Melatonin

- Functional Characterization of GNA1 as a Serotonin N-Acetyltransferase Reveals a Key Role in the Serotonin to Melatonin Pathway in Saccharomyces cerevisiae
- Research progress on microglial pyroptosis and inflammasomes: a comprehensive analysis
- Melatonin-induced Bacillus tequilensis enhanced the disease resistance of Camellia oleifera against anthracnose by modulating cell wall and phenylpropanoid metabolism
- Comparing Extracellular and Intracellular Antioxidants in Human Sperm Rapid Freezing: Hypotaurine Versus Melatonin
- Administration of Exogenous Kisspeptin Induces Breeding Competence in Post-pubertal Female Common Carp (Cyprinus carpio)
- Effects of repeated cryostimulation exposures on sleep quality in swimmers during an intense training period
- Unveiling mysteries of aging: the potential of melatonin in preventing neurodegenerative diseases in older adults
- The effect of melatonin implants on the embryo yield and oxidative stress levels in superovulated Holstein heifers

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Hormone that affects the modulation of sleep patterns in the circadian rhythms and seasonal functions.

Findings suggest that certain supplements, particularly valerian, hops, and melatonin, could be effective in improving sleep quality and reducing insomnia symptoms through modulation of neurotransmitter systems and regulation of sleep-wake cycles. However, the strength of the evidence varies with unestablished optimal dosages, formulations, and treatment durations. Although generally considered safe, these supplements are not without risks, such as rare but serious adverse effects associated with kava and potential interactions with prescription medications. The quality and purity of supplements also vary widely due to a lack of strict regulations.

Healthcare providers should remain informed about the latest research and work closely with patients to develop personalized treatment plans. Herbal and natural supplements may offer promising alternatives or adjunct treatments for insomnia and sleep disorders, but their use should be guided by the best available evidence and individual patient requirements. Larger, well-designed clinical trials are needed to establish the efficacy and safety of these supplements for clinical decision-making [1)]

Melatonin significantly attenuated mitochondrion and oligodendrocyte deficiency in the brain white matter of KarsR504H/P532S mice. The mice treated with melatonin also showed significantly restored myelination and cognitive function. A study first establishes Kars knock-in mammal models of leukoencephalopathy and cognitive impairment and indicates important roles of KARS in the regulation of mitochondria, oligodendrocyte differentiation and survival, and myelination during brain development and application prospects of melatonin in KARS (or even aaRS)-related diseases [2)].

A study aimed to explore the role of melatonin in oxidative stress-induced injury on retinal ganglion cells and the underlying mechanisms. The immortalized RGC-5 cells were treated with H2O2 to induce oxidative injury. Cell viability was measured by Cell Counting Kit-8, and apoptosis was determined by flow cytometry and western blot assays. Reactive oxygen species (ROS), lactate dehydrogenase (LDH), and malondialdehyde (MDA) levels were examined to evaluate oxidative stress levels. In addition, Thioredoxin-1 (Trx1) was silenced in RGC-5 cells using small interfering RNA followed by a signaling pathway examination to explore the underlying mechanisms of melatonin in alleviating oxidative injury. Melatonin pre-treatment significantly alleviated H2O2-induced apoptosis in RGC-5 cells. Melatonin also markedly reversed the upregulation of cleaved-caspase 3, cleaved-caspase 9, and Bax expression and the downregulation of Bcl-2 expression induced by H2O2. Further analyses presented that melatonin significantly attenuated the increase of ROS, LDH, and MDA levels in RGC-5 cells after H2O2 treatment. Melatonin also abolished the downregulated expression of Superoxide dismutase type 1, Trx1, and Thioredoxin reductase 1, and the reduced activity of thioredoxin reductase in RGC-5 cells after H2O2 treatment. Notably, Trx1 knockdown significantly mitigated the protective effect of melatonin in alleviating H2O2-induced apoptosis and oxidative stress, while administration of compound C, a common inhibitor of c-Jun N-terminal kinase (JNK) signaling, partially reversed the effect of Trx1 silencing, thereby ameliorating the apoptosis and oxidative injury induced by H2O2 in RGC-5 cells. Melatonin could significantly alleviate oxidative stress-induced injury of retinal ganglion cells via modulating the Trx1-mediated JNK signaling pathway [3].

