



Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

TRPM2 Inhibitors

Evidence Summary

TRPM2 inhibitors may protect against oxidative stress damage by preventing toxic Ca^{2+} overload, but effects are likely cell type and context dependent, and full safety risks are not clear.

Neuroprotective Benefit: TRPM2 inhibition may protect against oxidative stress and $\text{A}\beta$ -induced neuroinflammation. But protection against cerebral ischemic injury is male specific, and prolonged inhibition may disrupt cellular bioenergetics.

Aging and related health concerns: TRPM2 inhibition may inhibit tumor growth for some cancers and prevent the induction of neuropathic pain, but it may exacerbate diabetic hyperglycemia.

Safety: Safety data is confounded by a lack of specific inhibitors, but studies in TRPM2 knockout animals suggests chronic inhibition may increase infection risk. Organ type selective inhibitors are expected to have the best safety profile.



Availability: Non-specific inhibitors for research use	Dose: N/A	Chemical formula: N/A MW: N/A
Half-life: N/A	BBB: Varied	
Clinical trials: None	Observational studies: None for inhibitors. TRPM2 is overexpressed and associated with worse outcome in a variety of cancers.	

What is it?

Transient receptor potential melastatin 2 (TRPM2) is a non-selective cation channel localized to the plasma membrane with Ca^{2+} permeability [1]. It is a thermosensitive channel that can be activated upon exposure to temperatures above 35°C (95°F) in combination with an agonist. The preferred endogenous agonist for the TRPM2 channel is ADP ribose (ADPR), which is generated by poly (ADP-ribose) polymerase (PARP) through an NAD⁺ dependent mechanism. TRPM2 is also activated in response to Ca^{2+} , and the combination of Ca^{2+} with ADPR is synergistic with respect to channel activation. The production of ADPR increases under conditions with elevated production of reactive oxygen species (ROS), thus TRPM2 activity is highest in the context of oxidative stress. Ca^{2+} entry through TRPM2 regulates a variety of Ca^{2+} dependent processes, including cellular bioenergetics, in a cell type specific manner [2]. However, sustained elevated Ca^{2+} entry through TRPM2 can lead to cytotoxic Ca^{2+} overload. TRPM2 inhibitors have been in preclinical development to prevent pathological Ca^{2+} overload, but thus far it has been challenging to develop a specific inhibitor with good pharmacokinetic properties.

Neuroprotective Benefit: TRPM2 inhibition may protect against oxidative stress and $\text{A}\beta$ -induced neuroinflammation. But protection against cerebral ischemic injury is male specific, and prolonged inhibition may disrupt cellular bioenergetics.

Types of evidence:

- 1 gene association study for a TRPM2 variant in ALS and PD
- Numerous laboratory studies

[Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?](#) None



Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer's disease: POTENTIAL BENEFIT (Preclinical)

TRPM2 is widely expressed in the CNS, in neurons and glial cells [3]. It has not yet been established whether TRPM2 levels or activity is dysregulated in the Alzheimer's disease (AD) brain, but cell culture and animal models suggest that **TRPM2 mediates A β -related neurotoxicity, particularly with respect to neuroinflammatory responses and oxidative stress damage** [4]. TRPM2 is expressed in human hippocampal neurons, and hippocampal expression of TRPM2 has been shown to be upregulated in people with major depressive disorder [5], suggesting that changes to TRPM2 are associated with changes to neurological function.

Spatial memory deficits in the Barnes maze and Morris water maze, were reduced in aged (15 months old) male APP/PS1 AD mouse model mice deficient in TRPM2 [6]. While plaque burden was unchanged, these mice had reduced levels of ER stress and synaptic damage relative to APP/PS1 mice with TRPM2. Non-specific TRPM2 inhibitors, such as ACA (N-(p-amylcinnamoyl)anthranilic acid), have been shown to ameliorate okadaic acid and scopolamine-induced memory impairment in rats by preserving mitochondrial integrity and neuronal survival [7; 8]. The protective efforts were associated with a reduction of oxidative toxicity, including a preservation of the levels of glutathione and associated antioxidant enzymes (SOD, GSH-PX), and a reduction in the levels of oxidized lipids.

