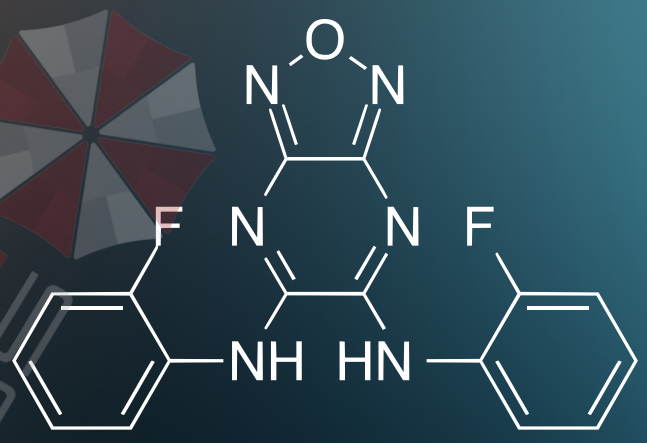


BAM15 - Investigating Its Potential in Metabolic Health Research

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History

In 2014, a large international consortium of researchers from the US and Japan reported the discovery of BAM15.[1] BAM15 is classified as mitochondrial uncoupler, which constitutes a larger group of compounds known since the beginning of the 20th century. Mitochondrial uncouplers create a “shortcut” in mitochondria, which allows the cell respiratory chain, which is normally coupled to ATP production, to produce heat instead. Hence the term “uncoupler”. This leads to an increased caloric demand, a faster metabolism and an increase in body temperature if the effect is sufficiently high. In the past, uncouplers like 2,4-dinitrophenol have been marketed as weight loss medication for this reason. These compounds are very effective as weight loss medication, but they have a number of undesirable short- and long-term side effects including dermatitis, rashes and cataracts. Most dangerous is that an overdose is extremely dangerous with a 12% lethality reported over the period between 2010 and 2020.[2] Overdose can also occur relatively easily, since the therapeutic index of 2,4-dinitrophenol and other mitochondrial uncouplers is small. The negative effects of mitochondrial uncouplers are partially due to off-target activity at other membranes that lead to a range of undesired effects including plasma membrane depolarization, mitochondrial inhibition, and cytotoxicity.

To find mitochondrial uncouplers without such off-target effects, the discoverers of BAM15 screened a large library to identify superior compounds. BAM 15 was reported to have no off- target effects and a lower rate of cytotoxicity.

Cell Culture Experiments

Compared to FCCP, an uncoupler of equal potency, BAM15 treatment of cultured cells stimulates a higher maximum rate of mitochondrial respiration, which suggests that BAM15 can achieve a higher metabolic rate in animals compared to FCCP.[1] Additional cell culture studies have showed signs of reduced production of pro-inflammatory substances in multiple studies.[3,4] These results lead to an array of research that has focused on BAM15 as a potential substance to downregulate immune responses in diseases.

Mitochondrial uncouplers reduce the amount of energy a cell can use since it does limit ATP production dose dependently. Cancer cells are notoriously active and need a large amount of ATP.

Hence, some research groups have hypothesized mitochondrial uncouplers could be effective pharmaceuticals to limit cancer growth. In fact, BAM15 has shown some potential in limiting the growth of aggressive breast cancer cells.[5] A similar effect has been shown in lung cancer cells.6 Whether this effect is large enough to lead to therapeutic benefits in cancer therapy is still unknown.

Animal Studies

Metabolic Impact

In the original publication, the authors reported that BAM15 can protect mice from kidney damage under specific conditions, just as other mitochondrial uncouplers can, which was the first evidence that BAM15 is indeed bioactive after injection.[6]

Mice which were fed with a diet rich in calories were protected against weight gain if BAM15 (85 mg/kg orally administered) was supplied in their food. BAM15 did also positively modulate body composition and glycemic control independently of its weight-reducing effects. Glycemic control is an important parameter for the development of diabetes type 2 and long-term health. The study did also suggest that cell damage occurs at higher doses compared to, DNP and FCCP, two other mitochondrial uncouplers.[7] Further experiments have confirmed the weight controlling effects in mice and other health promoting effects like a decreased serum level of inflammatory lipids.[8]

