Psychiatry Research 209 (2013) 253–258

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Review article

Fasting in mood disorders: neurobiology and effectiveness. A review of the literature

Guillaume Fond [a,b,*], Alexandra Macgregor [a], Marion Leboyer [b], Andreas Michalsen [c]

[a] INSERM U1061, Université Montpellier 1, Hôpital la Colombière, CHU Montpellier F-34000, France
[b] INSERM U955, University Paris-Est, FondaMental Fondation, Fondation de Coopération Scientifique, AP-HP, Groupe Hospitalier Mondor, 40, Rue de Mesly, Creteil F-94000, France
[c] Charite- University Medical Centre Berlin and Immanuel Hospital Berlin, Department for Internal and Integrative Medicine, Berlin, Germany

ARTICLE INFO

Article history:
Received 16 October 2012
Received in revised form
11 December 2012
Accepted 18 December 2012

Keywords:
Therapeutic fasting
Caloric restriction
Depression
Mood
Treatment
Ramadan

ABSTRACT

Clinicians have found that fasting was frequently accompanied by an increased level of vigilance and a mood improvement, a subjective feeling of well-being, and sometimes of euphoria. Therapeutic fasting, following an established protocol, is safe and well tolerated. We aim in this article to explore the biological mechanisms activated during fasting that could have an effect on brain function with particular focus on mood (we do not discuss here the mechanisms regulating eating behavior) and to provide a comprehensive review on the potential positive impact of therapeutic fasting on mood. We explored Medline, Web of Science and PsycInfo according to the PRISMA criteria (Preferred Reporting Items for Systematic reviews and Meta-Analysis). The initial research paradigm was: [(fasting OR caloric restriction) AND (mental health OR depressive disorders OR mood OR anxiety)]. Many neurobiological mechanisms have been proposed to explain fasting effects on mood, such as changes in neurotransmitters, quality of sleep, and synthesis of neurotrophic factors. Many clinical observations relate an early (between day 2 and day 7) effect of fasting on depressive symptoms with an improvement in mood, alertness and a sense of tranquility reported by patients. The persistence of mood improvement over time remains to be determined.

Contents

* Corresponding author at: INSERM U955, University Paris-Est, FondaMental Fondation, Fondation de Coopération Scientifique, AP-HP, Groupe Hospitalier Mondor, 40, Rue de Mesly, CMP Maison-Alfort, 21 rue Olof Palme, Creteil F-94000, France. Tel.: +01 78 68 23 72; fax: +01 78 68 23 81.
E-mail address: guillaume.fond@gmail.com (G. Fond).

0165-1781/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psychres.2012.12.018

1. Introduction

1.1. Fasting across time and cultures

Humanity, until recently, has been exposed to large fluctuations in the availability of its food, alternating periods of overfeeding and starvation. Periodic fasting with voluntary restriction of the intake of solid food is practiced around the world, mostly for cultural or religious reasons (fasting is thought to favor man's awakening to spirituality) (Buchinger, 1950, 1952; Heun, 1954a, b, 1956; Rooth and Carlstrom, 1970). Since Hippocrates, fasting has been offered as treatment of acute and chronic diseases, following the empirical observation that infection is frequently accompanied by an anorexic response (Exton, 1997; McCarthy et al., 1985). The deliberate choice of fasting in some religions as renunciation of external rewards in an ascetic approach could be strengthened by the concomitant increase in mental alertness, sense of calm and improved mood. Mood alleviation during fasting may represent an adaptive mechanism promoting phylogenetic struggle for survival and search for food. Thus, the human body may be programmed to cope with famine, but not with over-feeding.

1.2. Definitions of fasting, caloric restriction and modified/therapeutic fasting.

Very low calorie diets allow up to 800 kcal/day. Caloric restriction is defined by a decrease in daily calorie intake by 30–40% (Varady and Hellerstein, 2007). Dietary restriction below 500 kcal/day initially triggers a strong neuroendocrine activation that leads to rapid mobilization of glycogen stores (Phase I), followed after 24 h of fasting by the lipolysis of fat mass (phase II) that precedes a phase of accelerated protein catabolism (phase III). This protein catabolism is significantly reduced by the intake of 200–500 kcal/day in the form of fruits or soups: this defines fasting therapy, also called modified/therapeutic fasting, which is focused upon in this review (Varady and Hellerstein, 2007). Optimal medical fasting is defined as 2 days of 800 kcal/day diet in the form of fruit or rice or potatoes. The patient then receives a small amount of oral laxative. While fasting, it is recommended that the patient drink 2–3 liters of fluid per day (mineral water, small amounts of fruit juice, tea). Food is gradually reintroduced at the end of fasting (after 1–3 weeks) and ends with taking normal-calorie vegetarian dishes at day 4 after fasting cessation. This period of re-introduction is accompanied by a focus on feeding mindfulness.

1.3. Establishment protocol.

Medical fasting is still practiced on a voluntary patient basis, and its duration is limited and predefined (Michalsen, 2010). The recommended duration of fasting in the indication "chronic pain" is 1 to 2 weeks. Standardized methods of medical fasting were developed in the United States in the early 20th century by Dewey Tanner and Hazzard but have since disappeared from this country, although this method has been increasingly successful in Europe since the 1950s. The most used method is one proposed by the German physician Otto Buchinger: it is defined by fasting for 1–3 weeks with the ingestion of mineral water and fruit juice in limited amounts, accompanied by a moderate level of physical exercise (Buchinger, 1950, 1952, 1953, 1959a, b).

