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Mechanisms of action of compounds that mimic beneficial effects of calorie restriction such as lifespan extension: Is taurine a promising candidate?

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Abstract More than 80 years ago, McCay and colleagues first reported that limiting the amount of food provided to experimental animals (i.e. calorie restriction or CR) prolongs their lifespan and suppresses the onset and progression of various age-related diseases. Today, CR remains the most reliable method of delaying aging in experimental animals, and research into its underlying molecular mechanisms is ongoing. CR has been reported to have anti-aging and life-extension effects on primates, with progress being made toward applications for humans. Studies on mechanisms underlying the onset and prevention of lifestyle-related diseases such as diabetes have elucidated the cellular signaling pathways that regulate energy metabolism, and commonalities have been discovered between the targets of existing diabetes drugs and the signaling pathways affected by CR. This finding has led to research into the discovery of drugs that have the anti-aging effects of CR in the absence of food intake limitations, namely CR mimetics (CRM). Several drugs have been reported to extend the lifespan of experimental organisms, which may thus have the potential to also extend human lifespan. In this article, we outline and compare those drugs that have been reported to date and discuss the possibility of taurine as a CRM, which is a topic of our ongoing research.

Keywords: lifespan, age-related diseases, metabolic syndrome, oxidative stress

Introduction

From time immemorial, humans have been on a quest for an elixir granting eternal youth and immortality. Many legends claim that ingesting certain plants, organisms, or their extracts, engenders health benefits and prolongs the human lifespan, though many of these claims are anecdotal and few have been scientifically verified. One such claim that has been scientifically verified is calorie restriction (CR). Research shows that limiting the amount of food (calories) fed to laboratory animals, while providing them with the nutrients necessary for survival, suppresses various diseases and the aging process, compared with animals granted free access to food (ad libitum). This strategy has also been demonstrated to extend lifespan. These beneficial effects of CR are observed in several experimental organisms ranging from yeast to primates, suggesting the presence of an evolutionally-preserved lifespan regulation signaling system that is activated by CR. If this system is universal to all living animals, then humans may also benefit from CR.

To date, the anti-aging effects of CR on humans have not been elucidated. However, changes to biomarkers found in humans with potentially long lifespans, such as people with low body temperatures or low blood insulin levels, are similar to those found in calorie-restricted animals. In addition, reports from two independent research groups on rhesus macaques demonstrate that CR exerts anti-aging and lifespan extension effects on primates1-3).

Despite its potential lifespan-extending effects, CR is difficult to implement for a prolonged period in humans because it also exerts severe physiological and psychological side effects. Therefore, there is interest in developing calorie restriction mimetics (CRM) (i.e. compounds that mimic the effects of CR without limiting food intake). Developmental targets of CRM replicate the observed biomarker changes caused by CR in humans, such as an increase in insulin sensitivity. CRM are molecules that contribute to the regulation of not only glucose metabolism but also lipid metabolism, and enhance resistance to oxidative stress. The effects of CRM on energy metabolism are expected to help prevent obesity in humans and reduce the frequency of cardiovascular events, such as

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myocardial infarction, by suppressing diabetes and hyperlipidemia. It has also been suggested that the anti-tumor effect of oxidative stress reduction is related to the regulation of energy metabolism. Thus, research into CRM may contribute to the development of pharmaceuticals that treat diseases caused by aging and metabolic abnormalities, rather than directly prolonging lifespan.

Experiments using mouse models of Alzheimer’s disease and Parkinson’s disease suggest that CR can also inhibit the onset and progression of these neurodegenerative diseases. In addition, CR is effective in preventing the progression of rare diseases such as mitochondrial diseases. Thus, CRM development will likely play an important role in finding solutions to a range of medical problems including unmet medical needs in patients with rare disorders, and CRM research and development is regarded as an important novel approach to pharmaceutical development for this purpose. In this article, we outline the basic and clinical research performed to date on CRM candidate compounds and discuss taurine as a potential CRM that has attracted interest in recent years.

**CR biomarkers**

To research the potential effects of CR on humans, long-term CR studies using primates have been performed at the University of Wisconsin and the National Institute on Aging (NIA) in the United States. These studies have shown that changes in physiological and biological biomarkers observed in primates are similar to those observed in rodents. Research at the University of Wisconsin showed that CR extended the health span (healthy time without illnesses such as diabetes) and reduced the mortality rate with lifespan extension effects. Conversely, research at the NIA showed that CR extended the health span, but had no effect on the mortality rate. This contradiction is speculated to result from differences between the two facilities in the breeding environment, such as diet composition, timing of feeding, and the genetic background of the experimental animals. In a reanalysis of recent studies, CR was reported to extend the life expectancies of rhesus monkeys in NIA studies. These results suggest that CR has a lifespan-prolonging effect in primates and may improve the quality of life in humans by suppressing the development of age-related diseases.