A comparison of BAM15 with other common treatments of obesity and increased serum lipid levels in mice such as semaglutide, rosiglitazone and niclosamide ethanolamide showed that BAM15 was the most effective in decreasing body weight, glucose tolerance and high lipid levels. This study provided a comprehensive head-to-head comparison of several key treatment strategies for metabolic disease and highlight the efficacy of mitochondrial uncoupling to correct multiple facets of the metabolic disease milieu in mice.[9,10]

Additionally, there is limited evidence that BAM15 has a positive effect on the age related loss of muscle in mice. A series of biomarkers for muscle loss were found to be improved after mice received a high fat diet with 0.1 w% of BAM15 for 10 weeks.[11]

Use as anti-inflammatory agent

An interesting aspect of mitochondrial uncoupling is the reduction of mitochondrial reactive oxygen species (mtROS), which play a role in pathogenesis of sepsis and other diseases. Mice treated with BAM15 showed reduced sign of kidney damage and mortality after induction of sepsis, as well as increased survival of immune cells.[12] BAM15 also decreased the immune response in mice after the injection of pro-inflammatory substances.[3,13,14]

A further study has trialed BAM15 bound to specific particles as anti-inflammatory agent. The particles are designed to only target macrophages, specific cells of the native immune response system. In mice, these particles loaded with BAM15 were able to decrease the severity of immune system overstimulation during sepsis, which indicates BAM15 may be a useful therapeutic compound beyond currently envisioned applications.[14]

Since past experiments on the nematode C. elegans with 1,4-dinitrophenol (DNP) have shown a reduced rate of neurodegeneration during aging, similar experiments have been repeated using BAM15. The compound did indeed also showed reduced mechanosensory neuronal defects during aging in C. elegans, which correlates with the maintenance of touch responses and short-term memory during aging.[15] BAM15 also extended the lifespan of the nematodes by 28 BAM15 did also increase the lifespan of the fruit fly drosophila melanogaster between 9% and 25%, depending in the diet of the flies.[16] Whether these results can also been transferred to other organisms is currently unknown.

Infectious Diseases

Toxoplasma gondii is an opportunistic pathogenic protozoan that is widely distributed worldwide and can cause toxoplasmosis in both humans and animals, seriously threatening human health. The most common vector for toxoplasma injections are cats and mice. Previous strategies to treat an infection with this microbe have targeted toxoplasmas mitochondria to damage the pathogen selectively.

Interestingly, researchers found that toxoplasma is much more susceptible to BAM15 compared to human cells, which may indicate BAM15 could be a therapeutic option to treat toxoplasma infections without the use of commonly used antibiotics and hence prevent development of antibiotic resistance.[17]

PCOS

Polycystic ovary syndrome (PCOS) is a common endocrine condition characterized by endocrine, reproductive and metabolic dysfunction. At present, there is no cure for PCOS and current treatments are suboptimal. Obesity and adverse metabolic features are often found in women with PCOS, with weight loss having a beneficial effect on PCOS features. The use of dietary interventions aimed at weight loss have low long-term compliance in women suffering from PCOS. In a mouse model of PCOS, BAM15 treatment decreased insulin resistance, cholesterol and fasting triglyceride levels, as well as the degree of hepatic damage to levels comparable with controls. The positive effects are likely to due to weight-reducing properties of BAM15 and not due to a specific effect of BAM15 for the treatment of PCOS.[18],[19]

Conclusion

BAM15 has shown to have remarkably positive effects in mice. As it seems, it is superior to the mitochondrial decouplers of the earlier generations, especially regarding its safety profile, which was the main drawback of earlier compounds. BAM15 has large potential as a safe alternative to controlled symptoms of metabolic syndrome, reduce weight in overweight individuals, improve glucose tolerance and reduce blood lipid levels. Other potentially beneficial side effects to be researched include an increase in life span and anti-inflammatory effects. There is limited evidence suggesting the use in cancer therapy and treatment of infectious diseases.

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