Advanced prostate cancer often develops into bone metastases, which is characterized by aberrant bone formation with chronic pain and lower chances of survival. No treatment exists as yet for osteoblastic bone metastases in prostate cancer.

Melatonin has shown antiproliferative and antimetastatic activities, but has not yet been shown to be active in osteoblastic bone lesions of prostate cancer. A study investigation reveal that melatonin concentration-dependently decreases the migratory and invasive abilities of two osteoblastic prostate cancer cell lines by inhibiting FAK, c-Src and NF-κB transcriptional activity via the melatonin MT1 receptor, which effectively inhibits integrin α2 β1 expression. Melatonin therapy appears to offer therapeutic possibilities for reducing osteoblastic bone lesions in prostate cancer [4]

A study aimed to investigate the molecular mechanism of how melatonin (MT) interferes with hypoxia-inducible factor 1α (HIF1A) and toll-like receptor 4 (TLR4) expression, which is implicated in the management of delayed brain injury (DBI) after subarachnoid hemorrhage (SAH). Luciferase assay, real-time PCR, Western-blot analysis and immunohistochemistry (IHC) assays were utilized to explore the interaction among H19, miR-675, HIF1A and TLR4, and to evaluate the effect of MT on the expression of above transcripts in different groups. MT enhanced H19 expression by promoting the transcription efficiency of H19 promoter, and HIF1A was identified as a target of miR-675. HIF1A enhanced TLR4 expression via promoting the transcription efficiency of TLR4 promoter. Furthermore, administration of MT up-regulated miR-675 but suppressed the expressions of HIF1A and TLR4. Treatment with MT alleviated neurobehavioral deficits and apoptosis induced by SAH. According to the result of IHC, HIF1A and TLR4 protein levels in the SAH group were much higher than those in the SAH+MT group. Therefore, the administration of MT increased the levels of H19 and miR-675 which have been inhibited by SAH. In a similar way, treatment with MT decreased the levels of HIF1A and TLR4 which have been enhanced by SAH. MT could down-regulate the expression of HIF1A and TLR4

via the H19/miR-675/HIF1A/TLR4 signaling pathway, while TLR4 is crucial to the release of pro-inflammatory cytokines. Therefore, the treatment with MT could ameliorate post-SAH DBI [5)]

The circadian nature of melatonin has a protective effect on the progression of female reproductive cancers, including in breast and ovarian cancers. However, the effect of melatonin on the growth of uterine leiomyoma is still unclear. In this study, we found that the growth of uterine leiomyoma ELT3 cells was reduced by treatment with melatonin. Treatment with melatonin increased the distribution of sub-G1 phase and increased DNA condensation in ELT3 cells. Melatonin-induced apoptosis and autophagy cell death progression was observed in ELT3 cells. Melatonin exerts a highly selective effect on primary normal human uterine smooth muscle (UtSMC) cells. The UtSMC cell cycle was arrested by melatonin treatment through up-regulation of p21, p27, and PTEN protein expression, but melatonin did not further promote apoptosis program activation. Melatonin reduced cell proliferation in ELT3 cells underlying the activation of melatonin MT1 and MT2 receptors, which in turn down-regulated the Akt-ERK1/2-NFκB signaling pathway. Melatonin reduced ELT3 tumor growth in both xenograft and orthotopic uterine tumor mice models. The extracellular matrix of the tumor was also reduced by melatonin treatment. Taken together, these results suggest that melatonin potentially plays a role in suppression of uterine leiomyoma growth [6)].

In a study that provides the largest series of circulating melatonin levels in patients with severe TBI. The main findings were that non-survivors had higher serum melatonin levels than survivors, and the association between serum levels of melatonin levels and mortality, peroxidation state and antioxidant state [7)].