The results of a long-term longitudinal study of older males living in Baltimore indicate that hypothermia, low blood insulin levels, and high blood dehydroepiandrosterone sulfate (DHEA-S) levels are biomarkers for longevity in humans. These biomarkers and their levels were similar to those found in calorie-restricted rhesus monkeys. A human study called the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) is currently being performed at multiple research facilities, including the Pennington Biomedical Research Center. An interim report from this study suggests that CR may enhance the activity of antioxidant proteins in the bloodstream and reduce protein damage from oxidative stress, thereby producing an anti-aging effect.

**CRM candidates**

Recent studies have reported several clinically utilized drugs have an anti-aging effect. These are antidiabetic drugs, sirtuin activators, antihyperlipidemic drugs, anti-hypertensive agents, immunosuppressants, and hormone receptor activators.

**Antidiabetic drugs.** Metformin is a drug used for the treatment of type 2 diabetes. It is classified as a biguanide and is considered as a first-line drug for type 2 diabetes treatment in Europe and the United States. A study reported that the lifespan of mice can be extended by dietary metformin supplementation starting from when the mice were middle-aged. Mice that received metformin showed similar changes to those that were calorie-restricted, including increased insulin sensitivity and decreased blood low-density lipoprotein cholesterol (LDL-C) levels, with further enhancement of antioxidant activity and decreases in oxidative injury and chronic inflammation. However, it has been reported that metformin has no effect on lifespan in rats. This suggests that either there were differences in the metformin dosage and/or administration method used, or that metformin has species-specific effects. Though an unlikely candidate, metformin may function as an anti-aging drug. Clinical trials are being carried out in the United States to investigate this, the results of which are expected to be reported in the near future.

Rosiglitazone, a thiazolidine-based antidiabetic drug, is a peroxisome proliferator-activated receptor γ (PPARγ) activator that reduces insulin resistance and improves lipid metabolism. A meta-analysis of rosiglitazone use has reported that it may cause side effects such as myocardial infarction and heart failure; though subsequent clinical studies report no significant increase in cardiovascular risk from rosiglitazone use. Mice administered rosiglitazone show similar metabolism-related gene expression patterns in liver to calorie-restricted mice, though mice administered metformin show even stronger similarities in this respect to calorie-restricted mice.

**Sirtuin activators.** It has been reported that Sir2, an NAD+-dependent deacetylase, plays an important role in lifespan extension in model organisms. Moreover, sirtuin family proteins, including their orthologues such as SIRT1 in mammals, may not only affect lifespan, but also influence the development of various aging-related diseases. It was reported that resveratrol, a type of polyphenol found in grape skin, activated SIRT1 and extended the lifespan of mice fed a high-calorie diet. Enhancement of insulin sensitivity and activation of AMP-activated protein kinase (AMPK) and PPARγ coactivator-1 α (PGC-1α) are con-
sidered to be responsible for this effect. Lifespan extension was not observed when resveratrol was administered to mice fed a normal diet; however, these mice exhibited a gene expression pattern similar to that of calorie-restricted mice, as well as anti-aging effects such as suppression of decreases in motor ability and of cataract development\(^{12}\). There has been much debate on whether so-called sirtuin-activating compounds (STACs) (including resveratrol) do indeed activate sirtuins, but identification of SIRT1 amino acid residues targeted by STACs has clarified their mechanism of activation\(^{13}\). Further, unique substances are under development that are intended to imitate the CR-like beneficial effects by activating sirtuins via the NAD synthesis system\(^{14}\). A recent study using mice has revealed that nicotinamide mononucleotide (NMN), which activates the NAD synthesis system, could delay the onset of age-related diseases, making it an attractive CRM candidate\(^{15}\).

**Hyperlipidemic drugs.** Among the hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) used as therapeutic agents for patients with hyperlipidemia, pravastatin has been reported to significantly reduce cardiovascular events in hyperlipidemic patients\(^{16}\). In a study on the effects of pitavastatin and simvastatin in a patient with abnormal lipid metabolism, pitavastatin reduced LDL-C levels more effectively than simvastatin. In mice, it has been reported that pitavastatin has a protective action against the cardiomyopathy caused by doxorubicin administration-related oxidative stress\(^{17}\). Because CR decreases mortality rates in mice administered oxidative stress inducers, there has been an interest in this relationship. Likewise, simvastatin has a cardioprotective action in *Drosophila*, and may also extend lifespan\(^{18}\).

