

# Calorie Restriction Mimetics: Examples and Mode of Action

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**Abstract:** The search for Calorie Restriction Mimetics (CRM) - compounds that mimic the genetic, biochemical and physical actions of calorie restriction - is not a search for a 'lazy dieters pill'. It is a quest aiming to clarify the basic mechanisms of calorie restriction and develop strategies in order to prevent, treat or alleviate age-related conditions. The development of CRM will add new and important assets in our armamentarium of anti-ageing therapies, with the ultimate result of increasing healthy human lifespan. This Special Supplement on CRM is an attempt to discuss some agents which may be used instead of calorie restriction itself. Agents such as resveratrol, metformin, carnosine and Rimonabant are mainstream oral therapies already used by millions of people for other clinical indications. New CRM such as NADH, guggulipids and certain drugs that interfere with glucose metabolism can be also used as oral therapy. Less easily available CRM such as oxaloacetic acid, naloxone, leptin, adiponectin, rapamycin and sirtuins are further examples of promising agents. In order for the therapy to be effective, a combination of these must be used. This paper summarises the actions of calorie restriction and then suggests several examples of possible CRM. Some of these examples can be used in everyday clinical setting.

**Keywords:** Calorie restriction, calorie restriction mimetics, health-span, hormesis.

## INTRODUCTION

Calorie restriction (CR) is discussed elsewhere in this Supplement. Its practical aim is not only to increase average and maximum lifespan in humans, but also to prolong the 'health-span' which is the number of years an organism can live without any major chronic diseases [1]. It may be somewhat simplistic but practically useful to divide the effects of CR into three general categories: genetic, biochemical and physical. The following list is by no means exhaustive but highlights some examples.

- A. Genetic. These are effects at specific gene level which can modulate transcription of enzymes or other factors. Perhaps the most promising CRM are those which work on this level.
  - Decreases the activity of p53 [2], and therefore modulates apoptosis [3].
  - Regulates Sir-2 [4] and activates Sirt1 [5]. Sirt1 is activated to promote transcription of genes that deal with the stress response and adaptation.
  - Regulates Daf-16. AMPK (AMP Protein Activated Kinase) is activated in the presence of Daf-16 [6].
- B. Biochemical effects are those that directly influence macromolecules, without an identifiable genetic origin:
  - Reduces lipid peroxidation and generation of superoxides [7].
  - Reduces iNOS expression and COX2 expression [8], and increases NADH concentration within the mitochondria [9].

- Maintains DHEA levels [10].
  - Modulates PPAR [11]. Suppresses PGE-2, TNF-alpha and CRP (thus reduces the inflammation response) [12].
  - Stimulates Brain-Derived Neurotropic Factor (BDNF) [13].
- C. Physical changes include clinically relevant and measurable parameters, at the organismic level.:
    - Reduces body weight and body temperature [14].
    - Improves diastolic function. Lowers cholesterol, blood pressure and pulse rate, and reduces blood glucose levels [15].
    - Increases muscle mass and reduces fat mass (including intra-abdominal fat) [16].
    - Improves memory and cognition [17, 18].

## CANDIDATE CRM

Calorie restriction mimetics (CRM) are drugs or chemical compounds which mimic the actions of CR. It is not sufficient for a compound that mimics just one effect of CR to be classified as a CRM. As an arbitrary guide, I propose that, in order for a compound to be classified as a CRM, it has to mimic at least two biochemical plus one genetic, or five biochemical/physical effects of CR. This is a general attempt at defining a CRM and further discussion is needed, although initial attempts along these lines have already been made [19], and in particular with regards to defining biomarkers in calorie restriction has already taken place [20]. Examples of CRM that are already available and currently used for other indications are:

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## Metformin

Metformin is a receptor sensitizer, because it enhances the sensitivity of insulin receptors on the surface of muscle and fat cells [21]. It can activate genes which reduce hepatic production of glucose, thus reducing the risk of glycation and other age-related damage. In addition, metformin reduces gene expression of enzymes which increase oxidation of fatty acids. Further research is needed to clarify the approximate dose of metformin for CRM effects. Healthy people who take metformin for its general anti-ageing benefits use 500 mg twice a day. Side effects may include gastrointestinal problems and allergic reactions.

## Resveratrol

This is a polyphenol with proven beneficial cardiovascular effects and a potent CRM [22]. In yeast, it stimulates Sir2 (silent information regulator), increasing DNA stability and extending life-span by 70%. Resveratrol activates the human homologue SIRT1 which results in reduced apoptosis in the liver, blood and skin, and reduced risk of age-related chronic disease. The dose of resveratrol is normally between 5 mg and 15 mg daily, however the dose necessary to achieve CRM effects has not yet been calculated. Long term adverse effects are unknown, but no significant short term side effects have been reported.

