Redox Biology 2 (2014) 296–304

Contents lists available at ScienceDirect

Redox Biology

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

Review Article

Dietary restriction in cerebral bioenergetics and redox state ☆

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ARTICLE INFO

Article history:
Received 30 December 2013
Accepted 30 December 2013
Available online 11 January 2014

Keywords:
Caloric restriction
Neurological diseases
Mitochondria
Energy metabolism

ABSTRACT

The brain has a central role in the regulation of energy stability of the organism. It is the organ with the highest energetic demands, the most susceptible to energy deficits, and is responsible for coordinating behavioral and physiological responses related to food foraging and intake. Dietary interventions have been shown to be a very effective means to extend lifespan and delay the appearance of age-related pathological conditions, notably those associated with brain functional decline. The present review focuses on the effects of these interventions on brain metabolism and cerebral redox state, and summarizes the current literature dealing with dietary interventions on brain pathology.

Contents

Introduction

The brain is responsible for a large amount of energy consumption in vertebrate organisms, and especially in primates. Although it accounts for only 2% body weight, it consumes 20% of the oxygen and 25% of glucose from these organisms. This energy consumption is required to maintain ionic balance in neurons, produce action potentials, generate post-synaptic currents and recycle neurotransmitters [6]. Since metabolite diffusion from the blood is restricted by the brain–blood barrier, the brain must synthesize its own neuroactive compounds such as glutamate, aspartate, glycine or D-serine from glucose [71]. In addition, neurons are highly susceptible to oxidative damage and glucose oxidation in the pentose phosphate pathway is required to obtain NADPH and regenerate reduced glutathione, which is essential to maintain redox balance in the brain [12]. All these characteristics make the brain highly dependent on glucose and an organ extremely sensitive to energy deficits.

In addition to its high energy expenditure, the brain is also responsible for directly sensing and integrating energetic cues that are sent from peripheral tissues in the form of nutrients and

Abbreviations: AD, Alzheimer's disease; CR, caloric restriction; FR, food restriction; IF, intermittent fasting; KA, kainic acid; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NOS, nitric oxide synthase; PD, Parkinson's disease; PTZ, pentylenetetrazole; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle

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http://dx.doi.org/10.1016/j.redox.2013.12.021

