ChatGPT

Comprehensive Review of SR9009 Research

Introduction

SR9009 is a synthetic ligand for REV-ERB receptors (nuclear receptors NR1D1/NR1D2) that was originally developed as a circadian clock modulator. It has been studied for its effects on metabolism, circadian rhythms, exercise capacity, inflammation, cancer, immune responses and more. Because SR9009 is commercially available and has become popular in self-experimenting communities and sports, several studies have also investigated its metabolism and detection. Below is a comprehensive summary of **published studies** and accessible conference abstracts/posters that explicitly mention SR9009. Each entry includes study aims, methods, findings, significance and noted limitations.

Mechanistic and Circadian Studies

Sleep and Circadian Rhythms

- **Acute sleep regulation (2016)** – Mice treated with SR9009 exhibited increased wakefulness during the light phase without tolerance over three days. Effects were limited to a ~12-hour window, suggesting that SR9009 influences sleep/wake behaviour by activating REV-ERB receptors [1]. This demonstrates that pharmacological manipulation of the clock can alter sleep but long-term safety remains unknown.

- **REV-ERB-independent effects (2019)** – A study using hepatocytes from mice lacking both REV-ERBα and REV-ERBβ found that SR9009 still reduced cell viability and rewired metabolism [2]. This indicates off-target actions and cautions against attributing all SR9009 effects solely to REV-ERB activation.

- **Cardiac REV-ERB independence (2018)** – In pressure-overload mice, SR9009 improved heart function even when REV-ERB was genetically ablated in cardiomyocytes [3], supporting REV-ERB-independent cardioprotective mechanisms.

- **Kynurenine pathway (2025)** – Exhaustive exercise downregulated REV-ERBα and shifted the tryptophan kynurenine pathway towards neurotoxic metabolites. SR9009 treatment restored KAT1 expression and reduced KMO expression, shifting metabolism toward neuroprotective pathways [4]. This suggests REV-ERB activation may counteract exercise-induced fatigue and mood disturbances.

- **Stroke chronopharmacology (2024)** – In a mouse stroke model, SR9009 given at Zeitgeber time 06 reduced infarct volume and neuroinflammation but had no benefit at Zeitgeber time 18 [5]. SR9009 lowered NLRP3 and TNF-α and increased IL-10, highlighting time-of-day dependency.

Cell Models and Senescence

- **Neural stem cells** – In cultured rat hippocampal neural progenitor cells, SR9009 had dose-dependent effects: low doses enhanced neurite outgrowth whereas high doses suppressed it and reduced proliferation; REV-ERBβ knockdown partially rescued these effects, implicating REV-ERB in neurodevelopment [6].

- **Cellular senescence and SASP (2021)** – In therapy-induced and oncogene-induced senescence models, SR9009 suppressed the senescence-associated secretory phenotype (SASP), increased NRF2 activity, reduced reactive oxygen species and improved liver senescence models [7]. This suggests a potential anti-aging role but also emphasises off-target pathways (NRF2).

Synthetic Analogues

- **Structure–activity relationship** – Several analogues of SR9009 (5a, 5f, 5g, 5m, 5p) were synthesised and tested for REV-ERB agonist activity. Analogues 5m and 5p showed improved potency in vitro and increased exercise tolerance and lowered lipid/glucose levels in mice compared with SR9009 [8].

Metabolic Disorders and Energy Homeostasis

Obesity, Insulin Resistance and NASH

- **Constant light-induced metabolic syndrome (2019)** – In mice housed under constant light, chronic low-dose SR9009 suppressed weight gain, reduced insulin resistance and restored Rev-erb expression while inhibiting adipogenesis [1]. SR9009 had minimal effects on other metabolic pathways at this low dose.

- **High-fat diet-induced obesity and NASH** – Several studies examined SR9009 in non-alcoholic steatohepatitis (NASH) models:

- **Chronopharmacology (2023)** – High-fat-high-cholesterol diet mice treated with SR9009 at Zeitgeber time 0 (ZT0) or ZT12 showed improved hepatic steatosis, insulin resistance, inflammation, fibrosis, gut barrier function and microbiota composition, with stronger effects at ZT0 [9].

- **Intestinal permeability (2021)** – SR9009 bound promoters of tight-junction genes, reduced gut permeability and hepatic inflammation, improved hepatic lipid accumulation and insulin resistance, and again displayed stronger benefits when dosed at ZT0 [10].

- **Hepatic stellate cells and autophagy (2016)** – SR9009 reduced p70S6K phosphorylation and autophagy in hepatic stellate cells exposed to carbon tetrachloride, lowering fibrogenic gene expression and proliferation. TGF-β had opposite effects, showing differential regulation of autophagy and fibrogenesis [11].

