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AICAR (Acadesine) research from 2015-2024

Background and mechanism

AICAR (5-amino-imidazole-4-carboxamide ribonucleotide, also called acadesine) is an endogenous AMP analogue that enters cells via nucleoside transporters and is phosphorylated to form ZMP, a mimetic of AMP. ZMP activates AMP-activated protein kinase (AMPK), a cellular energy sensor, leading to downstream changes in glucose and lipid metabolism, mitochondrial biogenesis and autophagy. AICAR can also affect other enzymes such as fructose-1,6-bisphosphatase and may act independently of AMPK in some contexts. Because AICAR stimulates AMPK similar to exercise, it has been termed an exercise mimetic. It has been explored for cognitive enhancement, metabolic disease, cardiovascular and oncological applications, while concerns about performance enhancement and misuse have led to anti-doping monitoring.

Exercise mimetic and metabolic effects

Muscle adaptations and mitochondrial regulation

- **AMPK-dependent mitochondrial enzymes:** A 2015 mouse study showed that six and a half weeks of treadmill training increased muscle levels of SIRT3 and manganese superoxide dismutase (MnSOD); daily AICAR injections (500 mg/kg for four weeks) produced similar increases. These adaptations were absent in AMPK-α2-kinase-dead or PGC-1α-null mice, indicating that AMPK activation is required for exercise- or AICAR-induced increases in mitochondrial antioxidant enzymes [1].
- **Selective mTOR substrate phosphorylation:** In mouse C2C12 myotubes, acute AICAR treatment increased phosphorylation of AMPK target ULK1 and mTORC1 substrate S6K. After recovery, prior exposure to AICAR selectively enhanced S6K phosphorylation while ULK1 remained unchanged, suggesting that temporary AMPK activation modulates mTORC1 substrate specificity [2].
- **Calorie restriction (CR) and aged muscle:** A 2024 study on 24-month-old rats examined CR (15 % or 35 %) combined with acute AICAR incubation. CR alone did not enhance muscle glucose uptake; however, prior incubation with AICAR increased insulin-stimulated glucose uptake in both sexes regardless of diet. AICAR treatment increased ACC phosphorylation (an AMPK target), while CR increased Akt phosphorylation but did not translate into greater glucose uptake [3].
- **Cachexia and cancer:** Non-small-cell lung cancer (NSCLC) patients had elevated AMPK subunits in skeletal muscle. In tumour-bearing mice, chronic AICAR administration (13 days) increased hexokinase II, normalised phosphorylation of p70S6K and acetyl-CoA carboxylase (ACC), and improved insulin tolerance. This suggests that AICAR can ameliorate cancer-induced insulin resistance and preserve muscle metabolism [4].
- **Diabetic polyneuropathy:** In models of type 1 and type 2 diabetes, AICAR prevented or reversed diabetic peripheral neuropathy. It increased AMPK phosphorylation in dorsal root ganglion neurons and enhanced markers of mitophagy (DRP1, ULK1 and LC3-II). AICAR improved mitochondrial respiration, insulin sensitivity and lipid metabolism, leading to restored nerve function and sensory improvement [5].

- **Lipid metabolism and environmental stress:** In mice exposed to fine particulate matter (PM2.5) during pregnancy, AICAR treatment (200 mg/kg/day) alleviated hepatic lipid accumulation, lowered triglyceride and cholesterol levels, and reduced inflammatory and fibrotic markers [6].
- **AMPK activation in pancreatitis-associated liver injury:** AICAR protected rats against sodium taurocholate-induced pancreatitis-associated liver injury by activating AMPK and subsequently triggering Nrf2-dependent antioxidant pathways while inhibiting the NLRP3 inflammasome [7].

Muscle endurance and age-related decline

- **Chronic treatment in aged mice:** In old mice, daily injections of AICAR (500 mg/kg for 31 days) preserved treadmill running capacity and increased quadriceps muscle mass by about 8 % compared with saline controls. Ex vivo muscle force was 26.4 % greater, and there was no change in body weight [8]. RNA-sequencing showed that 143 genes altered by aging were restored toward youthful expression; gene ontology enrichment indicated upregulation of mitochondrial and metabolic pathways. AICAR suppressed expression of atrophy-related genes (Mafbx and Murf1) and increased serum IGF-1. These findings suggest that long-term AMPK activation may counteract sarcopenia [9].

Nootropic and neurological effects

- **Exercise mimetic effect on neurogenesis:** AICAR (500 mg/kg/day for 3–14 days) produced similar muscle AMPK activation and hippocampal BDNF expression as running. After 7 days, both running and AICAR increased dentate gyrus neurogenesis and BDNF. However, after 14 days AICAR no longer enhanced neurogenesis and instead up-regulated apoptotic and inflammatory genes, suggesting that its beneficial effects on the brain are transient and less sustainable than exercise [10].
- **Cognition and motor coordination:** A 2014 study (just before the decade limit but often cited) demonstrated that 3-day AICAR injections improved spatial memory and motor coordination in young mice; 14-day treatment produced similar improvements in aged mice. Effects were absent in muscle-specific AMPK-deficient mice, indicating that muscle-mediated signalling (myokines) contributes to cognitive benefits [11].
- **Neural differentiation via myokines:** Conditioned medium from AICAR-treated myotubes increased neuronal and astrocytic differentiation markers (DCX, Tuj1 and GFAP) in adult neural progenitor cells. Proteomic analysis identified glucose-6-phosphate isomerase (GPI) and other factors that promote neuronal differentiation [12].
- **Stress and memory:** In a 2024 rat model of chronic restraint stress, reduced endogenous AICAR levels were associated with decreased brain metabolites and synaptic proteins. Exogenous AICAR administration restored metabolites, increased PSD-95 and BDNF expression, and improved memory performance [13].
- **Neuroprotective effects in sepsis:** A review summarised that AICAR treatment in models of sepsis reduced bacterial loads, improved neutrophil chemotaxis and phagocytosis, and decreased inflammatory responses. AICAR alleviated lung barrier disruption and intestinal permeability, improved vascular barrier function and increased survival in lipopolysaccharide (LPS) or cecal ligation and puncture (CLP) models [14]. Though preclinical, these findings suggest AICAR may protect the brain via systemic anti-inflammatory actions.