## Rimonabant (Acompla)

Endocannabinoids are cannabis-like chemicals which stimulate appetite and regulate energy balance. Overstimulation of endocannabinoid receptor in the hypothalamus promotes appetite and stimulates lipogenesis [23]. It also blocks adiponectin. Rimonabant (an anti-obesity drug) is an endocannabinoid-1 receptor blocker, which reduces appetite, balances energy production and increases adiponectin which, in turn, reduces intra-abdominal fat [24]. Rimonabant improves lipid profile, glucose tolerance, and waist measurement. Therefore, it has effects similar to those of CR. It is taken 20 mg once daily, preferably with a mild calorie restricted diet. The efficacy and long term adverse effects of rimonabant have recently been questioned and further research is needed to clarify these.

## Anti-Glycators

Agents which reduce abnormal protein accumulation (aminoguanidine and carnosine) can also be CRM. These prevent glycation and therefore reduce AGEs (Advance Glycation End-products) formation [25]. AGEs contribute to extensive age-related damage such as accumulation of amyloid-beta implicated in Alzheimer's disease. CR reduces the concentration of AGEs. The same mechanism is shared by aminoguanidine and carnosine which prevent and eliminate AGEs, therefore contributing towards the prevention of chronic degenerative disease. No significant side effects have been reported, and mild gastrointestinal problems usually improve after reducing the dose.

## Exendin

The agent exendin (exanatide, exanadin) reduces plasma glucose, suppresses food intake and regulates glucose metabolism [26]. It is a GLP (Glucagon-Like Peptide) modulator, able to increase brain function and protect the brain

against toxicity. Exanatide (Byetta<sup>®</sup>) was approved by the Food and Drug Administration for treatment of Type 2 Diabetes in patients who are already on an oral diabetes medication. The product comes in pre-filled syringes and is injected subcutaneously twice daily.

## Olbetam (Acipimox)

This agent inhibits the release of fatty acids from adipose tissue and reduces blood concentration of very low density lipoproteins and low density lipoproteins with a subsequent reduction in triglyceride and cholesterol levels [27]. It improves growth hormone secretion and reduces lipid peroxidation. Olbetam is indicated as adjunctive therapy to diet and weight loss in the treatment of several lipid disorders. The dosage is between 500-750 mg/day.

## PPAR Gamma Modulators

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of transcription factors that are related to retinoid, steroid and thyroid hormone receptors. PPARs play an important role in many cellular functions including lipid metabolism, cell proliferation, differentiation, adipogenesis and inflammatory signaling. Modulation of PPAR gamma generally reduces inflammation, improves immunity and reduces blood glucose. Two examples of PPAR modulators are:

- a) Rosiglitazone (Avantia), an insulin-sensitizing drug that is a ligand for PPAR-gamma [28]. The dose is 4 mg once or twice a day.
- b) Gugulipids, from the plant *Commiphora mukul*, which block the PPAR-mediated differentiation of preadipocytes into mature adipocytes [29].

Two very promising CRM (NADH/oxaloacetic acid and Naloxone) are discussed elsewhere in this Supplement. Other candidate CRM which are not readily available are listed below. The list is merely an example of possible CRM and it is by no means exhaustive. Further research regarding the CRM effects of each compound may help in establishing their mode of action. Furthermore, the clinical adverse effects of these agents have not been clarified and are best used under expert specialist supervision.

## Leptin

This is a molecule, produced by adipocytes, that stimulates fat metabolism and reduces body weight. A reduction of dietary intake causes leptin levels to fall and this interferes with the secretion of testosterone, progesterone, growth hormone and thyroid hormones as a response for adaptation [30]. Therefore, leptin mediates the clinical effects of CR. As a result, agents which affect leptin production must also be classified as CRM. Together with insulin and ghrelin (a growth hormone stimulator) leptin balances the ratio of appetite promoters vs. appetite blockers in the hypothalamus in the brain and so regulates homeostasis and food intake. Leptin is stimulated by PPAR modulators such as rosiglitazone. Human recombinant leptin costs approximately \$140 for 0.5 mg, but nicotinic acid can help increase its concentration. However, leptin mediates the effects of diabetic cardiomyopathy [31] and its long term effects are not clear.

