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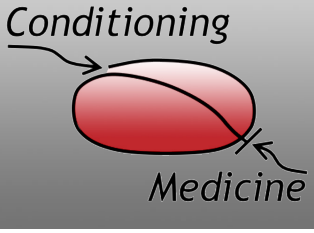

REVIEW ARTICLE | OPEN ACCESS

Dietary restriction as conditioning paradigms with implications for stroke

Zhishuo Wei[1], Wenting Zhang[2], Hongjian Pu[1], M. Victoria Bregy[1], Yanqin Gao[2], R. Anne Stetler[1]

Dietary restriction has been widely demonstrated to have beneficial effects at the organismal level. If initiated prior to injury or early life, dietary restriction can confer a conditioned-like state to protect against aging and or subsequent injury. The experimental paradigms used in the literature present a wide range of methods to induce dietary restriction. These different paradigms present vastly different systemic scenarios, leading to limitations in interpreting the general applicability of dietary restriction, and potentially confound identifying universal mechanisms. Taking the example of dietary restriction as a protective mechanism against ischemic injury, we discuss here some of the factors that need to be considered when evaluating the literature, including assumptions involved at the preclinical level of what is normal dietary consumption, methods of implementing dietary restriction, as well as the impacts of stroke relevant co-morbidities, including age and obesity. By highlighting these factors, we hope that future interpretations of dietary restriction in stroke models will be able to be better consolidated and compared.

Keywords: dietary restriction, caloric restriction, stroke, preconditioning

Introduction

Aging is often characterized as a degenerative process that evolves due to the accumulation of deleterious environmental impact and byproducts of physiological function. Likewise, brain injury often extends temporally far from the initial impact and can be impacted by the relative health of the individual when the injury occurred. When viewed as such, both aging and injury represent a biological and pathological phenomenon that potentially could benefit from intervention strategies. Currently, the only intervention that seemingly lessens aging effects is dietary or caloric restriction. Less considered a preventative strategy and more of a form of conditioning, dietary restriction is thought to elicit a systemic subtoxic stress response and subsequently confer an advantage when subjected to aging or other injury ("Hormesis Hypothesis") (Sinclair, 2005). Although reduction of energy metabolites can directly impose a conditioned state on cultured neurons, the systemic nature of dietary restriction is critical to consider. For this reason, it is particularly relevant to examine the hypothesis that dietary restriction enacts humoral dynamics that confer neuroprotective states against subsequent injury or brain deterioration associated with aging or injury such as stroke. In this regard, the particular context of the organism as a whole needs to be considered when interpreting the effects of dietary restriction. Interestingly, current progress in the literature is bringing out nuances of dietary restriction models that may fold in nicely with stroke co-morbidities or risk factors, including age, diet makeup, obesity, and hypertension.

Several models exist for inducing an energetically restricted state. Among these, two major paradigms are fairly widely used: intermittent fasting and restricted daily caloric intake. Restricted caloric intake typically involves the observation of *ad lib* food consumption of either the targeted cohort or a control group, and then progressive restriction of that averaged food consumption until attaining and maintaining 20-40% of the caloric intake of the *ad lib* observed group. Intermittent fasting, on the other hand, involves varying paradigms of extended time periods without food intake alternating with periods of *ad libitum* food access, often resulting in complete or near to complete depletion of glycogen stores. Because these

[1]Pittsburgh Institute of Brain Diseases and Recovery and the Department of Neurology, University of Pittsburgh, Pittsburgh PA 15213. [2]State Key Laboratory of Medical Neurobiology and MOE Frontiers Center for Brain Science, Institutes of Brain Science, Fudan University, Shanghai, China.

Correspondence should be addressed to R. Anne Stetler (stetler@pitt.edu).

two paradigms are quite distinct, this review will focus on the constant reduced dietary intake model (i.e., as opposed to intentional cycling paradigm of intermittent fasting).

Factors in modeling dietary restriction and the association with stroke risk factors

In formulating this review, considerable thought has been spent on evaluating the variations in the literature and what might be still missing. Interestingly, after compiling lists of issues remaining unaddressed, a recent review article surfaced during a search voicing similar concerns of unanswered questions. We will touch on those concepts here, but for an additional voice focused on calorie restriction (CR) in particular, we would like to point the reader to Ingram and de Cabo (2017). Our focus is more specific to CR effects in the context of stroke models, but the prior article broadens the scope to general organismal aging.

What is a normal dietary state, and how much restriction is required?

