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without appropriately considering their relationships to the circadian oscillator system [27].

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Melatonin is usually known as the hormone of the pineal gland, which is, however, only the main source of circulating melatonin, but not the main site of overall synthesis, since quantities in extrapineal sources exceed by orders of magnitude those in the pineal gland [1,17]. From the pineal gland, melatonin is released both into the circulation and, *via* the pineal recess, into the third ventricle of the brain [28-30]. As melatonin is synthesized and released by the pineal gland preferentially at night, the chronobiological information of high melatonin is delivered *via* the circulation primarily to the peripheral tissues. Although melatonin can also cross the blood-brain barrier and is taken up *via* the choroid plexus, the direct release into the third ventricle has been recently judged to be more important with regard to the in uence on the hypothalamic circadian master clock, the Suprachiasmatic Nucleus (SCN) [29,30]. Additional routes of melatonin delivery to the brain are possible *via* the aqueduct of the midbrain into the fourth ventricle, from there *via* the medial foramen of Magendie and the two lateral foramina of Luschka to the subarachnoid space [29]. However, in quantitative terms, highest concentrations are found in the third ventricle, from where the adjacent SCN pair is easily reached [29,30]. Moreover, melatonin is formed in some parts of the central nervous system [1,31]. A recent study demonstrated enhanced melatonin synthesis in response to in ammation in the cerebellum, however, without substantial release to other parts of the brain [32].

In mammals, melatonin is mutually interconnected to the SCN, in terms of being both an output and an input factor of the master clock [33]. e light/dark information that the SCN receives from melanopsin-containing retinal ganglion cells is transmitted *via* a neuronal pathway to the pineal gland, where melatonin synthesis is mainly stimulated by norepinephrine from postganglionic sympathetic bers, with some modulation by other neuronal connections [34]. On the other hand, the SCN receives information from melatonin by virtue of a high density of melatonin receptors present in this place [1]. Melatonin can phase shi circadian rhythms generated in the SCN [1,35], but there is additional evidence that it also in uences semi-autonomous and almost autonomous peripheral and other central oscillators [27,36]. Although the mammalian pineal gland also harbors an endogenous clock [37], this is sensitive to the input by norepinephrine, and melatonin synthesis strongly declines when this input is reduced. erefore, a functional weakening of the SCN, e.g., by reduced light transmission or by neurodegeneration, and likewise by degenerative impairments of the neural transduction pathway to the pineal gland, also lead to a attening of the melatonin rhythm in the pineal gland, in the circulation and, expectably, in the third ventricle [2,27]. In fact, aging is typically associated with functional losses of the circadian system. is concerns the rhythm amplitudes in both the SCN [38] and numerous peripheral clocks [39]. In some oscillators, amplitudes are reduced, in others shi ed and, thus, more poorly coupled, whereas some are only moderately a ected. In other peripheral clocks, overt rhythmicity appears to be completely lost, but can be reactivated by appropriate stimuli [39]. Reductions of nocturnal melatonin levels are typically observed during aging, but also occur in numerous diseases and disorders of di erent etiologies [2,40]. e decrease in pineal and circulating melatonin levels is particularly obvious in neurodegenerative diseases and, in these cases, clearly associated with SCN dysfunction. In AD, melatonin levels are not only reduced, but the remaining small maxima also dysphased and temporally strongly scattered [41]. In post-mortem pineals of AD patients, the melatonin rhythm seemed to be completely lost, whereas this rhythmicity was clearly preserved in age-matched controls [42]. As a consequence, age- or disease-related reductions of melatonin signify the loss of an important orchestrating regulator molecule that displays numerous bene cial actions. ese concern antioxidant, antiexcitatory, anti-in ammatory, and anti brillogenic e ects [1-3,6,27,43-46], in addition to the losses in coordinative functions within the circadian system [1]. With regard to neuroin ammation, the antiexcitatory, mitochondria-protective and activation of microglia suppressing e ects are of particular importance. Moreover, recent ndings concerning an increase of α-secretase activity in cells overexpressing human β-Amyloid Precursor Protein (βAPP) to generate the non-amyloidogenic and neuroprotective fragment sAPPα [47] and the inhibition of the amyloidogenic β- and γ-secretases [48] indicate additional neuroprotective properties. Generally, neuroprotection belongs to the most amply documented actions of melatonin, which have been studied under various conditions and multiply reviewed, e.g., in refs. [1,6,31,43,44,49-53].