**Antihypertensive drugs.** Large-scale clinical trials are being conducted to investigate the inhibitory effect of angiotensin II receptor blockers (ARBs), antihypertensive agents, on cardiovascular events. A study comparing the cardiovascular protective effects of telmisartan (an ARB), ramipril (an angiotensin-converting enzyme [ACE] inhibitor that inhibits angiotensin II generation), or a combination of the two, was conducted on patients with a high risk of cardiovascular events\(^{19}\). This study demonstrated that the onset of cardiovascular death, myocardial infarction, and stroke was suppressed by the administration of telmisartan or ramipril alone, but a combination of the two drugs was associated with more adverse effects without any increase in benefit. The potential for suppression of cognitive dysfunction was also analyzed; however, no significant reduction in cognitive dysfunction risk was observed. Since type-1 angiotensin II receptor (AT1), but not type-2 (AT2), knockout mice typically show a decrease in cardiovascular injuries and a longer lifespan than wild type mice\(^{20}\), it was proposed that this elongation of lifespan involves an increase in the quantity of mitochondria in the kidney and activation of nicotinamide phosphoribosyltransferase (Nampt), which suggests a link with the activation of the sirtuin pathway. ARBs such as telmisartan are highly selective for AT1, and thus have an AT2 inhibitory effect that can cause side effects. Research into pharmaceuticals that selectively inhibit AT1 could involve CRMs.

β1-adrenergic receptor antagonists (β-blockers) suppress the myocardial contractility lowering effect and are used as antihypertensive agents because of their vasodilatory effect. Among the β-blockers, it was recently reported that metoprolol and nebivolol extend the lifespan of mice\(^{21}\). It has been hypothesized that this lifespan extension effect is the result of an off-target effect different from that of the original target molecule of the drug.

**Immunosuppressive drugs.** The first compound added to the normal diet of mice to extend their lifespan was the immunosuppressant rapamycin\(^{22}\). In this study, a lifespan extension effect was observed even when rapamycin administration was not started until the mice were 20 months old. Rapamycin inhibits mammalian target of rapamycin (mTOR) and, accordingly, a decrease was observed in the phosphorylation of downstream target protein S6K (p70 S6 kinase) in mice administered rapamycin. In S6K knockout mice, the age-related decline in the immune system and motor ability were suppressed, thereby extending the lifespan compared to the age-matched controls, suggesting that the mTOR-S6K pathway plays an important role in mammals\(^{23}\). Various age-related changes, including changes in heart function and physical activity, were suppressed in mice that were administered rapamycin. However, side effects of rapamycin administration have also been reported, including the emergence of insulin resistance, testicular lesions, and the onset of cataracts. Other side effects, including an increased risk of developing diabetes, have been reported for human organ transplant recipients who are taking rapamycin\(^{24}\).

**Hormone receptor activators.** Adiponectin, an adipocyte-derived factor, is thought to play a role in the suppression of obesity, diabetes, and arteriosclerosis because it is only found at low levels in the blood of patients affected by these conditions\(^{25}\). Moreover, it has been reported that the serum adiponectin levels of centenarians are significantly higher than those of younger people, suggestive of a relationship with longevity\(^{26}\). Since blood adiponectin levels are increased in both calorie-restricted and long-lived rats, the intracellular signal transduction system mediated by adiponectin may act as a longevity signal\(^{27}\). Indeed, transgenic mice with high levels of adiponectin expression had less fat accumulation and premature death than did wild-type mice, even when fed a high-calorie diet\(^{28}\). Two adiponectin receptors, AdipoR1 and AdipoR2, are known to exist, and low-molecular-weight compounds that activate these receptors may be CRM
candidates. Indeed, it has been reported that AdipoRon, a small compound AdipoR agonist, ameliorated diabetes in genetically obese rodent model (leptin receptor-deficient) \( db/db \) mice, and extended the shorter lifespan of \( db/db \) mice fed a high-fat diet\(^{29}\).

Ghrelin is a hormone secreted by the stomach that acts as a ligand for growth hormone secretagogue receptor (GHS-R) and plays a role as an orexigenic hormone\(^ {30}\). The primary target of ghrelin is hypothalamic neuropeptideY (NPY) neurons; and serum ghrelin levels and NPY gene expression are increased in the hypothalamus of calorie-restricted rats\(^ {31}\). Furthermore, calorie-restricted NPY knockout mice exhibit no increase in oxidative stress tolerance or longevity\(^ {25}\). Small-molecule compounds that target NPY receptors may thus be CRM candidates. For instance, it was recently reported that a traditional Japanese medicine, Rikkunshito, which contains atractylochin, promotes NPY activation and extends the lifespan of premature aging model mice\(^ {33}\).