## Deoxyglucose

The first CRM described, inhibits glycolysis and mimics some of the effects of CR, particularly increased insulin sensitivity, reduced glucose levels and other biochemical changes [32]. Research is still under way to identify more about its possible benefits on humans. What is known about deoxyglucose is that it can be toxic in high dosages.

## Modulators of Sirtuins

Sirtuins are histone deacetylases that catalyze deacetylation reaction in an NAD(+)-dependent manner [33]. Activation of sirtuins improves longevity and health span in many species. This can be achieved by STAC –sirtuin activating compounds. Examples of STAC are chalcone [34], sirtinol, which among other actions, reduces pro-inflammation mediators [35] and fisetin (a flavonoid, antioxidant compound). Fisetin is a potent suppressor of some inflammatory cytokines/chemokines and an angiogenic factor [36].

## 4-Phenylbutyrate (PBA)

Increases median and maximum lifespan in flies. In addition, it increases histone deacetylation [37].

## Hydroxycitrate

An active ingredient extracted from the *Garcinia cambogia*, reduces caloric intake and cholesterol [38] and it is currently used in weight control [39].

## Gymnemoside

Isolated from the leaves of *Gymnema sylvestre* [40], gymnemoside modulates glucose metabolism.

## Adiponectin

Together with leptin, it takes part in fat metabolism. It is activated by PPAR modulators such as rosiglitazone [41]. It enhances phosphorylation of AMPK [42], although it can increase total and cardiovascular mortality [43]. Human recombinant adiponectin is available for sale costing approx \$350 per 50 mcg.

## Iodoacetate

An alkylating agent, it protects against toxic metabolites of glucose. Iodoacetate prevents formation of disulfide bonds, is a glycolysis-inhibitor and an anti-cancer agent [44].

## DPP-4 Inhibitors

Diapetidyl peptidase-4 (DPP-4) is an enzyme that modulates Glucagon-Like Peptide, allowing glucagon to increase glucose concentration [45]. DPP-4 inhibitors have the opposite effect, reducing glucose plasma levels, and are candidate CRM.

## Peptide PYY3-36

This protein fragment is released from the bowel following a meal. It then inhibits food intake by acting on the hunger centre in the hypothalamus [46]. By reducing appetite and glucose metabolism (actions similar to those seen in CR), it can meet some of the criteria for consideration as a CRM.

## Modulators of NPY

The neuropeptide Y (NPY) is a small protein fragment which increases appetite, induces obesity and reduces the metabolic rate. CR modulates the production of NPY by selectively blocking receptors in the hippocampal region of the brain and by stimulating others in the hypothalamus. Any modulation of NPY release would result in exactly the same clinical effects as those seen in CR [47].

## Rapamycin

It is known that CR downregulates TOR (target of rapamycin) [48]. Many longevity genes encode components of TOR pathway, so rapamycin which is a TOR inhibitor, can be classified as a CRM.

## Galanin Antagonists

These block galanin (which increases appetite and reduces insulin) [49,50]. An example is the antagonist M35.

## Aldifen (2,4-Dinitrophenol)

is a hormetic metabolic poison [51] that causes mild mitochondrial uncoupling, interfering with energy production. However, overdose is lethal. Nevertheless, metabolic poisons with hormetic effects (such as oligomycin, carbonyl-cyanide, rotenone, antimycin, and malonate) are being investigated as having not only CRM actions but also other health benefits [52].

## GENERAL CONCLUSIONS

Clearly, a CRM cannot mimic all of the actions of CR, so it must be combined with other CRM which complement each other, in order to cover as many actions of CR as possible.

For example, Acomplia, metformin and resveratrol can be combined for maximum effect. It is worth noting that Intermittent Fasting (IF) is an intervention that may mimic the effects of CR itself. However, IF increases lifespan even when the overall calories are not reduced. It appears that it is the stress of fasting rather than the reduced calories that cause the benefit. This supports the view that the stress of fasting is a hormetic challenge which helps activate the protection pathways that are also active in CR [53]. A search for CRM can be extended to find IF mimetics such as RHEB, a GTPase, which is a mediator through Daf16 and TOR [54].

The increased amount of research into CR has given us promising directions into identifying effective agents which reproduce the exact benefits of CR, without the need to follow long calorie-restricted diets. The most promising and clinically relevant CRM are those that reproduce at least one genetic and two biochemical, or at least five biochemical/clinical benefits of CR. While research is continuing, many physicians who already recommend these compounds to their patients for other indications, have now started realising that their treatment has an added possible health-extending bonus.

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Received: April 22, 2009

Revised: May 14, 2009

Accepted: October 05, 2009

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