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Investigators have mostly regarded the bene cial e ects of melatonin from a non-dynamic point of view, which would, however, be important with regard to its role in the circadian system. Circadian rhythmicity itself contributes to protection against damage by free radicals and mitochondrial malfunction [54]. Nevertheless, melatonin can act both directly on cellular processes that are susceptible to melatonergic signaling and indirectly *via* modulation of circadian oscillators [36]. Changes in the expression of circadian core oscillator components by melatonin have been repeatedly observed [36] and melatonin-de cient mice exhibited attened, almost undetectable variations of such components, contrary to well-pronounced rhythms in melatonin-pro cient strains [55,56]. ese ndings strongly indicate that melatonin represents an amplitude-enhancing regulator in the circadian system [36].

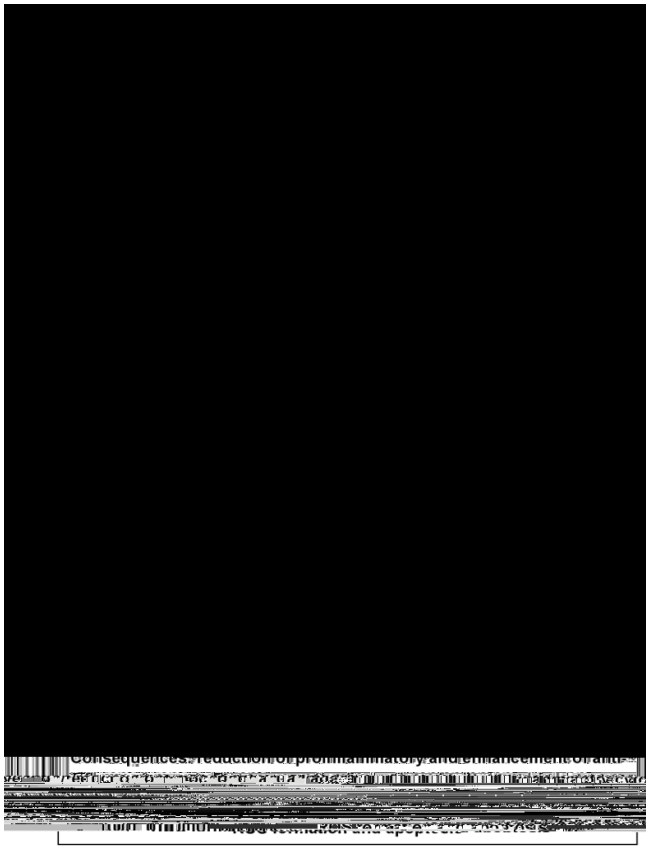
e modes by which melatonin exerts these amplitude-enhancing e ects on oscillators has remained for quite some time rather unclear. Although one of the melatonergic signaling pathways, that of PKC-dependent ERK1/2 activation [57], has been shown to be decisive for phase shi ing of circadian oscillations [58], this may not yet explain the increases of rhythm amplitudes. Recent data on the relationship between melatonin and SIRT1 may provide a link to this problem. Initially, this connection was largely overlooked, because studies in cancer cells or tissue revealed strong reductions of SIRT1 expression by melatonin. However, melatonin behaves entirely di erently in nontumor cells. Especially in the context of aging, melatonin was shown to upregulate SIRT1 expHoIRlhis i-6b5 (d s)5 Td[( )4 (h)3ts,3 (s)-8 (e ,ir)13 (c)-f (o)0.5 (

concentration, which drives the activities of various sirtuins which use NAD^+ as a substrate and activator. Notably, rhythmic expression of SIRT1 is not required, because the decisive parameter is SIRT1 activity rather than protein concentration.

