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

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ABSTRACT. Clinicians have found that fasting was frequently accompanied by an increased level of vigilance and a mood improvement, a subjective feeling of wellbeing, 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, 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.

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 over-feeding and starvation. Periods of 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 Hippocrate, fasting was offered as treatment of acute and chronic diseases, following the empirical observation that infection was 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 / d. Caloric restriction is defined by a decrease in daily calorie intake by 30 to 40%(Varady and Hellerstein, 2007). Dietary restriction below 500 kcal / d 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 to 500 kcal / d in the form of fruits or soups: this defines fasting therapy, also called modified/therapeutic fasting focused upon in this review (Varady and Hellerstein, 2007) . Optimal medical fasting was defined by two days of 800 kCal/d 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 drinks 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 to 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 it's duration is limited and predefined (Michalsen, 2010). The recommended duration of fasting in the indication "chronic pain" is one to two weeks. Standardized methods of medical fasting were developed in the United States in the early twentieth century by Dewey Tanner and Hazzard but have

since disappeared from this country, although this method has been increasingly successful in Europe since the 50s. The most used method is one proposed by the German physician Otto Buchinger: it is defined by fasting for 1 to 3 weeks with the ingestion of mineral water and fruit juice in limited amounts, accompanied by a moderate physical exercise(Buchinger, 1950, 1952, 1959b, a; Buchinger, 1953).

Well established, medical fasting has proven its safety. 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, medication with diuretics (in order to avoid hyponatremia).

The reported patient adherence rate is known among chronic pain disorders. Periods of prolonged fasting (>8d) 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 report 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, therapeutic fasting may be an treatment of interest in addition or in relay to psychotropic medication. Moreover, therapeutic fasting has a low cost and is easier to carry out than other treatments for resistance, like electro-convulsive therapy for example.

1.4 Objectives

As we found no review on therapeutic fasting and its effectiveness on 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 (Figure 1). 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 papers. Additional items were added after examining the referenced articles

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 d) 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 (2-7d) 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/d) showed a significant mood improvement after 5 days independantly 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 eight days of modified fasting (Michalsen et al., 2003a). Polysomnography recordings reported a significant decrease in periods of 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 hours of fasting and 2 during the first 48 hours (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. (Table 1)

Clinicians have found that fasting was frequently accompanied by increased vigilance and mood improvement, a subjective feeling of wellbeing, and sometimes a feeling of euphoria (Busse Grawitz, 1952; Chtourou et al., 2011; Michalsen, 2010; Michalsen et al., 2009; Michalsen et al., 2006; Michalsen et al., 2002; Roky et al., 2000). Some observations report an improved mood during phase II (between D2 and D7).

Studies examining the association of fasting and mood can be divided into 2 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 (ie 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 / d) for 2 weeks in 52 inpatients 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 GNB3 C825T polymorphism (Michalsen et al., 2009).

The other group of studies are observational studies on the effects of Ramadan on mood, ie a partial fasting for one month per year. Interestingly, Farooq et al. 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 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 Maleysian population can not 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, assessment of mood can not initiate 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, we may have missed studies in other languages or unpublished data.

Clinical observations report an improvement in mood between D2 and D7, it is still unclear whether this improvement is maintained over time. This treatment may remain an effective 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 ten 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.

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