Medical fasting is well established and has been shown to be safe. Rare side effects include irritability, headache, fatigue, nausea and stomachache. Contra-indications (Bol'shova and Malinovs'ka, 2008; Henry and Gumbiner, 1991; Le Bourg, 2005) are eating disorders, a body-mass index below 20 or above 40, kidney or liver disease, gastric ulcer, severe comorbidities, including cancer, immunosuppressive premedication (except corticosteroids), alcoholism, psychosis, pregnancy, lactation, unexplained weight loss, and medication with diuretics (in order to avoid hyponatremia).

The reported patient adherence rate is known among chronic pain disorders. Periods of prolonged fasting (>8 days) seem to be better tolerated than periods of intermittent fasting, where the sensation of hunger is more poorly tolerated during the days of food restriction. Similarly, periods of prolonged fasting seem easier to set up than caloric restriction in daily life (Bol'shova and Malinovs'ka, 2008; Buchinger, 1959b; Busse Grawitz, 1952).

Intermittent fasting and caloric restriction increase life expectancy of all animal species in which they have been tested (Bartke et al., 2007; Barzilai and Bartke, 2009; Cox and Mattison, 2009; Everitt and Le Couteur, 2007; Gillette-Guyonnet and Vellas, 2008; Masoro, 2007, 2009; Omodei and Fontana, 2011; Segall, 1977; Skulachev, 2011; Trepanowski et al., 2011; Willcox et al., 2007). They have also recently demonstrated in humans an efficacy in the prevention of degenerative diseases (such as Alzheimer's or Parkinson's) (Jadiya et al., 2011; Love, 2005; Mattson, 2003; McCarty, 2001; Patel et al., 2005; Srivastava and Haigis, 2011) of cardiovascular disease (Ahmadi et al., 2011; Cefalu et al., 1997; Cefalu et al., 2004; Cruzen and Colman, 2009; Gerstenblith, 2006; Mattson and Wan, 2005; Shinmura, 2011; Williams et al., 2002), diabetes (Hammer et al., 2008; Henry et al., 1985; Nagulesparan et al., 1981; Polonov et al., 1982; Skripchenko et al., 2002; Ugochukwu and Figgers, 2007; Wycherley et al., 2008) and cancer (Buschemeyer et al., 2010; Elias et al., 2007; Kritchevsky, 1993, 2001; Manjgaladze et al., 1993; Michels and Ekbom, 2004; Sell, 2003; Steinbach et al., 1994; Thompson and McTiernan, 2011) and in the treatment of rheumatoid arthritis, chronic pain syndromes and migraine (Michalsen, 2010; Michalsen et al., 2006; Michalsen et al., 2003b; Michalsen et al., 2002). All studies found that the modified fast is safe and is not associated with a feeling of hunger that may potentially lead patients to discontinue treatment (Michalsen et al., 2005).

A significant proportion of patients in psychiatry have a lack of response to drugs, sotherapeutic fasting may be a treatment of interest in addition to or in place of psychotropic medication. Moreover, therapeutic fasting has a low cost and is easier to carry out than other treatments for drug-resistant patients, such as electroconvulsive therapy, for example.

1.4. Objectives

As we found no review on therapeutic fasting and its effectiveness in mood improvement, this study aims to explore the biological mechanisms activated during fasting that could have an effect on brain function with particular focus on mood (we do not discuss here the mechanisms regulating eating behavior) and to provide a review of data suggesting the efficacy of therapeutic fasting on mood.

2. Method

2.1. Process

The Medline, Web of Science, and Psycinfo databases were searched from their inception until October 2012 according to the PRISMA criteria (Preferred Reporting Items for Systematic reviews and Meta-Analysis). English, German and French language restrictions were applied. As the words "mood" or "depression" were too restrictive, we checked all data on fasting's effects and selected relevant articles. Duplicates were eliminated. Reference lists of identified original and review papers were hand-searched to locate additional articles. Additional items were added after examining the referenced articles (Fig. 1).