In cell culture, the addition of A β , augments the activity of the TRPM2 channel [9]. TRPM2 activation is part of a feedback loop that propagates oxidative stress damage and neuroinflammation [4; 10]. A β stimulates the production of ROS and activates PARP-1, which leads to the production of ADPR, the endogenous agonist of the TRPM2 channel. The activation of the TRPM2 channel leads to a rise in intracellular Ca $^{2+}$ levels, which influences the activity of Ca $^{2+}$ sensitive proteins and downstream signaling. PARP-1 can be activated by Ca $^{2+}$ sensitive signaling pathways, such as the MEK/ERK signaling pathway, leading to further activation of TRPM2. Excessive activation of TRPM2 can lead to ionic dyshomeostasis, particularly with respect to calcium and zinc, and subsequent neurotoxicity.

Excessive activation of TRPM2 leads to lysosomal and mitochondrial dysfunction. Homeostatic maintenance of the free intracellular Zn $^{2+}$ is crucial for the preservation of the antioxidant response [11]. Zn $^{2+}$ is a component of some antioxidant enzymes which reduce the generation of ROS, but at high



intracellular concentrations it enters mitochondria where it induces mitochondrial fragmentation and dysfunction and promotes the production of ROS, leading to the activation of apoptotic processes [12]. The ROS-mediated activation of TRPM2 can induce the release of Ca^{2+} and Zn^{2+} from lysosomes, which further increases intracellular levels, and leads to lysosomal dysfunction [13]. In lung cells, TRPM2 mediated Ca^{2+} and Zn^{2+} dyshomeostasis results in a reduction in the degradative capacity of lysosomes and impairment of autophagic flux [14]. It is not yet clear whether a similar impairment occurs in neurons, but if it does, it could contribute to the buildup of toxic misfolded proteins in neurodegenerative diseases.

TRPM2 is also involved in $\text{A}\beta$ -related microglial activation in cell culture. The addition of $\text{A}\beta$ to cultured microglia can promote the secretion of proinflammatory cytokines, such as $\text{TNF}\alpha$, in a TRPM2 dependent manner [9]. The influx of Ca^{2+} following TRPM2 channel activation promotes NLRP3 inflammasome activation, the cleavage of caspase-1, and secretion of $\text{IL-1}\beta$ [15]. These Ca^{2+} mediated changes transform microglia into a proinflammatory state. Ca^{2+} overload can also disrupt astrocyte signaling and function, which utilize Ca^{2+} waves for cellular communication.

TRPM2 overactivation can also induce neurovascular dysfunction and damage. $\text{A}\beta$ can induce oxidative and nitrosative stress on cerebrovascular endothelial cells, leading to DNA damage, PARP-1 activation, APDR generation, TRPM2 activation, and Ca^{2+} overload [16]. The nitration of TRPM2 (at tyrosine residue Y1485 in mice), can promote pathogenic autophagy, leading to brain pericyte injury, and disruption of the microvasculature [17].

Age-related cognitive impairment: POTENTIAL BENEFIT (Preclinical)

TRPM2 knockout male mice were found to be resistant to age-related cognitive impairment, based on performance on the Y-maze and novel object recognition tasks [18]. These aged mice also had less neuroinflammation and white matter damage. TRPM2 activation is projected to be increased with age due to age-related changes in the expression of endogenous antioxidants. The antioxidant glutathione (GSH) has been found to act as an endogenous inhibitor of the TRPM2 channel, thus as GSH levels decline, TRPM2 activity increases [19]. The combination of low GSH and high TRPM2 then increases the susceptibility of aged neurons to oxidative damage [20].

Parkinson's disease: POTENTIAL BENEFIT

TRPM2 overactivation is implicated in oxidative stress mediated neurotoxicity in the substantia nigra. TRPM2 expression was found to be increased in the substantia nigra of patients with Parkinson's disease



(PD), based on postmortem brain tissue analysis (n=8 PD, n=6 controls) [21]. TRPM2 channel activation may participate in ROS modulated spontaneous firing rate and burst firing in the substantia nigra and thus may contribute to altered firing patterns in PD patients [22, 23]. Mitochondrial toxins, such as paraquat and MPTP, used to induce a PD-like state in cellular and animal models, increase ROS levels and activate TRPM2, leading to a cycle of Ca^{2+} overload, neuroinflammation, and cell death [21; 24; 25; 26]. Aged male rats were found to be more susceptible to paraquat-mediated neurotoxicity than their younger counterparts, due to increased TRPM2 activation and Zn^{2+} dysregulation [24]. The mechanisms of TRPM2-associated oxidative stress damage appear to be similar for dopaminergic neurons as those described for hippocampal neurons following $\text{A}\beta$ -related oxidative stress damage.

