both studies are correct and that the differences are related to the levels and time course of melatonin after administration, including the possibility of transient receptor desensitization. At least, the unfavourable results should be taken as a caveat concerning the belief that pharmacological levels of melatonin may easily readjust metabolic deviations. However, data on melatonergic treatment of diabetic patients will finally be decisive for judging the suitability of melatonin in this complex of pathologies.

A connection between insulin secretion and another metabolic sensor, AMPK (adenosine 5′-monophosphate kinase), seems to also be influenced by melatonin. This enzyme is activated *via* phosphorylation by AMPK kinase (AMPKK) and pAMPK levels were found to be reduced by melatonin in INS-1E insulinoma cells.[39] Similar reductions were observed in the immortalized hippocampal cell line HT22 exposed to $A\beta_{1\text{-}42}$,[40] but increased expression was reported in steatotic liver[41] as well as in the muscles and liver of aging rats,[42] whereas no changes were observed in pre-myoblastic skeletal muscle cells[43] and in HepG2 hepatoma cells.[44] Therefore, it seems important to discriminate between developmental stages, tissues and transformed *vs.* non-transformed cells. More information is required on melatonin effects on AMPK in the gerontological context. This demand is presumably important under a further aspect of aging concerning circadian rhythmicity.[11,45] AMPK was shown to act as an accessory component of cellular circadian oscillators and, thereby, to phase-shift circadian rhythms.[46] Moreover, the AMPK activator, metformin, otherwise used as an anti-diabetic drug, reduced the amplitude of the melatonin rhythm in ewes.[47] This role is of particular interest with regard to declining rhythm amplitudes in the course of senescence as well as rhythm-supporting effects of melatonin on central and peripheral oscillators.[6] However, the findings on AMPK activation are rather in favour of a negative relationship between melatonin and this metabolic sensor.

Sirtuin-1 (SIRT1) is another metabolic sensor with relevance to circadian oscillators and regulation by melatonin. Primarily known as an aging suppressor with protein deacetylase activity,[48] it is also intertwined with AMPK signalling,[11] calorie restriction,[49] and mitochondrial proliferation.[11,49] Again, SIRT1 acts as an accessory component of circadian oscillators. In this role, it displays a profound regulatory function on the so-called core oscillator and is required for high rhythm amplitudes of *Per2*, *Cry1*, *Bmal1* and *RORγ* transcription.[50–54] In brief, it promotes the degradation of the core oscillator protein PER2 by deacetylation and exerts a crucial effect *via* binding to the BMAL1/CLOCK complex at E-box containing promoters, where it acts as an activator in the presence of its substrate, NAD^+. The ternary protein complex activates E-box-dependent genes, including *Per1*, *Per2*, *Cry1*, *Cry2*, *Rev-erbα* and that of the key enzyme of the NAD^+ salvage pathway, NAMPT (nicotinamide phosphoribosyltransferase). The resulting cycle of NAD^+, thus, drives the expression levels of the mentioned core oscillator components and, indirectly *via* additional feedback loops, those of other components.

With regard to the aging-dependent decreases in circadian rhythm amplitudes, including that of melatonin secretion, an utmost important question