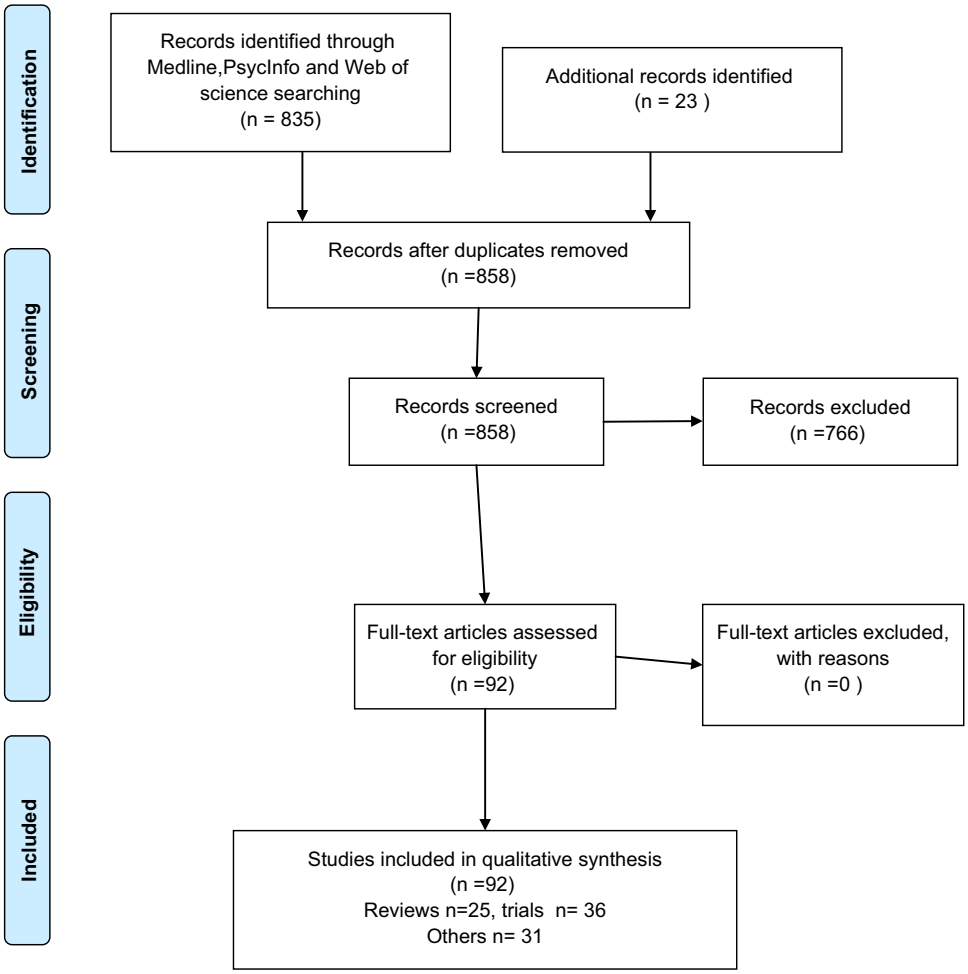

Fig. 1. PRISMA flow diagram.

2.2. Eligibility criteria

Two authors (G.F and A.M) independently selected full-text articles after checking abstracts, with limitation to clinical trials, observational studies, reviews and meta-analyses. Disagreements were resolved by consensus.

3. Results

Nighty-two articles were included in the qualitative synthesis.

3.1. The Neurobiology of mood improvement during fasting.

Prolonged fasting (>8 days) is a strong physiological stimulus equivalent to a biological stress that activates the hypothalamic-pituitary-adrenal axis (HPA, said "stress axis") (Brecchia et al., 2006; Fekete et al., 2006; Kim et al., 2008; Park et al., 2004; Shahab et al., 1997; Steiner et al., 2003). The biological mechanisms of this activation are unclear and could include the reduced availability of cerebral glucose, reduced insulin and leptin levels, or the sensation of hunger (Brecchia et al., 2006; Fekete et al., 2006; Kim et al., 2008; Park et al., 2004; Shahab et al., 1997; Steiner et al., 2003). Change in leptin levels has been identified as a strong signal of biological adaptation of the organism to starvation, and has been associated with mood disorders (Tichomirowa et al., 2005). Modified fasting in humans is accompanied during the early phase (2–7 days) by an increase in urinary and plasma norepinephrine, epinephrine, dopamine and cortisol levels and decreased plasma levels of thyroid hormones T3 and T4 (Michalsen et al., 2003b; Palmblad et al., 1977). Normalization of blood pressure could be explained by an increase in diuresis and natriuresis.

The serotonin system is strongly involved in diet regulation (Haleem, 1993; Noach, 1994). Studies on rats have reported an increase in the availability of brain tryptophan and serotonin during fasting (Ishida et al., 1997; Knott et al., 1973) that could explain a significant improvement of migraine symptoms clinically observed among humans (Busse Grawitz, 1952).

In a controlled exploratory study of 55 subjects with chronic pain, 8-day fasting (300 kcal/day) showed a significant mood improvement after 5 days independently of weight loss, decreased leptin level or increase of plasmatic cortisol (Michalsen et al., 2006). Another uncontrolled study reported an improvement in subjective sleep quality, mood and concentration after 8 days of modified fasting (Michalsen et al., 2003a). Polysomnographic recordings reported a significant decrease in periodic limb movements and nocturnal awakenings, and a non-significant increase in REM sleep. Improved mood may thus be achieved through improved sleep.

Another mechanism behind mood improvement during fasting could be the release of endogenous endorphins, found in humans after 5–10 days of fasting with no correlations with weight loss. One study reported an increase by 5 levels of endogenous opiate production in rats during the first 24 h of fasting and second during the first 48 h (Molina et al., 1995).

The cerebral glucose decrease could promote neurogenesis, synthesis of neurotrophic factors, receptors for neurotransmitters

and chaperone proteins (Araya et al., 2008; Fontan-Lozano et al., 2008; Stanek et al., 2008). For example, intermittent fasting causes an increase in BDNF (brain-derivated neurotrophic factor) that is involved in the regulation of serotonin metabolism, synaptic plasticity, improved cognitive function, and increasing the brain's ability to resist aging (Araya et al., 2008; Chung et al., 2002; Fontan-Lozano et al., 2008; Stanek et al., 2008).

Finally, the production of ketone bodies could be involved in improving mood, decreasing pain sensation, and promoting neuro–neuronal protection against hypoglycemia and different types of brain damage (Brown, 2007; Maalouf et al., 2009; White et al., 2007) possibly through anticonvulsant properties (Gasior et al., 2007; Hasebe et al., 2010; Likhodii et al., 2003; Zarnowska et al., 2009). Further studies are needed to determine the role of ketone bodies in the neurobiological effects of fasting.

In summary, catecholamines and gluco-corticoids are massively released in the first phase of fasting (the first 7 days). In order to protect itself from the potentially deleterious effects of these hormones, the brain's cellular mechanisms of stress resistance are activated. Mood improvement that occurs during these first few days of fasting, could be a direct consequence of this activation (Lavin et al., 2011).

3.2. Clinical efficacy of therapeutic fasting on depressive symptoms

Clinicians have found that fasting was frequently accompanied by increased vigilance and mood improvement, a subjective feeling of well-being, and sometimes a feeling of euphoria (Busse Grawitz, 1952; Roky et al., 2000; Michalsen et al., 2002, 2006, 2009; Michalsen, 2010; Chtourou et al., 2011). Some observations report an improved mood during phase II (between day 2 and day 7) (Table 1).