Although TRPM2 overactivation is associated with Ca^{2+} overload and neurotoxicity, physiological **activation of TRPM2 appears to influence mitochondrial function and metabolism.** In a gene association study involving individuals of Western Pacific descent, a missense variant in TRPM2 was found to confer susceptibility to Guamanian amyotrophic lateral sclerosis (ALS) and parkinsonian-dementia [27]. The variant, TRPM2P1018L, produces a missense change in the channel protein whereby proline 1018 is replaced by a leucine, and this change produces channels that inactivate, especially under conditions of high Ca^{2+} . This suggests that disruption to the tonic influx mediated by TRPM2 under physiological conditions may impair neuronal metabolism and increase their vulnerability to oxidative damage. Consequently, chronic inhibition of TRPM2 may negatively impact mitochondrial function. Additionally, TRPM2 has the features of being a chanzyme, or an ion channel with an enzymatic motif. It contains the enzymatic domain NudT9-H in its C-terminus, and may play a role in ADPR catabolism [28]. ADPR is hydrolyzed by NudT9 pyrophosphatase in most organs, but this enzyme is defective in the brain. In mice, the loss of TRPM2 was found to disrupt ADPR catabolism, leading to an excess accumulation of ADPR and a reduction in AMP levels. This shift, particularly the decline in AMP can lead to an impairment in autophagy, as well as an imbalance in synaptic transmission. If TRPM2 has similar enzymatic activity in the human brain, chronic inhibition could further disrupt brain metabolism. Notably, the enzymatic activity is not associated with its channel activity, therefore, it should be possible to specifically target the channel activity of TRPM2 in the development of therapeutic inhibitors.

Cerebral ischemic injury: POTENTIAL BENEFIT FOR MALES (Preclinical)

Preclinical animal models indicate that TRPM2 plays a role in ischemic/hypoxic cerebral injury. Deletion or inhibition of TRPM2 protects against neuronal loss, neuroinflammation, and cognitive dysfunction in models where damage is driven by the generation of ROS and oxidative stress [29]. Neuroprotection was not demonstrated in the context of permanent middle cerebral artery occlusion (pMCAO), which is a



model that lacks reperfusion [30]. Under these conditions, pathological mechanisms other than ROS generation may predominate, and/or the damage may be too severe for TRPM2 inhibition to compensate. Notably, **the neuroprotective effect of TRPM2 inhibition during ischemic insult has a sex effect, and is only observed in males**. In a focal transient MCAO model, inhibition of TRPM2 before the ischemic injury, or (3 hours) after reperfusion reduced infarct volume in both young and aged male mice, but had no effect in female mice [31]. A similar sex effect was seen in neuroprotection against oxygen-glucose in primary neurons derived from male and female mice [32]. It is hypothesized that the use of alternative metabolic pathways in the metabolism of NAD+ and production of ADPR may contribute to the male-specific effects of TRPM2 activation and inhibition in the context of ischemic injury [32].

APOE4 interactions: Not known

Aging and related health concerns: TRPM2 inhibition may inhibit tumor growth for some cancers and prevent the induction of neuropathic pain, but it may exacerbate diabetic hyperglycemia.

Types of evidence:

- 4 observational studies for TRPM2 expression in cancer
- Numerous laboratory studies

Diabetes: POTENTIAL MIXED (Preclinical)

Based on the roles for TRPM2 in different cell types, inhibition of TRPM2 would be expected to exacerbate pancreatic dysfunction in the context of diabetes, but to alleviate some of the associated conditions, such as vascular dysfunction, neuropathy, and cognitive dysfunction.

TRPM2 is involved in the stimulation of glucose-stimulated insulin secretion in pancreatic β -cells [33]. It potentiates Ca^{2+} -dependent insulin granule exocytosis from β -cells. Glucagon like peptide-1 (GLP-1) promotes this process, while ghrelin attenuates it by affecting levels of cAMP to activate or inhibit TRPM2, respectively [34; 35]. **TRPM2 deficient mice have reduced levels of insulin secretion and impaired glucose tolerance** [33]. The importance of this pathway in humans has not yet been established, but a gene association study suggests that it may play a role. In a case-control study of type 2 diabetics (n=922), three TRPM2 variants, rs2838553, rs2838554, and rs4818917 were inversely associated with homeostasis model assessment of β -cell function (HOMA-%B), but were not significantly associated with HOMA-insulin resistance (HOMA-IR), fasting glucose levels, hemoglobin A1c levels [36].



