed enzymatically rather than by free radicals, but is also prevented by melatonin.

19.2.3 Immunological Actions and Prevention of Inflammaging

Melatonin is an immune modulator with both pro- and anti-inflammatory properties.[5,11,118] Although the conditions under which anti-inflammatory actions prevail over pro-inflammatory responses are not entirely understood, suppression or prevention of inflammation have been almost unanimously reported in the gerontological context.[11,85] For this reason, the aging-associated decline of melatonin levels is of particular relevance. Although anti-inflammatory actions have been also reported in high-grade inflammation caused by sepsis or endotoxemia,[5,85] mechanistic differences to aging have to be considered, because the age-related changes are rather characterized by a low-grade, often lingering inflammation progression. Therefore, it seems important to analyse the role of melatonin in reducing causes of inflammation initiation as far as they contribute to aging.

Leaving apart infectious causes, inflammation-promoting processes can be elicited by the recruitment of macrophages and, in the central nervous system, microglia. This may be favoured by changes towards an immune risk profile (IRP) in the course of the senescence-associated immune remodelling[85,119,120] and by the senescence-associated secretory phenotype (SASP).[121–123] SASP has become known as a response by DNA-damaged, division-arrested non-immune cells, which release various factors including