**Taurine**

Taurine, a sulfur-containing amino acid present in high concentrations in animal tissues, is available from dietary sources and can be synthesized in vivo from other amino acids. Taurine is involved in many physiological functions including osmoregulation, antioxidation, calcium modulation, and membrane stabilization\(^ {34}\). An analysis of taurine transporter knockout mice suggests that taurine has a significant role in maintaining normal cellular function, with knockouts showing a premature aging phenotype\(^ {25}\). While this does not necessarily imply that taurine ingestion will have an anti-aging effect, it does show that taurine has some effect on aging and age-related diseases.

Dietary taurine has various physiologic and pharmacological actions, including hypocholesterolemic and antiatherogenic effects\(^ {36}\). Taurine also lowers blood lipid levels and raises ketone bodies levels. Liver perfusion experiments have revealed that a taurine-induced reduction in hepatic cholesteryl ester accumulation was associated with reduced hepatic secretion of this lipid molecule, and was inversely related to enhanced ketone body production and fatty acid oxidation in rats fed a high-cholesterol diet\(^ {27}\). This suggests that taurine has a similar mechanism of action as statins and adiponectin, both of which are CRM candidates. Interestingly, several studies have reported that taurine increases plasma adiponectin levels\(^ {34}\). Moreover, it has been reported that taurine inhibits angiotensin II\(^ {38}\), suggesting that taurine may have a similar effect as that of the ARBs.

Higher serum ketone body levels are one of the characteristics of calorie-restricted animals\(^ {39}\). When ketone body levels increase because of fasting or CR, the expression of stress response genes such as FoxO3a also increases, which reportedly relieves oxidative stress\(^ {40}\). We report that the transcription factor FoxO3a plays an important role in the mechanisms of the anti-aging effects of CR\(^ {41}\). Taurine is also reported as having antioxidant activity\(^ {42}\), so clarifying how FoxO3a and NPY are involved in its mechanism of action may be important future avenues of research. Furthermore, it has been reported that taurine improves obesity-induced inflammatory responses in adipose tissue and ameliorates insulin resistance in mice\(^ {43}\). The versatility of taurine thus makes it a promising CRM candidate compound. Notably, taurine has already been shown to reduce tunicamycin-induced endoplasmic reticulum stress and extend the lifespan of lower organisms (C. elegans)\(^ {44}\), offering further promise as a CRM for higher

**Table 1.** Calorie restriction mimetic candidates currently in clinical use or being clinically trialed.

| Compound       | Function                  | Target            | Lifespan extension\# | Reference |
|----------------|---------------------------|-------------------|----------------------|-----------|
| Metformin      | Antidiabetic              | LKB1              | yes                  | 6)        |
| NMN            | Sirtuin activator         | SIRT1             | possible             | 15)       |
| Simvastatin    | Antihyperlipidemic        | HMG-CoA reductase | yes                  | 18)       |
| Telmisartan    | Antihypertensive          | AT1               | possible             | 20)       |
| Metoprolol     | Antihypertensive          | ACE               | yes                  | 21)       |
| Rapamycin      | Immunosuppressive         | mTOR              | yes                  | 22)       |
| Rikkunshito    | Neuropeptide Y activator  | GHS-R             | yes                  | 33)       |
| Taurine        | Anti-congestive heart failure | various     | yes                  | 44)       |

ACE: angiotensin-converting enzyme, AdipoR: adiponectin receptor, AT1: type-1 angiotensin II receptor, GHS-R: growth hormone secretagogue-receptor, HMG-CoA: hydroxymethylglutaryl-CoA reductase, LKB1: liver kinase B1, mTOR: mammalian target of rapamycin, NMN: nicotinamide mononucleotide, SIRT1: sirtuin 1

\#As reported for model organisms or in experimental animal models.
organisms.

Table 1 provides a summary of the CRM candidates described in this review that are currently in clinical use or being clinically trialed for various age-related diseases. Taurine is used for the treatment of congestive heart failure and hyperbilirubinemia. Taurine also affects the function of the central nervous system, adipose tissue, and muscle, including in the heart, liver\(^{(3)}\) and other organs that are also affected by CR. While there are some differences between taurine and CR in their effects on these organs, further research into the mechanisms of taurine action could reveal CRM functions.

**Perspective**

Although it is not yet known whether the human lifespan can be extended via CRM, these compounds have been reported to suppress the onset and progression of age- and lifestyle-related diseases. Consequently, patients receiving CRM candidates as treatment for these diseases may experience healthier, longer lives. Research into the mechanisms underlying CR, including the organs, tissues, timing, and target molecules involved, will be important to our understanding of the organ-specific beneficial effects of CR. As discussed in this review, taurine administration is likely to achieve (1) decreased serum lipid levels, (2) increased ketone body production, (3) decreased blood pressure, and (4) decreased oxidative stress. In mice, a deficiency in taurine utilization can result in premature aging. Therefore, taurine exerts several of the effects shown by the other CRM candidates described in this paper and is a promising new CRM candidate.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this article.

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