- **Atherosclerosis (2015)** – In LDL receptor-deficient mice, SR9009 reduced aortic plaque size and shifted macrophage polarisation from pro-inflammatory M1 to anti-inflammatory M2 [12].

- **Synthetic REV-ERB analogues and exercise** – As noted above, analogues improved exercise tolerance and lipid/glucose profile; these data highlight metabolic benefits but not all analogues have been widely studied [8].

Renal and Musculoskeletal Effects

- **Renal fibrosis (2024)** – In unilateral ureteral obstruction and TGF-β1-treated NRK-49F cells, SR9009 reduced fibrosis by inhibiting NOX4 expression and p38/ERK phosphorylation independent of REV-ERBα [13].

- **Intervertebral disc degeneration (2024)** – SR9009 activation of NR1D1 inhibited NLRP3 inflammasome and IL-1β production, promoted extracellular matrix synthesis in nucleus pulposus cells, and delayed disc degeneration in vivo [14].

- **Osteoarthritis analgesia (abstracts)** – Research abstracts report that intra-articular SR9009 reduces mechanical hypersensitivity in a monoiodoacetate-induced osteoarthritis model and intrathecal SR9009 suppresses spinal microglial activation and pro-inflammatory cytokines, producing antinociceptive effects [15] [16]. These findings await peer-reviewed publication.

- **Bone metabolism** – SR9009 inhibited osteoclast differentiation, reduced reactive oxygen species and prevented ovariectomy-induced bone loss via upregulation of FABP4 and suppression of NF-κB/MAPK signalling [17].

Exercise Capacity and Kynurenine Metabolism

- **Exercise and kynurenine** – As mentioned, exhaustive exercise downregulated REV-ERBα leading to a neurotoxic kynurenine profile; SR9009 increased KAT1 and decreased KMO, shifting metabolism toward neuroprotection [4].

Cancer

Hematological and Solid Tumours

- **Multiple myeloma (2020)** – SR9009 combined with the proteasome inhibitor bortezomib synergistically reduced viability and proliferation of multiple myeloma cells by inhibiting autophagy and lipogenesis. SR9009 downregulated GRP78, FASN and other survival proteins and improved survival in mice [18]. This suggests REV-ERB agonists may potentiate existing therapies.

- **Small-cell lung cancer (2019)** – SR9009 was selectively lethal to small-cell lung cancer cells, including chemosensitive and resistant lines, by inhibiting autophagy through repression of Atg5. REV-ERBα involvement was confirmed, hinting at a targeted therapy [19].

- **Prostate cancer (2020)** – SR9009 inhibited proliferation, migration and induced apoptosis in prostate cancer cell lines, particularly the aggressive PCS1 subtype. The mechanism involved activation of LXRα and suppression of FOXM1 and was independent of REV-ERB [20].

- **Glioblastoma (review)** – A review article on glioblastoma treatment mentioned that circadian clock modulators such as SR9009 and SR9011 may provide new therapeutic avenues [21]. However, direct experimental data in glioblastoma models remain limited.

Other Cancer-related Observations

- **Myocardial ischemia/reperfusion** – Access restrictions prevented full analysis, but some sources suggest SR9009 might reduce ischemia-reperfusion injury via Nrf2 activation. This needs confirmation from primary literature.

Immune Response and Inflammation

Allergy and Asthma

- **Mast cell activation (2019)** – SR9009 suppressed IgE- and IL-33-mediated mast cell degranulation by inhibiting Gab2/PI3K and NF-κB signalling. Effects persisted in circadian Clock mutant cells, indicating a clock-independent mechanism [22].

- **House dust mite-induced allergic asthma (poster, 2020)** – In an acute house dust mite model, SR9009 reduced airway inflammation, decreased Th2 cytokines IL-4/IL-5, lowered muc5ac and Tslp expression and attenuated mucus production [23]. This suggests potential for allergic airway disease, though data are from a conference poster.

Sepsis and Acute Lung Injury

- **Sepsis-induced lung injury (2023)** – SR9009 ameliorated lipopolysaccharide-induced acute lung injury by suppressing TLR4/NF-κB signalling, reducing malondialdehyde and lactate, increasing SOD and glutathione and improving acid–base balance [24].

- **Ischemia–reperfusion lung injury (2023)** – In an ex vivo rat model, SR9009 reduced lung edema and cytokine production (TNF-α, IL-6, CINC-1) and restored IκB-α; these protective effects were lost upon Rev-Erbα inhibition or knockdown, indicating REV-ERB dependence [25].