Studies examining the association of fasting and mood can be divided into two groups: the first group concerns experimental studies focusing on subjects with chronic inflammatory diseases (including rheumatoid arthritis and bowel disorders), using therapeutic fasting as previously defined (i.e., 300–500 kcal/day). These studies used a visual analog scale to assess daily mood. In a prospective uncontrolled trial, the effects of modified fasting (250 kcal/day) for 2 weeks in 52 in patients with chronic pain and metabolic syndrome were reported (Michalsen et al., 2002). Over 80% of fasters showed a rapid decrease in depression and anxiety scores with an average weight loss of 6.6 kg and a normalization of blood pressure. Mood improvement after 8 days of fasting (350 kcal/d) have been shown to depend on the GNB3 C825T polymorphism (Michalsen et al., 2009).

The other group of studies are observational studies on the effects of Ramadan on mood, i.e., partial fasting for 1 month per year. Interestingly, Farooq et al. (2010) reported improved scores for depression and mania in bipolar patients treated with lithium during Ramadan, without significant changes in lithium blood-levels. The recent study of Teng et al. (2011) found no difference in depressive scores between their groups, but their fasting protocol was different and both groups received caloric restriction for 3 months before the Muslim fasting, and baseline depressive scores were very low. Moreover, these results in a Malaysian population cannot be extrapolated to Western countries.

All these studies were conducted without antidepressant drugs.

4. Limits and perspectives

Randomized controlled clinical trials studying the effectiveness of fasting on major depression have yet to be carried out. The heterogeneity of available studies, regarding samples, fasting process, and assessment of mood cannot form the basis for a meta-analysis, and it is not possible to date to conclude that fasting significantly improves mood, even if clinical findings are encouraging. We limited this review to published studies written in English French and German, so we may have missed studies in other languages or unpublished data.

Clinical observations report an improvement in mood between day 2 and day 7, but it is still unclear whether this improvement is maintained over time. This treatment may remain an effective

Table 1
Clinical studies evaluating mood in populations under fasting condition. BDI: Beck Depression Inventory. HDRS: Hamilton Depression Rating Scale. HADS: Hospital Anxiety and Depression Scale. YMRS: Young Mania Rating Scale. CES-D: Center for Epidemiological Studies-Depression Scale. QOL: quality of life. CR: caloric restriction. MF: Muslim fasting. BSI Brief Symptom Inventory. VAS: Visual Analog Scale.

Study	Fasting protocol	Study design and population	Mood evaluation	Major findings
Teng et al. (2011)	3-month clinical trial on CR (reduction of 300–500 kcal/day) combined with 2 days/week of MF.	Randomized controlled trial Healthy individuals, $N=25$	BDI-II, QOL, Pittsburgh Sleep Quality Index, Perceived Stress Scale	Significant energy increase in QOL questionnaire ($p<0.05$). No significant changes in depression and stress level, but baseline levels were very low. No change in sleep quality.
Farooq et al. (2010)	MF during Ramadan	Open-labelled bipolar affective disorder, $N=62$	HDRS, YMRS	Significant decrease in HDRS and YMRS during Ramadan ($F=34.12$, $p<0.01$, for HDRS and $F=15.6$, $p<0.001$ for YMRS)
Michalsen et al. (2009)	8-day modified medical fasting treatment (total energy intake <350 kcal/day)	Controlled healthy subjects, $N=108$	Daily ratings of mood (VAS)	Significant mood improvement ($p=0.036$)
Tavvakoli et al. (2008)	MF during Ramadan	Controlled trial with irritable bowel syndrome, $N=60$	HADS, QOL	Decrease of anxiety score (from 12.7 (6.0) to 9.8 (4.4) after fasting ($p=0.026$)
Lepage et al. (2008)	CR based on patient's self-declaration	Observational study female with CR vs. non-CR, $N=486$	CES-D, BSI	Significant group differences on the BSI, $F(3, 289)=4.84$, $p<0.005$, while results for the CES-D neared significance, $F(3, 309)=3.03$, $p=0.03$.
Kanazawa and Fukudo (2006)	Complete fasting during 10 days	Controlled trial Irritable-bowel syndrome, N=58	Clinical interview	Fasting significantly improved anorexia ($p=0.02$) and anxiety ($p<0.001$), and interference with life in general ($p<0.001$).
Michalsen et al. (2006)	8-day modified fast (300 kcal/day)	Controlled trial chronic pain syndromes, $N=36$	Daily ratings of mood (VAS)	Mood ratings increased significantly in the late phase of fasting ($p<0.01$) but were not related to weight-loss, leptin-depletion or cortisol increase.
Willcox (2007)	Complete fasting during 10 days	Observation study depression, $N=36$	Clinical interview	Reported remission rate of 86%

treatment in the initiation phase of antidepressant treatment, that is generally not effective until the third week.

We were unable, by examining the literature, to determine the reason why psychosis has been placed among the contra-indications of therapeutic fasting. This may be due to the patient's inability to express consent or to comply with the treatment program. We did not find any neurobiological justification, except for a disturbance of dopamine metabolism, but no delusion increase during fasting periods has been reported to our knowledge.

5. Conclusion

Therapeutic fasting has been a safe practice in the medical community for a century, and in some religions for millennia. Research on therapeutic fasting is similar in some aspects to date to research on anti-inflammatory drugs in psychiatric disorders 10 years ago. At the time, only observations on populations of patients with chronic diseases (cancer, Crohn's disease, psoriasis in this case) reported an improvement in mood in patients treated with anti-inflammatory drugs. Today many studies have demonstrated the effectiveness of anti-inflammatory drugs in psychiatric disorders. Our goal in this article was to increase psychiatrists' awareness of the potential positive effects of adjunctive fasting therapy on mood.