Recent studies have shown that melatonin treatment induces cytotoxicity in glioma-initiating cells and reduces the invasion and migration of glioma cell lines, inhibiting the nuclear factor κB (NFκB) oncopathway. Given that C6 rat glioma cells produce melatonin, we investigated the correlation between the capacity of gliomas to synthesize/metabolize melatonin and their overall malignancy. We first characterized the melatonergic system of human gliomas cell lines with different grades of aggressiveness (HOG, T98G and U87MG) and demonstrated that glioma-synthesized melatonin exerts an autocrine antiproliferative effect. Accordingly, the sensitivity to exogenous melatonin was higher for the most aggressive cell line, U87MG, which synthesized/accumulated less melatonin. Using The Cancer Genome Atlas RNAseq data of 351 glioma patients, we designed a predictive model of the content of melatonin in the tumor microenvironment, the ASMT:CYP1B1 index, combining the gene expression levels of melatonin synthesis and metabolism enzymes. The ASMT:CYP1B1 index negatively correlated with tumor grade, as well as with the expression of pro-proliferation and anti-apoptotic NFκB target genes. More importantly, the index was a grade- and histological type-independent prognostic factor. Even when considering only high-grade glioma patients, a low ASMT:CYP1B1 value, which suggests decreased melatonin and enhanced aggressiveness, was strongly associated with poor survival. Overall, our data reveal the prognostic value of the melatonergic system of gliomas and provide insights into the therapeutic role of melatonin [8)].

Results clearly revealed that the histopathological changes in the cerebellum were reversed by systemic melatonin administration in infantile rats with kaolin-induced hydrocephalus. Nevertheless,

further studies are needed to suggest melatonin as a candidate protective drug in children with hydrocephalus [9].

Survivors of aneurysmal subarachnoid hemorrhage (aSAH) commonly experience sleep disorders resulting in asthenia. The objective of this prospective study was to determine, in a cohort of patients with treated ruptured intracranial aneurysm (IA), the proportion of asthenia at 2months, in a cohort of patients treated with melatonin and in a control cohort.

Twenty consecutive patients admitted for the treatment of ruptured IA and able to answer a standardized questionnaire were included in the study. After evaluation for fatigue at discharge, we divided our population into 2 cohorts of 10 patients: the first cohort was treated with melatonin for a period of 2months; the second cohort had no specific treatment for fatigue. The primary endpoint was the proportion of asthenia at 2months in both groups. Confounding factors, such as depression, autonomy and apathy were evaluated at the same time.

At discharge, there was no significant difference observed between both groups in terms of mean age and initial clinical status (WFNS, Rankin Scale and Fatigue Severity Scale). At 2months, the mean FSS score in the control group was of 4.7±1.0 versus 3.8±0.9 in the melatonin group (P=0.03). The mean MADRS score in the control group was of 1.1±1.45 versus 2.7±2.5 in the melatonin group (P=0.10). The mean LARS score in the control group was of -32.5±1.7 versus -31.7±1.9 in the melatonin group (P=0.24).

In a prospective evaluation of post-aSAH fatigue, we suggest that melatonin could decrease fatigue. There is no significant impact on depression and apathy. Further studies would be necessary to improve our comprehension of fatigue physiopathology in a context of aSAH [10].

Wang et al. designed a study to investigate the therapeutic effects and mechanisms of melatonin on the secondary brain injury (SBI) after intracerebral hemorrhage (ICH). An in vivo ICH model was induced via autologous whole blood injection into the right basal ganglia in Sprague-Dawley (SD) rats. Primary rat cortical neurons were treated with oxygen hemoglobin (OxyHb) as an in vitro ICH model. The results of the in vivo study showed that melatonin alleviated severe brain edema and behavior disorders induced by ICH. Indicators of blood brain barrier (BBB) integrity, DNA damage, inflammation, oxidative stress, apoptosis, and mitochondria damage showed a significant increase after ICH, while melatonin reduced their levels. Meanwhile, melatonin promoted further increasing of expression levels of antioxidant indicators induced by ICH. Microscopically, TUNEL and Nissl staining showed that melatonin reduced the numbers of ICH-induced apoptotic cells. Inflammation and DNA damage indicators exhibited an identical pattern compared to those above. Additionally, the in vitro study demonstrated that melatonin reduced the apoptotic neurons induced by OxyHb and protected the mitochondrial membrane potential. Collectively, the investigation showed that melatonin ameliorated ICH-induced SBI by impacting apoptosis, inflammation, oxidative stress, DNA damage, brain edema, and BBB damage and reducing mitochondrial membrane permeability transition pore opening, and melatonin may be a potential therapeutic agent of ICH [11].

