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PubMed and PMC studies that investigate or reference the REV-ERB agonist SR9011

Microglia, neuroinflammation and neurogenesis

- **SR9011 disrupts microglial clock genes and dampens inflammatory responses (Frontiers in Immunology 2020)** – Primary mouse microglia show daily rhythms in cytokine and metabolic gene expression. Pretreatment with the REV-ERBα agonist SR9011 altered core clock gene expression and lowered pro-inflammatory cytokines during a subsequent immune challenge while increasing the anti-inflammatory cytokine IL-10 and decreasing phagocytic activity [1]. SR9011 also suppressed mitochondrial respiration and ATP production, illustrating that Rev-erbα integrates circadian regulation with microglial immunometabolism [1]. The authors propose SR9011 as a tool to shift microglia toward a neuroprotective state and reduce neuroinflammation.

- **REV-ERB agonists suppress LPS-induced microglial activation (Acta Pharmacol Sin 2019)** – In BV-2 and primary mouse microglia, SR9011 and another agonist (GSK4112) reduced LPS-induced expression of inflammatory cytokines. Pre-treatment blocked phosphorylation of IκB kinase, preventing nuclear translocation of NF-κB p65 and decreasing nitric oxide production [2]. SR9011 therefore inhibits microglial activation via the NF-κB pathway and protects neurons from microglia-mediated neurotoxicity [2].

- **Re-erβ agonist SR9011 promotes dopaminergic neurogenesis and alleviates Parkinson's disease symptoms (Free Radic Biol Med 2024)** – Rev-erbα regulates differentiation of neuronal precursors by repressing the transcription factor Sox2. In cell culture and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPP+) mouse models, SR9011 promoted differentiation of undifferentiated neuronal cells into dopaminergic neurons and reduced locomotor impairment, cognitive decline and neuronal apoptosis [3]. The study indicates that SR9011-mediated activation of Rev-erbα may be therapeutic for Parkinson's disease [3].

- **Circadian gene Nr1d2 down-regulation and postoperative dry eye disease (Ocul Surf 2025)** – In a model of postoperative dry eye, the lacrimal gland showed reduced expression of the clock gene Nr1d2 (encoding Rev-erbβ). Activation of Nr1d2 with SR9011 restored lacrimal gland function, improved tear secretion, normalized lipid metabolism and mitochondrial function, and alleviated dry eye symptoms [4]. The findings suggest that circadian disruption contributes to postoperative dry eye and that SR9011 could be explored as therapy.

Cancer and anti-proliferative effects

- **REV-ERB activation kills cancer cells and senescent cells (Nature 2018)** – This landmark study proposed circadian clock modulation as a therapeutic strategy for cancer. SR9009 and SR9011 were selectively lethal to various cancer cell lines and to oncogene-induced senescent fibroblasts while

sparing non-transformed cells [5]. The compounds suppressed autophagy and de novo lipogenesis; inhibiting either process sensitized cancer cells to SR9011. In a mouse model of glioblastoma, SR9011 treatment reduced tumor growth and prolonged survival [5]. The authors concluded that REV-ERB activation represents a metabolic vulnerability in cancer.

- **Synthetic REV-ERB agonist arrests breast-cancer proliferation (Biochem Pharmacol 2015)** – SR9011 suppressed proliferation across estrogen-receptor-positive, HER2-positive and triple-negative breast-cancer cell lines but did not affect non-tumoral MCF10A cells [6]. The compound induced cell-cycle arrest before M-phase, and cyclin A (CCNA2) was identified as a direct REV-ERB target gene. These results suggest that REV-ERB agonists may provide novel therapeutics for cancers driven by uncontrolled proliferation [6].

- **New biochemical approaches for glioblastoma (J Biol Chem 2025 review)** – This review notes that current glioblastoma therapy (surgery, radiotherapy and temozolomide) provides median survival of ~12 months. The authors summarize new approaches targeting DNA or the circadian clock, including REV-ERB agonists such as SR9009 and SR9011 [7]. Although the review does not present new data, it highlights the potential of circadian modulators like SR9011 to improve glioblastoma treatment when combined with existing therapies.

Metabolic and circadian regulation

- **Synthetic REV-ERB agonists alter circadian behavior and metabolism (Nature 2012)** – SR9009 and SR9011 were designed as potent REV-ERB agonists. In mice, SR9011 administration altered the expression of core clock genes, shifting circadian behavioral rhythms and suppressing locomotor activity during the normally active phase [8]. Gene expression profiling showed reduced lipogenesis, cholesterol synthesis and bile acid synthesis in the liver, increased mitochondrial content and fatty-acid oxidation in skeletal muscle, and decreased lipogenesis in adipose tissue [8]. Treated mice exhibited increased energy expenditure, reduced body weight and improved dyslipidaemia and glucose tolerance in diet-induced obesity models [8], suggesting that SR9011 may be beneficial for metabolic and sleep-related disorders.

- **REV-ERB activation affects sleep architecture (Nat Commun 2014)** – Pharmacological activation of REV-ERB with SR9011 increased wakefulness and reduced slow-wave and rapid-eye-movement sleep for ~2 hours following injection, particularly when administered during the light phase [9]. The wake-promoting effect was time-dependent: dosing at ZT18 (late dark phase) had no effect on sleep. These findings demonstrate that REV-ERB plays a role in sleep homeostasis and that SR9011 can acutely modulate sleep architecture [9].