Acknowledgments

Dr Jean-Benoit Cottin and Dr Isabelle Chaudieu (INSERM 1061, Montpellier, France).

References

Ahmadi, N., Eshaghian, S., Huizenga, R., Sosnin, K., Ebrahimi, R., Siegel, R., 2011. Effects of intense exercise and moderate caloric restriction on cardiovascular risk factors and inflammation. American Journal of Medicine 124, 978–982.

Araya, A.V., Orellana, X., Espinoza, J., 2008. Evaluation of the effect of caloric restriction on serum BDNF in overweight and obese subjects: preliminary evidences. Endocrine 33, 300–304.

Bartke, A., Masternak, M.M., Al-Regaiey, K.A., Bonkowski, M.S., 2007. Effects of dietary restriction on the expression of insulin-signaling-related genes in long-lived mutant mice. Interdisciplinary Topics in Gerontology 35, 69–82.

Barzilai, N., Bartke, A., 2009. Biological approaches to mechanistically understand the healthy life span extension achieved by calorie restriction and modulation of hormones. Journals of Gerontology Series A, Biological Sciences and Medical Sciences 64, 187–191.

Bol'shova, O.V., Malinovs'ka, T.M., 2008. Diet therapy of obesity in children and adolescents. Likars'ka Sprava, 70–79.

Brecchia, G., Bonanno, A., Galeati, G., Federici, C., Maranesi, M., Gobbetti, A., Zerani, M., Boiti, C., 2006. Hormonal and metabolic adaptation to fasting: effects on the hypothalamic–pituitary–ovarian axis and reproductive performance of rabbit does. Domestic Animal Endocrinology 31, 105–122.

Brown, A.J., 2007. Low-carb diets, fasting and euphoria: Is there a link between ketosis and gamma-hydroxybutyrate (GHB)? Medical Hypotheses 68, 268–271.

Buchinger, O., 1950. Thoughts on therapeutic fasting-after 30 years' experience. Hippokrates 21, 448–452.

Buchinger, O., 1959a. Fasting treatment. Minerva Medica 50, 1296.

Buchinger Jr., O., 1952. Therapeutic fasting in general practice. Hippokrates 23, 66–72.

Buchinger Sr., O., 1959b. 40 Years of fasting therapy. Hippokrates 30, 246–248.

Buchinger, O.H., 1953. Management and conduct of hunger therapy. Hippokrates 24, 362–365.

Buschemeyer 3rd, W.C., Klink, J.C., Mavropoulos, J.C., Poulton, S.H., Demark-Wahnefried, W., Hursting, S.D., Cohen, P., Hwang, D., Johnson, T.L., Freedland, S.J., 2010. Effect of intermittent fasting with or without caloric restriction on prostate cancer growth and survival in SCID mice. The Prostate 70, 1037–1043.

Busse Grawitz, P., 1952. Clinical observations made during 40-day fasting therapy. La Semana Medica 101, 411–415.

Cefalu, W.T., Wagner, J.D., Wang, Z.Q., Bell-Farrow, A.D., Collins, J., Haskell, D., Bechtold, R., Morgan, T., 1997. A study of caloric restriction and cardiovascular aging in cynomolgus monkeys (*Macaca fascicularis*): a potential model for aging research. Journals of Gerontology Series A, Biological Sciences and Medical Sciences 52, B10–19.

Cefalu, W.T., Wang, Z.Q., Bell-Farrow, A.D., Collins, J., Morgan, T., Wagner, J.D., 2004. Caloric restriction and cardiovascular aging in cynomolgus monkeys (Macaca fascicularis): metabolic, physiologic, and atherosclerotic measures from a 4-year intervention trial. Journals of Gerontology Series A, Biological Sciences and Medical Sciences 59, 1007–1014.

Chtourou, H., Hammouda, O., Souissi, H., Chamari, K., Chaouachi, A., Souissi, N., 2011. The effect of ramadan fasting on physical performances, mood state and perceived exertion in young footballers. Asian Journal of Sports Medicine 2, 177–185.

Chung, H.Y., Kim, H.J., Kim, K.W., Choi, J.S., Yu, B.P., 2002. Molecular inflammation hypothesis of aging based on the anti-aging mechanism of calorie restriction. Microscopy Research and Technique 59, 264–272.

Cox, L.S., Mattison, J.A., 2009. Increasing longevity through caloric restriction or rapamycin feeding in mammals: common mechanisms for common outcomes? Aging Cell 8, 607–613.

Cruzen, C., Colman, R.J., 2009. Effects of caloric restriction on cardiovascular aging in non-human primates and humans. Clinics in Geriatric Medicine 25, 733–743 ix-x.

Elias, S.G., Peeters, P.H., Grobbee, D.E., van Noord, P.A., 2007. Transient caloric restriction and cancer risk (The Netherlands). Cancer Causes and Control 18, 1–5.

Everitt, A.V., Le Couteur, D.G., 2007. Life extension by calorie restriction in humans. Annals of the New York Academy of Sciences 1114, 428–433.

Exton, M.S., 1997. Infection-induced anorexia: active host defence strategy. Appetite 29, 369–383.

Farooq, S., Nazar, Z., Akhtar, J., Irfan, M., Subhan, F., Ahmed, Z., Khan, E.H., Naeem, F., 2010. Effect of fasting during Ramadan on serum lithium level and mental state in bipolar affective disorder. International Clinical Psychopharmacology 25, 323–327.