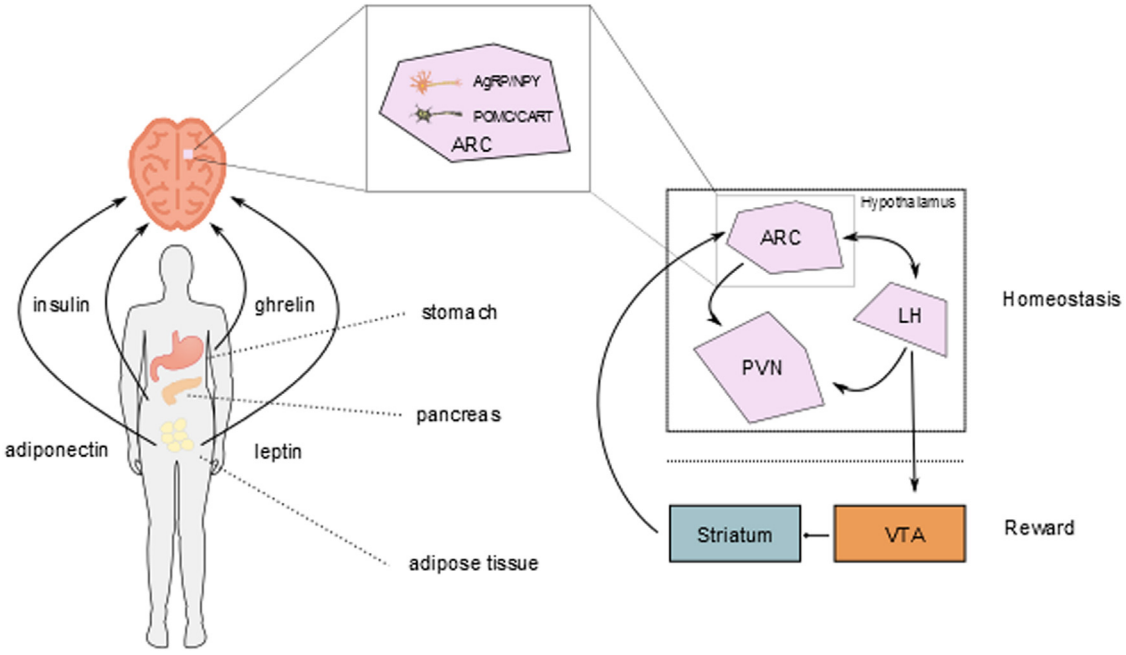

Fig. 1. The brain as a master regulator of body energy control. The figure represents a simplified scheme of how the brain receives signals from peripheral tissues in the hypothalamus. Orexigenic (AgRP/NPY) and anorexigenic (POMC/CART) neurons in the arcuate nucleus (ARC) of the hypothalamus sense these and other cues, such as circulating blood glucose levels. These signals are further integrated by interaction with other hypothalamic nuclei (LH—lateral hypothalamus; PVN—paraventricular nucleus) and finally project into the areas of the brain involved in the reward system, including the ventral tegmental area (VTA) and the nucleus accumbens in the striatum.

hormones (see Fig. 1), orchestrating physiological and behavioural responses [31]. Therefore, the brain acts as a master regulator for energy balance in the organism, determining food intake and expenditure, at the same time as it is the primary energy consumer of the body and the organ most susceptible to oxidative damage.

Dietary restriction prolongs lifespans in a wide range of organisms, spanning from yeast to rodents. More importantly, animals not only live longer, but their health is improved and the appearance of aging markers delayed [39]. Despite huge interest in the effects of dietary limitation, the causes that underlie these beneficial effects are still incompletely understood, due both to physiological and methodological reasons. Dietary restriction produces large-scale systemic effects, with predicted synergic interactions among tissues. For example, reducing total caloric intake prevents the metabolic syndrome, which in turn is a risk factor for other pathological conditions, such as stroke [41]. Therefore, discriminating between systemic and tissue-specific effects is not always straightforward, hampering the identification of molecular targets or specific pathways involved. Moreover, the relevance of each of these targets or pathways might differ between different pathological conditions. On the other hand, methodological issues hampering the understanding of the effects of restricted diets include the lack of consensus on how to perform dietary restriction. The term "caloric restriction" is often used to describe different diets, including some which don't even limit the amount of calories ingested [21]. As will be detailed below, the latest literature is beginning to unveil important differences between these diets. Interestingly, recent results show that, although the final effects of different diets can sometimes be similar, the pathways and mechanisms involved in these outcomes may not be the same [3,22,67,70]. In addition, important differences arise based on the animal model used, the duration of the diet and the age in which the diet is started.

This review will briefly discuss the effects of different dietary interventions on brain metabolism, redox balance and function, focussing on some of the most important age-related brain pathologies.

Systemic effects of different dietary interventions

Dietary restriction has pleiotropic effects that far exceed simple reduction in body weight. Reducing food intake induces a concomitant decrease in body fat, which in turn affects the levels of circulating adipokines, endocrine molecules produced by the white adipose tissue. Low levels of fat are usually correlated with decreased circulating levels of insulin and leptin, and an increase in adiponectin (see Fig. 1), all of which favour a better regulation of glucose homeostasis [89]. Keeping fat tissue at low levels also favours the production of anti-inflammatory over pro-inflammatory cytokines, with inflammation now being regarded as an important player in the pathogenesis of obesity-related insulin resistance [56]. Inflammatory signals can in turn induce oxidative imbalance and reactive oxygen species (ROS) production in many tissues. One of the means to promote oxidative stress by these signals is the stimulation of the inducible nitric oxide synthase (iNOS), which produces high levels of nitric oxide, facilitating the formation of other reactive oxygen and nitrogen species [17].

Historically, a number of different diets have been referred to under the term "calorie restriction" [21]. In recent years, there has been an increasing awareness of the particular effects of each different dietary intervention and their specific mechanisms are now beginning to be separately unravelled. In the present work, we will focus on the three most prevalent protocols in the literature: intermittent fasting (IF), food restriction (FR) and caloric restriction (CR), and will use the term 'dietary restriction' to refer generically to any of the three.

IF, also known as "every other day feeding", is a dietary protocol in which animals alternately fast and have access to food *ad libitum* every 24 h. Under these conditions, body weight usually decreases, although with 10–20% oscillations between feeding and fasting days [69]. Interestingly, although animals kept on this diet for short periods may eat less than their *ad libitum*-fed counterparts, food intake may be similar after longer periods, due to overeating on feeding days [22]. Consistently with reduced food intake, short periods of IF improve glucose tolerance. However,