- **Pneumonia and bacterial clearance** – A research summary reported that blue light or SR9009 increased REV-ERB expression, improved bacterial clearance and survival in bacterial pneumonia, reduced neutrophil infiltration and lowered chemokine/cytokine levels [26].

Macrophage Polarisation and Miscarriage

- **Decidual macrophages and miscarriage (2021)** – In human and mouse decidua, lipopolysaccharide induced an M1-like phenotype with decreased Rev-erbα. SR9009 (Rev-erbα agonist) reduced PI3K-dependent M1 polarisation, lowered embryonic resorption and improved pregnancy outcomes [27].

Atherosclerosis and Macrophage Polarisation

- As noted earlier, SR9009 decreased atherosclerotic plaque size and shifted macrophages from M1 to M2 phenotype in LDL receptor-deficient mice [12].

Bone and Connective Tissue

- **Osteoclastogenesis** – SR9009 suppressed differentiation of osteoclasts, reduced reactive oxygen species and prevented ovariectomy-induced bone loss partly via upregulation of FABP4 [17].

- **Intervertebral disc degeneration** – NR1D1 activation via SR9009 reduced inflammasome activation and pyroptosis and enhanced extracellular matrix synthesis, delaying disc degeneration [14].

- **Osteoarthritis (abstract)** – SR9009 reduced mechanical hypersensitivity in a monoiodoacetate-induced osteoarthritis model and suppressed spinal microglial inflammation [15] [16], suggesting analgesic potential.

Brain and Nervous System

- **Neural stem cells** – Described above, high concentrations of SR9009 suppressed neurite outgrowth while low concentrations enhanced it [6].

- **Stroke chronopharmacology** – SR9009 showed time-of-day dependent protection in stroke models, effective at ZT06 but not at ZT18 [5].

- **Potential antinociceptive effects** – The osteoarthritis abstracts and microglial study suggest that SR9009 may reduce pain through dampening spinal microglial activation and pro-inflammatory cytokines [16].

Lung Disease and Fibrosis

- **Acute lung injury** – SR9009 mitigated sepsis-induced acute lung injury and improved metabolic parameters in mice [24]. In ischemia–reperfusion models, it reduced lung edema and inflammatory cytokines in a REV-ERBα-dependent manner [25].

- **Renal fibrosis** – As noted, SR9009 reduced TGF-β1-induced fibrotic responses by inhibiting NOX4/p38 signalling independent of REV-ERBα [13].

Doping and Metabolism Studies

Because SR9009 is marketed as a “legal steroid alternative,” multiple studies focus on its detection and metabolism to prevent misuse.

- **Equine and human liver metabolism (2017-2019)** – In vitro studies using equine and human liver microsomes identified multiple phase I metabolites of SR9009 and SR9011. They highlighted

N-dealkylated metabolites and recommended doping laboratories include SR9009 in screening tests [28] [29]. Feature-based molecular networking revealed at least 15 metabolites and emphasised the need for detection protocols [30].

Limitations and Future Directions

1. **Specificity** – Many beneficial effects attributed to SR9009 occur even in REV-ERB knockout models [3] [2]. Off-target actions such as LXRα activation, NRF2 activation and PI3K inhibition may mediate some outcomes. Future studies must dissect these pathways and develop more selective REV-ERB agonists.

2. **Translational relevance** – Most data come from animal models or cell culture. The pharmacokinetics and safety of SR9009 in humans are unclear. Clinical trials are needed to evaluate therapeutic potential and toxicology.

3. **Chronopharmacology** – Several studies highlight time-of-day differences in SR9009 efficacy (NASH, stroke). Understanding circadian timing could improve therapeutic strategies but requires careful dosing schedules and human trials.

4. **Dosing and off-target toxicity** – SR9009 interacts with multiple nuclear receptors. High doses may produce undesired effects (e.g., suppression of neural stem cell proliferation [6]). Detailed dose–response studies and more selective analogues are necessary.

5. **Doping concerns** – Because SR9009 is available online and unapproved, misuse may occur in sports. Enhanced detection methods and regulation are needed, and researchers should avoid over-hyping untested “exercise mimetics.”

Conclusion

SR9009 has been widely used in experimental models to probe circadian and metabolic pathways. It improves metabolic parameters in obesity and NASH models, reduces inflammation and tissue injury in lung, kidney and cardiovascular models, and shows antitumor activity in multiple cancers. SR9009 also suppresses osteoclastogenesis, alleviates pain and delays intervertebral disc degeneration. However, many effects occur independently of REV-ERB, raising questions about specificity. Because human safety and efficacy remain undefined, SR9009 should be viewed as a tool compound rather than a therapeutic drug. Future research should develop selective REV-ERB agonists, investigate chronopharmacology, and conduct rigorous clinical studies before considering SR9009 for human use.

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