Fekete, C., Singru, P.S., Sanchez, E., Sarkar, S., Christoffolete, M.A., Riberio, R.S., Rand, W.M., Emerson, C.H., Bianco, A.C., Lechan, R.M., 2006. Differential effects of central leptin, insulin, or glucose administration during fasting on the hypothalamic–pituitary–thyroid axis and feeding-related neurons in the arcuate nucleus. Endocrinology 147, 520–529.

Fontan-Lozano, A., Lopez-Lluch, G., Delgado-Garcia, J.M., Navas, P., Carrion, A.M., 2008. Molecular bases of caloric restriction regulation of neuronal synaptic plasticity. Molecular Neurobiology 38, 167–177.

Gasior, M., French, A., Joy, M.T., Tang, R.S., Hartman, A.L., Rogawski, M.A., 2007. The anticonvulsant activity of acetone, the major ketone body in the ketogenic diet, is not dependent on its metabolites acetol, 1,2-propanediol, methylglyoxal, or pyruvic acid. Epilepsia 48, 793–800.

Gerstenblith, G., 2006. Cardiovascular aging: what we can learn from caloric restriction. Journal of the American College of Cardiology 47, 403–404.

Gillette-Guyonnet, S., Vellas, B., 2008. Caloric restriction and brain function. Current Opinion in Clinical Nutrition and Metabolic Care 11, 686–692.

Haleem, D.J., 1993. Serotonergic neurotransmission in the regulation of appetite: a receptor approach. Pakistan Journal of Pharmaceutical Sciences 6, 89–96.

Hammer, S., Snel, M., Lamb, H.J., Jazet, I.M., van der Meer, R.W., Pijl, H., Meinders, E.A., Romijn, J.A., de Roos, A., Smit, J.W., 2008. Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases myocardial triglyceride content and improves myocardial function. Journal of the American College of Cardiology 52, 1006–1012.

Hasebe, N., Abe, K., Sugiyama, E., Hosoi, R., Inoue, O., 2010. Anticonvulsant effects of methyl ethyl ketone and diethyl ketone in several types of mouse seizure models. European Journal of Pharmacology 642, 66–71.

Henry, R.R., Gumbiner, B., 1991. Benefits and limitations of very-low-calorie diet therapy in obese NIDDM. Diabetes Care 14, 802–823.

Henry, R.R., Scheaffer, L., Olefsky, J.M., 1985. Glycemic effects of intensive caloric restriction and isocaloric refeeding in noninsulin-dependent diabetes mellitus. Journal of Clinical Endocrinology and Metabolism 61, 917–925.

Heun, E., 1954a. Fasting among ancient Christians. Hippokrates 25, 328–329.

Heun, E., 1954b. Fasting in ancient Israel. Hippokrates 25, 294–295.

Heun, E., 1956. Therapeutic fasting. Med Klin (Munich) 51, 947–949.

Ishida, A., Nakajima, W., Takada, G., 1997. Short-term fasting alters neonatal rat striatal dopamine levels and serotonin metabolism: an in vivo microdialysis study. Brain Research Developmental Brain Research 104, 131–136.

Jadiya, P., Chatterjee, M., Sammi, S.R., Kaur, S., Palit, G., Nazir, A., 2011. Sir-2.1 modulates 'calorie-restriction-mediated' prevention of neurodegeneration in *Caenorhabditis elegans*: implications for Parkinson's disease. Biochemical and Biophysical Research Communications 413, 306–310.

Kanazawa, M., Fukudo, S., 2006. Effects of fasting therapy on irritable bowel syndrome. International Journal of Behavioral Medicine 13, 214–220.

Kim, E., Seo, S., Chung, H., Park, S., 2008. Role of glucocorticoids in fasting-induced changes in hypothalamic and pituitary components of the growth hormone (GH)-axis. The Korean Journal of Physiology and Pharmacology 12, 217–223.

Knott, P.J., Joseph, M.H., Curzon, G., 1973. Effects of food deprivation and immobilization on tryptophan and other amino acids in rat brain. Journal of Neurochemistry 20, 249–251.

Kritchevsky, D., 1993. Colorectal cancer: the role of dietary fat and caloric restriction. Mutation Research 290, 63–70.

Kritchevsky, D., 2001. Caloric restriction and cancer. Journal of Nutritional Science and Vitaminology (Tokyo) 47, 13–19.

Lavin, D.N., Joesting, J.J., Chiu, G.S., Moon, M.L., Meng, J., Dilger, R.N., Freund, G.G., 2011. Fasting induces an anti-inflammatory effect on the neuroimmune system which a high-fat diet prevents. Obesity (Silver Spring) 19, 1586–1594.

Le Bourg, E., 2005. [Is caloric restriction a means of delaying ageing and increasing longevity?]. La Presse Medicale 34, 121–127.