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Yeom JW, Cho CH. Herbal and Natural Supplements for Improving Sleep: A Literature Review. Psychiatry Investig. 2024 Aug 2. doi: 10.30773/pi.2024.0121. Epub ahead of print. PMID: 39086164.
2)
Yu L, Chen Z, Zhou X, Teng F, Bai QR, Li L, Li Y, Liu Y, Zeng Q, Wang Y, Wang M, Xu Y, Tang X, Wang

X. KARS Mutations Impair Brain Myelination by Inducing Oligodendrocyte Deficiency: One Potential Mechanism and Improvement by Melatonin. J Pineal Res. 2024 Aug;76(5):e12998. doi: 10.1111/jpi.12998. PMID: 39087379.

3) Gao S, Cheng Q, Hu Y, Fan X, Liang C, Niu C, Kang Q, Wei T. Melatonin antagonizes oxidative stress-induced apoptosis in retinal ganglion cells through activating the thioredoxin-1 pathway. Mol Cell Biochem. 2024 Feb 14. doi: 10.1007/s11010-024-04924-2. Epub ahead of print. PMID: 38353878.

4) Tai HC, Wang SW, Swain S, Lin LW, Tsai HC, Liu SC, Wu HC, Guo JH, Liu CL, Lai YW, Lin TH, Yang SF, Tang CH. Melatonin suppresses the metastatic potential of osteoblastic prostate cancers by inhibiting integrin α2 β1 expression. J Pineal Res. 2022 Feb 16. doi: 10.1111/jpi.12793. Epub ahead of print. PMID: 35174530.

5) Xu Z, Zhang F, Xu H, Yang F, Zhou G, Tong M, Li Y, Yang S. Melatonin affects hypoxia-inducible factor 1α and ameliorates delayed brain injury following subarachnoid hemorrhage via H19/miR-675/HIF1A/TLR4. Bioengineered. 2022 Feb;13(2):4235-4247. doi: 10.1080/21655979.2022.2027175. PMID: 35170388.

6) Lin PH, Tung YT, Chen HY, Chiang YF, Hong HC, Huang KC, Hsu SP, Huang TC, Hsia SM. Melatonin activates cell death programs for the suppression of uterine leiomyoma cell proliferation. J Pineal Res. 2019 Nov 11:e12620. doi: 10.1111/jpi.12620. [Epub ahead of print] PubMed PMID: 31710386.

7) Lorente L, Martín MM, Abreu-González P, Pérez-Cejas A, Ramos L, Argueso M, Solé-Violán J, Cáceres JJ, Jiménez A, García-Marín V. Serum melatonin levels in survivor and non-survivor patients with traumatic brain injury. BMC Neurol. 2017 Jul 19;17(1):138. doi: 10.1186/s12883-017-0922-2. PubMed PMID: 28724361.

8) Kinker GS, Oba-Shinjo SM, Carvalho-Sousa CE, Muxel SM, Marie SK, Markus RP, Fernandes PA. Melatonergic system-based two-gene index is prognostic in human gliomas. J Pineal Res. 2015 Oct 29. doi: 10.1111/jpi.12293. [Epub ahead of print] PubMed PMID: 26510398.

9) Uyanıkgil Y, Turgut M, Baka M. Effects of Melatonin on the Cerebellum of Infant Rat Following Kaolin-Induced Hydrocephalus: a Histochemical and Immunohistochemical Study. Cerebellum. 2016 Apr 25. [Epub ahead of print] PubMed PMID: 27113349.

10) Gilard V, Ferracci FX, Langlois O, Derrey S, Proust F, Curey S. Effects of melatonin in the treatment of asthenia in aneurysmal subarachnoid hemorrhage. Neurochirurgie. 2016 Nov 16. pii: S0028-3770(16)30125-4. doi: 10.1016/j.neuchi.2016.06.010. [Epub ahead of print] PubMed PMID: 27865517.

11) Wang Z, Zhou F, Dou Y, Tian X, Liu C, Li H, Shen H, Chen G. Melatonin Alleviates Intracerebral Hemorrhage-Induced Secondary Brain Injury in Rats via Suppressing Apoptosis, Inflammation, Oxidative Stress, DNA Damage, and Mitochondria Injury. Transl Stroke Res. 2017 Aug 1. doi: 10.1007/s12975-017-0559-x. [Epub ahead of print] PubMed PMID: 28766251.