Although the inhibition of TRPM2 may exacerbate glucose intolerance, it may also protect against high-glucose induced oxidative stress damage in the vasculature and nervous system. In human vascular endothelial cells, stress-induced TRPM2 channel activation led to the redistribution of Zn²⁺ from lysosomes to mitochondria, leading to mitochondrial fragmentation [37]. In a rat model of streptozotocin-induced diabetes, treatment with a TRPM2 inhibitor (2-aminoethoxydiphenyl borate, 2-APB) ameliorated cognitive impairment based on behavioral tasks, and restored expression of memory-associated proteins, including CaMKII, PSD95, and BDNF [38]. Treatment with the antioxidant N-acetylcysteine (NAC) was protective against oxidative stress damage and Ca²⁺ overload in diabetic neurons in this model through inhibition of TRPM2 [39]. TRPM2 deficiency was also found to be protective against streptozotocin -induced diabetic neuropathy resulting from hyperglycemia-related oxidative stress in peripheral sensory neurons [40].

Cardiovascular: POTENTIAL MIXED (Preclinical)

There is conflicting evidence based on preclinical models as to whether TRPM2 promotes or protects against cardiac ischemic damage, suggesting that it has **context dependent activity in cardiac tissue** [2]. In the heart, low levels of ROS are produced in respiring mitochondria, and may lead to the tonic entry of TRPM2 mediated Ca²⁺ entry, which is important for bioenergetic maintenance under physiological conditions [41]. However, in response to ischemic/reperfusion injury, sustained elevated Ca²⁺ entry through TRPM2 channels can lead to pathogenic Ca²⁺ overload and disrupt bioenergetic maintenance [2]. Consequently, whether TRPM2 activity is beneficial or deleterious depends on the degree of activation and the injury conditions. This suggests that TRPM2 inhibition may be beneficial during acute ischemic cardiac injury to dampen oxidative stress damage, but prolonged inhibition may impair basal respiratory function in cardiac tissue.

TRPM2 plays a role in regulating endothelial Ca²⁺ homeostasis and endothelial function [16]. Endothelial Ca²⁺ signaling is involved in angiogenesis, and endothelial TRP channels play a role in vascular endothelial growth factor (VEGF) mediated vascular remodeling [42]. This could promote aberrant vascularization of tumor tissue, but also promote the restoration of blood flow following injury. ROS increase vascular endothelial permeability, and TRPM2 inhibition may help reduce vascular oxidative damage, mitigate inflammation, and maintain barrier integrity [43].

Cancer: POTENTIAL BENEFIT (Preclinical)

TRPM2 is highly expressed in a variety of cancers including, breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, melanoma, leukemia, and neuroblastoma [2; 44]. In cell culture and



xenograft models, TRPM2 activity promotes cancer cell survival. **Ca²⁺ influx through TRPM2 channels is important for the maintenance of the cellular bioenergetics that facilitate tumor cell growth**, and when this influx is inhibited tumor cells show evidence of mitochondrial dysfunction and increased ROS production [44]. TRPM2 is normally localized to the plasma membrane, but in tumor cells a large percentage of TRPM2 is localized to the nucleus, which may account for its unique roles in DNA damage repair and the promotion of cell survival in these cells [44]. However, the role of TRPM2 is cancer type dependent, as TRPM2 activation has been found to promote tumor cell apoptosis in some cancer cells, including bladder cancer and glioblastoma [44].

Gastric cancer: TRPM2 expression was found to be inversely associated with survival in patients with gastric cancer (n=876; Hazard Ratio HR: 1.261, p=0.0071) [45]. In cell culture, inhibition of TRPM2 reduces cell survival, impairs mitochondrial function, dysregulates autophagy, and sensitizes gastric cancer cells to chemotherapeutic agents [45; 46].

Pancreatic cancer: In patients with pancreatic ductal adenocarcinoma (n=159), the mutation status of TRPM2 was significantly inversely correlated with patient survival ($P=1.0416\times 10^{-2}$), and high expression of TRPM2 was also associated with worse survival ($P=4.2253\times 10^{-2}$) [47]. In cell culture, TRPM2 overexpression was associated with increased proliferation and migratory capacity.

Lung cancer: In cancerous tissue from non-small cell lung cancer patients (n=60) the long noncoding RNA (lncRNA), TRPM2-AS, was found to be upregulated (5.78 ± 1.35 fold) and positively correlated with tumor stage and size [48]. Elevated TRPM2-AS expression was also associated with worse survival (HR: 1.239, p=0.003). In cell culture, knockdown of TRPM2-AS inhibited proliferation and promoted apoptosis of the lung cancer cells. TRPM2-AS is a lncRNA that is an antisense to TRPM2, but its *in vivo* function, including its potential ability to modulate TRPM2 activity or expression is not well understood.