Lepage, M.L., Crowther, J.H., Harrington, E.F., Engler, P., 2008. Psychological correlates of fasting and vigorous exercise as compensatory strategies in undergraduate women. Eating Behaviors 9, 423–429.
Likhodii, S.S., Serbanescu, I., Cortez, M.A., Murphy, P., Snead 3rd, O.C., Burnham, W.M., 2003. Anticonvulsant properties of acetone, a brain ketone elevated by the ketogenic diet. Annals of Neurology 54, 219–226.
Love, R., 2005. Calorie restriction may be neuroprotective in AD and PD. Lancet Neurology 4, 84.
Maalouf, M., Rho, J.M., Mattson, M.P., 2009. The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. Brain Research Reviews 59, 293–315.
Manjgaladze, M., Chen, S., Frame, L.T., Seng, J.E., Duffy, P.H., Feuers, R.J., Hart, R.W., Leakey, J.E., 1993. Effects of caloric restriction on rodent drug and carcinogen metabolizing enzymes: implications for mutagenesis and cancer. Mutation Research 295, 201–222.
Masoro, E.J., 2007. The role of hormesis in life extension by dietary restriction. Interdisciplinary Topics in Gerontology 35, 1–17.
Masoro, E.J., 2009. Caloric restriction-induced life extension of rats and mice: a critique of proposed mechanisms. Biochimica Et Biophysica Acta 1790, 1040–1048.
Mattson, M.P., 2003. Will caloric restriction and folate protect against AD and PD? Neurology 60, 690–695.
Mattson, M.P., Wan, R., 2005. Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems. Journal of Nutritional Biochemistry 16, 129–137.
McCarthy, D.O., Kluger, M.J., Vander, A.J., 1985. Suppression of food intake during infection: is interleukin-1 involved? American Journal of Clinical Nutrition 42, 1179–1182.
McCarty, M.F., 2001. Does a vegan diet reduce risk for Parkinson's disease? Medical Hypotheses 57, 318–323.
Michalsen, A., 2010. Prolonged fasting as a method of mood enhancement in chronic pain syndromes: a review of clinical evidence and mechanisms. Current Pain and Headache Reports 14, 80–87.
Michalsen, A., Frey, U.H., Merse, S., Siffert, W., Dobos, G.J., 2009. Hunger and mood during extended fasting are dependent on the GNB3 C825T polymorphism. Annals of Nutrition and Metabolism 54, 184–188.
Michalsen, A., Hoffmann, B., Moebus, S., Backer, M., Langhorst, J., Dobos, G.J., 2005. Incorporation of fasting therapy in an integrative medicine ward: evaluation of outcome, safety, and effects on lifestyle adherence in a large prospective cohort study. Journal of Alternative and Complementary Medicine 11, 601–607.
Michalsen, A., Kuhlmann, M.K., Ludtke, R., Backer, M., Langhorst, J., Dobos, G.J., 2006. Prolonged fasting in patients with chronic pain syndromes leads to late mood-enhancement not related to weight loss and fasting-induced leptin depletion. Nutritional Neuroscience 9, 195–200.
Michalsen, A., Schlegel, F., Rodenbeck, A., Ludtke, R., Huether, G., Teschler, H., Dobos, G.J., 2003a. Effects of short-term modified fasting on sleep patterns and daytime vigilance in non-obese subjects: results of a pilot study. Annals of Nutrition and Metabolism 47, 194–200.
Michalsen, A., Schneider, S., Rodenbeck, A., Ludtke, R., Huether, G., Dobos, G.J., 2003b. The short-term effects of fasting on the neuroendocrine system in patients with chronic pain syndromes. Nutritional Neuroscience 6, 11–18.
Michalsen, A., Weidenhammer, W., Melchart, D., Langhorst, J., Saha, J., Dobos, G., 2002. [Short-term therapeutic fasting in the treatment of chronic pain and fatigue syndromes–well-being and side effects with and without mineral supplements]. Forschende Komplementarmedizin und klassische Naturheilkunde 9, 221–227.
Michels, K.B., Ekbom, A., 2004. Caloric restriction and incidence of breast cancer. JAMA :The Journal of the American Medical Association 291, 1226–1230.
Molina, P.E., Hashiguchi, Y., Meijerink, W.J., Naukam, R.J., Boxer, R., Abumrad, N.N., 1995. Modulation of endogenous opiate production: effect of fasting. Biochemical and Biophysical Research Communications 207, 312–317.
Nagulesparan, M., Savage, P.J., Bennion, L.J., Unger, R.H., Bennett, P.H., 1981. Diminished effect of caloric restriction on control of hyperglycemia with increasing known duration of type II diabetes mellitus. Journal of Clinical Endocrinology and Metabolism 53, 560–568.
Noach, E.L., 1994. Appetite regulation by serotoninergic mechanisms and effects of d-fenfluramine. Netherlands Journal of Medicine 45, 123–133.
Omodei, D., Fontana, L., 2011. Calorie restriction and prevention of age-associated chronic disease. FEBS Letters 585, 1537–1542.
Palmblad, J., Levi, L., Burger, A., Melander, A., Westgren, U., von Schenck, H., Skude, G., 1977. Effects of total energy withdrawal (fasting) on thelevels of growth hormone, thyrotropin, cortisol, adrenaline, noradrenaline, T4, T3, and rT3 in healthy males. Acta Medica Scandinavica 201, 15–22.
Park, S., Sohn, S., Kineman, R.D., 2004. Fasting-induced changes in the hypothalamic–pituitary–GH axis in the absence of GH expression: lessons from the spontaneous dwarf rat. Journal of Endocrinology 180, 369–378.
Patel, N.V., Gordon, M.N., Connor, K.E., Good, R.A., Engelman, R.W., Mason, J., Morgan, D.G., Morgan, T.E., Finch, C.E., 2005. Caloric restriction attenuates Abeta-deposition in Alzheimer transgenic models. Neurobiology of Aging 26, 995–1000.