An important and, in the beginning, surprising property of SIRT1 is its capability of enhancing circadian oscillation amplitudes. is has been explained in two di erent ways, (1) By physical interaction of SIRT1 with the BMAL1/CLOCK heterodimer; and (2) By SIRT1-dependent deacetylation of PGC-1α (peroxisome proliferator-activated receptor-γ coactivator-1α), binding of deacetylated PGC-1α to RORα (retinoic acid receptor-related orphan receptor-α), an activator at the ROR response elements in the promoters of the *Bmal1* and *Clock* genes [38]. Regarding these two possibilities, di erences may exist between the various cellular oscillators in central and peripheral tissues. An important aspect of aging is the observed senescence-associated decline of SIRT1 expression [17,27,38]. e above-mentioned upregulation of SIRT1 expression by melatonin in the context of aging [27], thus, indicates a mode by which exogenous melatonin might increase circadian amplitudes indirectly by re-initiating enhanced SIRT1 expression. Whether melatonin also upregulates other sirtuin subforms, in particular, the mitochondrially located SIRT3 and the constitutively chromatin-associated SIRT6, would be of great interest, but would still require a broader experimental basis. Both SIRT3 and SIRT6 are driven by the NAD^+ cycle and transmit circadian information [62,63], but do not seem to feed back to the core oscillator components.

C c . .

A concept of jointly increasing melatonin and SIRT1 levels is highly attractive in gerontological terms, especially with regard to neuroin ammation. Melatonin, which is very short-lived in the circulation because of a half-life mostly in the range of 20-30 min, may induce more persistent e ects by upregulating SIRT1, which, as a protein, should have a considerably longer half-life. In cultured glomerular mesangial cells, the half-life of SIRT1 was about 8 h [64]. Under certain conditions and in certain cells, this may be shortened by stimuli that enhance SIRT1 ubiquitinylation, followed by proteasomal degradation [64]. Corresponding data in brain tissue would be required for a de nite judgment, but the half-life of SIRT1 in neurons will be, with some likelihood, in the range of several hours and, therefore, much longer than that of melatonin. Independently of the rather moderate e ects of melatonin on sleep maintenance [2], daily repeated and appropriately timed application of this hormone may improve, *via* SIRT1, circadian rhythms in elderly patients, as far as the decline in the circadian system has not been caused by irreversible neurodegeneration. Moreover, the antioxidant, mitochondria-protective and anti-in ammatory actions of melatonin might be complemented and enhanced by corresponding actions of SIRT1, which displays bene cial e ects in the same elds and may, according to recent data, partially mediate actions by melatonin [65-74] (Figure 1). Anti-in ammatory e ects of SIRT1 deserve further attention and extension towards studies on levels of proin ammatory cytokines in the brain would be required, especially concerning TNF-α, IL-2 and IL-6. To date, most pertinent information has been based on the application of powerful proin ammatory agents such as LPS (bacterial lipopolysaccharide) in combination with sirtuin activators and inhibitors, whereas investigations on upregulation of SIRT1 in the otherwise non-compromised aging brain, along with measurements of cytokine levels, are urgently desired. Nevertheless, the already available data on neuroprotection and anti-in ammatory properties of SIRT1 are encouraging [75]. e enhancement of melatonin, SIRT1 activity and, thereby, circadian amplitudes seems to be a worth-while aim for reducing low-grade neuro-in ammation and for improving health and life quality in elderly subjects. As a consequence, the hypothesis should be experimentally examined that, in aging mammals, exogenous melatonin not only elevates the levels of SIRT1, but that this upregulation also increases circadian amplitudes, which may also in uence the rhythmicity of endogenous melatonin. With regard to



Connections between the circadian system, melatonin and Sirtuin 1

master clock (SCN), peripheral oscillators, melatonin and SIRT1 in a youthful organism. Thickness of arrows indicates differences in coupling strength. While some peripheral oscillators are tightly coupled to the SCN, others are

not necessarily all peripheral oscillators directly, and feeds back to the SCN. B. Deviations caused by aging. Melatonin and SIRT1 are reduced and the various oscillators are differently affected. Additional deviations such as phase shifts have not been incorporated in the scheme. C. A mechanism of circadian amplitude enhancement by SIRT1, as demonstrated for the SCN oscillator [38].

of cases, effects of melatonin have been suppressed by SIRT1 inhibitors or knockdown, indicating a mediation of these actions by SIRT1. Additional

the anti-in ammatory actions of both melatonin and SIRT1 and to the circadian control of several immunological functions, concomitant improvements of the three orchestrating regulators, melatonin, SIRT1 and the circadian system, may reduce aging-related in ammation and enhance physiological functioning.

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