Prostate cancer: The antisense lncRNA, TRPM2-AS, was found to be overexpressed in prostate cancer based on both tumor tissues and prostate tumor cell lines [49]. In an analysis of clinical parameters, high TRPM2-AS expression was associated with poor prognosis, as these tumors had an enhanced proliferation rate.

Neuropathic pain: POTENTIAL BENEFIT DURING INDUCTION PHASE (Preclinical)

The role of TRPM2 in neuropathic pain is derived from its ability to modulate peripheral and central neuroinflammation, rather than influencing physiological nociceptive pain mechanisms [40]. TRPM2 activation contributes to the secretion of chemokines and cytokines from immune cells that results in the induction of neuropathic pain, including increased mechanical allodynia and heat pain sensitivity [50]. In rodent models, TRPM2 expression is increased in the spinal cord and dorsal root ganglia acutely



after peripheral nerve injury, and TRPM2 inhibition during this acute phase can block the induction of neuropathic pain [50]. The protective effects are associated with the reduction of oxidative stress induced neuroinflammation and circuit modification. TRPM2 deficiency was found to be protective against the induction of neuropathic pain in a variety of models that involve oxidative stress, including the monosodium iodoacetate-induced osteoarthritis pain model, the inflammatory demyelinating (multiple sclerosis-like) experimental autoimmune encephalomyelitis model, paclitaxel-induced peripheral neuropathy model, and streptozotocin-induced diabetic neuropathy model [40]. However, it was not protective in models where pain was not associated with neuroinflammation and oxidative stress injury. Additionally, **TRPM2 activity appears to play a role in the acute induction of neuropathic pain, but not in its maintenance**, as inhibition of TRPM2 during the chronic phase offered no benefit [50].

Safety: Safety data is confounded by a lack of specific inhibitors, but studies in TRPM2 knockout animals suggests chronic inhibition may increase infection risk. Organ type selective inhibitors are expected to have the best safety profile.

Types of evidence:

- Numerous laboratory studies

Due to the difficulty in developing specific TRPM2 inhibitors with good *in vivo* pharmacokinetic properties, animal studies have primarily used non-specific inhibitors, thus it can be difficult to tease apart the exact contribution for TRPM2 in terms of potential side effects [51]. Similarly, interpretation of potential safety signals from TRPM2 knockout animals can be confounded by developmental or compensatory effects.

Based on preclinical studies, the primary potential safety concerns for TRPM2 inhibitors are the impairment of glucose tolerance and increased risks for complications from infection due to immune system dysregulation.

TRPM2 plays an important role in immune and inflammatory responses. The loss of TRPM2 is associated with impairment of monocyte activation and neutrophil migration [43]. This impairment of innate immune responses may increase vulnerability to infection. The loss of TRPM2 is not expected to interfere with normal thermosensation, however, it may compromise the ability of the body to regulate temperature in the context of high fevers [52]. It has been hypothesized that TRPM2 may serve as a



brake to prevent excessive fever responses, as TRPM2 deficiency was found to reduce survival in rodents exposed to endotoxins and some types of pathogens [52].

Since TRPM2 expression is widespread, and it plays various cell-type dependent roles, it may be necessary to develop inhibitors that preferentially target TRPM2 in different organ systems. TRPM2 channels form tetramers, so the association of different splice variants may modulate the channel structure and function [2]. If certain combinations are organ type specific, it may be possible to specifically target them, and minimize side effects in other organ systems.

Sources and dosing: There are currently no specific TRPM2 inhibitors available for clinical use. Non-specific inhibitors including - 2-aminoethoxydiphenyl borate (2-APB), N-(p-amylocinnamoyl)anthranilic acid (ACA), clotrimazole and flufenamic acid, are available for research use.

Research underway: Research into the function and disease contribution of TRPM2 has been hampered by the lack of specific inhibitors with good PK properties. A variety of research groups have been involved in development of these inhibitors. A group at Janssen recently reported on the development of JNJ-28583113, which is a potent, brain penetrant inhibitor for TRPM2, but has poor metabolic stability [51]. Further optimization is necessary to develop an inhibitor that would be suitable for clinical use.

Search terms:

Pubmed, Google: TRPM2 Inhibitors

- Alzheimer's disease, Parkinson's disease, ischemia, oxidative stress, inflammation, aging, cardiovascular, diabetes, cancer, pain, thermosensation

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