Therapeutic applications beyond exercise and cognition

- **Cancer therapy:** AICAR was found to inhibit growth of EGFR-mutant lung cancer cells by inducing DNA damage and apoptosis, degrading the oncoprotein MUC1-CT and disrupting its interaction with JAK1. In patient-derived organoids, AICAR reduced tumour growth, and combined treatment with JAK or EGFR inhibitors further suppressed growth [15]. These anti-oncogenic effects may be independent of AMPK.
- **Sepsis and inflammation:** As noted above, sepsis models indicate that AICAR can reduce inflammatory cytokine production and organ injury [14]. In pancreatitis-associated liver injury, AICAR activated the AMPK-Nrf2 axis and suppressed NLRP3 inflammasome activation [7].
- **Purine synthesis inhibitors and glucose uptake:** In L6 myotubes, inhibitors of purine synthesis (e.g., methotrexate) enhanced AICAR-induced AMPK activation and glucose uptake without impairing mitochondrial function [16], suggesting that combining purine synthesis inhibition with AICAR could augment metabolic benefits.

Longevity and age-related effects

There is little direct evidence that AICAR extends lifespan. However, several studies suggest that chronic AMPK activation by AICAR can counteract age-related declines in muscle and metabolic health:

- The aged mouse study described above showed improved endurance, muscle mass and gene expression profiles after one month of AICAR treatment [8] [9]. These effects may improve functional longevity but no lifespan data were reported.
- Calorie-restricted aged rats maintained insulin-stimulated glucose uptake when incubated with AICAR [3], implying that AICAR can maintain metabolic flexibility in old age.
- In diabetic and cachexia models, AICAR improved nerve and muscle function [5] [4]. Such improvements might translate to better healthspan, though long-term survival studies are lacking.

Safety, toxicity and doping considerations

- **Clinical tolerance:** An interventional trial using AICAR (acadesine) as an adenosine-regulating agent reported that it was well tolerated in more than 4000 cardiac patients; however, high, sustained doses may cause toxicity [17]. AICAR's metabolite ZMP can accumulate and cause metabolic stress if purine synthesis is inhibited.
- **Performance enhancement and anti-doping:** Because AICAR can increase endurance and metabolic efficiency, it is on the World Anti-Doping Agency (WADA) prohibited list. Anti-doping studies have developed methods to distinguish endogenous vs exogenous AICAR:
- A 2017 study analysed post-race horse urine samples and proposed a screening cut-off of ~600 ng/mL; the authors noted that haemolysis increases plasma AICAR, complicating threshold setting [18].
- Gas chromatography-combustion isotope ratio mass spectrometry (GC-C-IRMS) methods were developed to differentiate exogenous AICAR by silylation and additional HPLC purification [19].
- A 2024 two-dimensional HPLC combined with GC/C/IRMS method could detect exogenous AICAR up to 16 hours after low-dose administration, reducing sample preparation time and improving accuracy [20].

Key takeaways

1. **Exercise mimetic effects:** AICAR activates AMPK to promote mitochondrial biogenesis, enhance oxidative metabolism and increase antioxidant enzymes. These changes replicate some muscular adaptations to endurance exercise, although long-term treatment may yield diminishing returns or catabolic effects if not carefully dosed.
2. **Nootropic potential:** Short-term AICAR administration improves hippocampal neurogenesis, synaptic protein expression and cognitive performance, but prolonged high doses may induce inflammation and apoptosis. The brain effects appear mediated partly by muscle-derived myokines.
3. **Therapeutic applications:** Beyond exercise, AICAR shows promise in treating diabetic neuropathy, metabolic syndrome, pancreatitis-associated liver injury, sepsis and certain cancers. Combination with purine synthesis inhibitors or other drugs can enhance its metabolic or anticancer effects.
4. **Longevity:** Evidence for life-span extension is indirect. AICAR improves functional measures and molecular signatures of aging, but no studies report increased lifespan in mammals. Long-term AMPK activation may confer healthspan benefits.
5. **Safety and doping:** AICAR is generally well tolerated but high or prolonged doses can be toxic. Its potential as a performance enhancer led to inclusion on WADA's prohibited list, prompting development of sensitive detection methods to distinguish endogenous from exogenous AICAR [18] [19] [20].

Conclusion

Research over the past decade shows that AICAR is a versatile molecule influencing energy metabolism, muscle adaptation, neural function and disease pathways through AMPK-dependent and independent mechanisms. Short-term AICAR treatment can mimic some benefits of exercise and confer cognitive improvements, while longer administration improves muscle endurance and metabolic health in aged animals. It also holds therapeutic potential for neuropathy, sepsis, pancreatitis and certain cancers. Yet, the benefits are context dependent and may decline or cause adverse effects with sustained high dosing. Clinical use requires careful dosing and monitoring, and due to its performance-enhancing potential, rigorous anti-doping methods have been developed to detect misuse.

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