- **Small-molecule modulators of the circadian clock (Front Mol Neurosci 2019)** – This review discusses the development of synthetic REV-ERB ligands. The first agonist GSK4112 lacked favorable pharmacokinetics, but subsequent compounds, including SR9009 and SR9011, showed improved potency and in vivo efficacy [10]. SR9009/9011 demonstrated therapeutic effects in models of metabolic disease and sleep disorders [11]. The authors note that REV-ERB agonists like SR9011 may be useful for treating circadian rhythm–related metabolic diseases and sleep disturbances but caution that no antagonists are clinically available [12].

Doping detection and metabolism studies

- **In vitro metabolic studies of SR9009 and SR9011 (Int J Mol Sci 2016)** – Recognizing that SR9009 and SR9011 are attractive performance-enhancing agents, the authors developed methods to detect these compounds for doping control. Human liver microsomal assays combined with liquid-chromatography high-resolution mass spectrometry (LC-HRMS) identified eight metabolites for SR9009 and fourteen metabolites for SR9011 [13]. Structural elucidation by product-ion scans allowed incorporation of metabolites into screening methods, and retrospective analysis of 1,511 doping-control samples found no evidence of SR9009/9011 use [14]. The study emphasizes that including SR9009 and SR9011 in doping tests will help deter illicit use [15].

- **LC–MS/MS detection of SR9009 and SR9011 in equine plasma (Drug Testing & Analysis 2022)** – SR9009 and SR9011 have been marketed illegally as metabolic modulators in horse racing. Researchers developed a liquid-chromatography tandem mass-spectrometry (LC-MS/MS) method using protein precipitation and a C18 column to quantify SR9009 and SR9011 in equine plasma [16]. The assay displayed good linearity, precision and accuracy, and limits of quantification suitable for doping control. Application to plasma samples from horses injected with SR9009 confirmed the method's utility [16].

Additional considerations and reviews

- **Effects of SR9011 on microglial phagocytosis and metabolism** – Figures in the 2020 Frontiers in Immunology article show that SR9011 decreases microglial phagocytic capacity and reduces mitochondrial respiration, linking Rev-erbα to energy metabolism [1].

- **Circadian modulators in neuropsychiatric disorders** – The 2019 Front Mol Neurosci review notes that SR9009/9011 have beneficial effects in high-fat diet–induced metabolic disturbances and may correct circadian misalignment in neuropsychiatric conditions [11]. Administration of SR9011 in mice increases wakefulness and reduces sleep, implicating REV-ERB as a target for sleep disorders [9].

- **Limitations of available data** – Some referenced articles (e.g., the 2025 glioblastoma review) mention SR9011 only in passing and do not provide new experimental data [7]. Additionally, several doping-control or clinical studies are behind paywalls or blocked by Cloudflare; the summary relies on accessible abstracts and reviews. Despite these limitations, current literature consistently describes SR9011 as a potent REV-ERB agonist that modulates circadian and metabolic pathways, exhibits anti-inflammatory and anti-proliferative effects, and shows promise as a therapeutic agent and a target in doping control.

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[1] The Effect of Rev-erbα Agonist SR9011 on the Immune Response and Cell Metabolism of Microglia - PubMed
https://pubmed.ncbi.nlm.nih.gov/33101272/

[2] Pharmacological activation of REV-ERBα represses LPS-induced microglial activation through the NF-κB pathway - PubMed
https://pubmed.ncbi.nlm.nih.gov/29950615/

3 Rev-erbα regulate neurogenesis through suppression of Sox2 in neuronal cells to regenerate dopaminergic neurons and abates MPP+ induced neuroinflammation - PubMed
https://pubmed.ncbi.nlm.nih.gov/39084577/

4 Downregulation of the core circadian gene Nr1d2 in the lacrimal gland contributes to postoperative dry eye disease by impairing lipid metabolism - PubMed
https://pubmed.ncbi.nlm.nih.gov/40885436/

5 Pharmacological activation of REV-ERBs is lethal in cancer and oncogene-induced senescence - PubMed
https://pubmed.ncbi.nlm.nih.gov/29320480/

6 Anti-proliferative actions of a synthetic REV-ERBα/β agonist in breast cancer cells - PubMed
https://pubmed.ncbi.nlm.nih.gov/26074263/

7 New Biochemical Approaches for Treatment of Glioblastoma - PubMed
https://pubmed.ncbi.nlm.nih.gov/40983311/

8 Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists - PubMed
https://pubmed.ncbi.nlm.nih.gov/22460951/

9 Pharmacological Targeting of the Mammalian Clock Regulates Sleep Architecture and Emotional Behavior - PMC
https://pmc.ncbi.nlm.nih.gov/articles/PMC4495958/

10 11 12 Small Molecule Modulators of the Circadian Molecular Clock With Implications for Neuropsychiatric Diseases - PMC
https://pmc.ncbi.nlm.nih.gov/articles/PMC6348269/

13 14 15 In Vitro Metabolic Studies of REV-ERB Agonists SR9009 and SR9011 - PMC
https://pmc.ncbi.nlm.nih.gov/articles/PMC5085709/

16 A quantitative method for the simultaneous detection of SR9009 and SR9011 in equine plasma using liquid chromatography-electrospray ionization-tandem mass spectrometry - PubMed
https://pubmed.ncbi.nlm.nih.gov/35396832/