Polonov, K., Nocheva, M., Balabanski, L., Andreev, D., 1982. [Diet with maximum restriction of caloric intake in diabetes mellitus and obesity]. Vutreshni Bolesti 21, 66–72.
Roky, R., Iraki, L., HajKhlifa, R., Lakhdar Ghazal, N., Hakkou, F., 2000. Daytime alertness, mood, psychomotor performances, and oral temperature during Ramadan intermittent fasting. Annals of Nutrition and Metabolism 44, 101–107.
Rooth, G., Carlstrom, S., 1970. Therapeutic fasting. Acta Medica Scandinavica 187, 455–463.
Segall, P., 1977. Long-term tryptophan restriction and aging in the rat. Aktuelle Gerontologie 7, 535–538.
Sell, C., 2003. Caloric restriction and insulin-like growth factors in aging and cancer. Hormone and Metabolic Research 35, 705–711.
Shahab, M., Zaman, W., Bashir, K., Arslan, M., 1997. Fasting-induced suppression of hypothalamic-pituitary-gonadal axis in the adult rhesus monkey: evidence for involvement of excitatory amino acid neurotransmitters. Life Sciences 61, 1293–1300.
Shinmura, K., 2011. Cardiovascular protection afforded by caloric restriction: essential role of nitric oxide synthase. Geriatrics and Gerontology International 11, 143–156.
Skripchenko, N.D., Sharafetdinov, K., Plotnikova, O.A., Meshcheriakova, V.A., 2002. [Influence of caloric restriction diet on clinical and biochemical parameters in patients with type 2 diabetes mellitus]. Voprosy Pitaniia 71, 13–17.
Skulachev, V.P., 2011. SkQ1 treatment and food restriction–two ways to retard an aging program of organisms. Aging (Albany NY) 3, 1045–1050.
Srivastava, S., Haigis, M.C., 2011. Role of sirtuins and calorie restriction in neuroprotection: implications in Alzheimer's and Parkinson's diseases. Current Pharmaceutical Design 17, 3418–3433.
Stanek, K., Gunstad, J., Leahey, T., Glickman, E., Alexander, T., Spitznagel, M.B., Juvancic Heltzel, J., Murray, L., 2008. Serum brain-derived neurotrophic factor is associated with reduced appetite in healthy older adults. Journal of Nutrition, Health and Aging 12, 183–185.
Steinbach, G., Heymsfield, S., Olansen, N.E., Tighe, A., Holt, P.R., 1994. Effect of caloric restriction on colonic proliferation in obese persons: implications for colon cancer prevention. Cancer Research 54, 1194–1197.
Steiner, J., LaPaglia, N., Kirsteins, L., Emanuele, M., Emanuele, N., 2003. The response of the hypothalamic-pituitary-gonadal axis to fasting is modulated by leptin. Endocrine Research 29, 107–117.
Tavakkoli, H., Haqhdani, S., Emami, M.H., adilipour, H., Tavakkholi, M., Tavakkoli, M., 2008. Ramadan fasting and inflammatory bowel disease. Indian Journal of Gastroenterology 27, 239–241.
Teng, N.I., Shahar, S., Manaf, Z.A., Das, S.K., Taha, C.S., Ngah, W.Z., 2011. Efficacy of fasting calorie restriction on quality of life among aging men. Physiology and Behaviour 104, 1059–1064.
Thompson, H.J., McTiernan, A., 2011. Weight cycling and cancer: weighing the evidence of intermittent caloric restriction and cancer risk. Cancer Prevention Research (Philadelphia) 4, 1736–1742.
Tichomirowa, M.A., Keck, M.E., Schneider, H.J., Paez-Pereda, M., Renner, U., Holsboer, F., Stalla, G.K., 2005. Endocrine disturbances in depression. Journal of Endocrinological Investigation 28, 89–99.
Trepanowski, J.F., Canale, R.E., Marshall, K.E., Kabir, M.M., Bloomer, R.J., 2011. Impact of caloric and dietary restriction regimens on markers of health and longevity in humans and animals: a summary of available findings. Nutrition Journal 10, 107.
Ugochukwu, N.H., Figgers, C.L., 2007. Dietary caloric restriction improves the redox status at the onset of diabetes in hepatocytes of streptozotocin-induced diabetic rats. Chemico-Biological Interactions 165, 45–53.
Varady, K.A., Hellerstein, M.K., 2007. Alternate-day fasting and chronic disease prevention: a review of human and animal trials. American Journal of Clinical Nutrition 86, 7–13.
White, A.M., Johnston, C.S., Swan, P.D., Tjonn, S.L., Sears, B., 2007. Blood ketones are directly related to fatigue and perceived effort during exercise in overweight adults adhering to low-carbohydrate diets for weight loss: a pilot study. Journal of the American Dietetic Association 107, 1792–1796.
Willcox, B.J., Willcox, D.C., Todoriki, H., Fujiyoshi, A., Yano, K., He, Q., Curb, J.D., Suzuki, M., 2007. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. Annals of the New York Academy of Sciences 1114, 434–455.
Williams, T.D., Chambers, J.B., Henderson, R.P., Rashotte, M.E., Overton, J.M., 2002. Cardiovascular responses to caloric restriction and thermoneutrality in C57BL/6 J mice. American Journal Of Physiology Regulatory, Integrative and Comparative Physiology 282, R1459–1467.
Wycherley, T.P., Brinkworth, G.D., Noakes, M., Buckley, J.D., Clifton, P.M., 2008. Effect of caloric restriction with and without exercise training on oxidative stress and endothelial function in obese subjects with type 2 diabetes. Diabetes, Obesity and Metabolism 10, 1062–1073.
Zarnowska, I., Luszczki, J.J., Zarnowski, T., Buszewicz, G., Madro, R., Czuczwar, S.J., Gasior, M., 2009. Pharmacodynamic and pharmacokinetic interactions between common antiepileptic drugs and acetone, the chief anticonvulsant ketone body elevated in the ketogenic diet in mice. Epilepsia 50, 1132–1140.