The bulk of dietary restriction models rests on initiating dietary restriction in animals with normal (laboratory) weight compared to control animals kept on an *ad libitum* diet. The assumption in most interpretations is then that the *ad libitum* consumption is "normal." However, in the laboratory setting, ad libitum access to food in the absence of significant physical challenges could be reflective of sedentary or overweight mice compared to normal wild mice, and thus alter contextual interpretation (Martin et al., 2010). This concept is furthered by the observation that mice incrementally gain weight as they age in the laboratory and that this may be independent of developmental growth. To address the issue that laboratory mice may themselves be a model of overconsumption by *ad libitum* access and relatively sedentary behavior, Austad and Kristan (2003) confirmed that the laboratory setting does not significantly skew mice to consume higher calories than mice in the wild, supporting that the laboratory environment is not leading to caloric overconsumption as a baseline (Austad and Kristan, 2003). On the basis of this, CR continues to be based off of observing consumption by controls. (As a note, in order to successfully control caloric consumption, dominant behavior must be mitigated to ensure equal caloric consumption. For this reason, mice are usually separated during the time they need to consume the diet, then returned to social housing in the interim period (personal observation).) Despite the equivalence in caloric consumption observed between wild sourced mice and laboratory bred mice, controversy remains as to whether laboratory bred mice develop strain- or context-specific energy imbalances that create a specific and potentially pathological background to allow for the observed protection by CR (Martin et al., 2010; Sohal and Forster, 2014). In addition, the context of weight itself brings up another critical factor in evaluating the dietary restriction literature: the grade or degree of the restrictive paradigm. There is wide variation in the literature as to how much diet to limit – some reports use a mild (but likely more translatable) cut in dietary intake of approximately 10-15%, a majority of studies use 20-30% reduction of caloric intake, whereas other reports use severe restrictions, upwards of 50% reduction in caloric intake. Extreme reductions in diet can lead to deleterious outcomes, which then could mask or confound the interpretations surrounding the mechanisms or effects of dietary restriction. Likewise, the percent reduction of intake is also dependent on the definition of "normal," as mentioned above. If the "normal" intake is actually leading to spontaneous obesity-like conditions, then caloric restrictions may actually reflect a biological normal scenario, rather than a restricted scenario. While this possibility remains plausible, clinical extrapolation may be still relevant and help shed light on why human studies may also show benefit of long-term CR (Redman et al., 2018).

Diet composition

Nutrient issues and degree of CR are critical differences between the reported findings in the literature. Because the most simplistic approach to CR is an across the board reduction of chow, deficiencies in vital nutrients may be missing from the CR diet and contribute to the perceived conditioning effects of CR or deleterious outcomes. Thus, the effects of CR might not actually be attributed to the "caloric" component and instead be attributable to reduction of specific macromolecules or other nutrients, including proteins, fats, or vitamins.

Consistent with this possibility, several studies specifically reduced protein levels in the diet while maintaining the caloric intake in rats and found similar results on reduced levels of oxidative damage and survival as observed in the cruder CR model (Sanz et al., 2004; Ayala et al., 2007). A post-hoc analyses of experimental paradigms in two large rhesus monkey CR studies found differences in the nutritional composition of the caloric restrictive diets formulated with a similar caloric density (Mattison et al., 2017). In particular, the study performed at the University of Wisconsin used a defined diet that contained less protein and more fat, correlating with improved lifespan and physiological outcomes pointing to improved health overall, compared to the NIH study (Mattison et al., 2017). Stroke risk in humans has been positively associated with higher red meat protein intake compared to poultry, nuts, or fish intake (Bernstein et al., 2012); however, other studies failed to find statistically significant associations (Preis et al., 2010).

In preclinical stroke studies, transient medial cerebral artery occlusion (MCAO) outcomes were improved by acute protein reduction independent of caloric reduction in Sprague-Dawley rats (Varendi et al., 2014), and a recent report found that acute protein restriction (that was not caloric restrictive) prior to transient MCAO improved stroke outcomes in male C57BL6 mice (de Carvalho et al., 2019). Interestingly, protein restriction and CR might exert mechanistically distinct functions. In a model of renal ischemia, acute paradigms found that either protein restriction or CR were beneficial in terms of renal ischemic outcomes (serum urea), but that the combination of the protein restriction with CR was additive rather than redundant (Robertson et al., 2015).

Rigorous teasing apart of the particular elements involved in CR (e.g., calories vs protein) that contribute to conditioning against cerebral ischemia are critical; not only will this contribute to more precisely identifying targets for preventative (and potentially restorative) interventions but also to a better understanding of the brain-system response to metabolic alterations.

Age and conditioning time-window

As with stroke models, much of the last 20 years of studies revolving around CR initiated restricted feeding during young adulthood. In rats maintained on lifelong dietary restriction initiated during young adulthood, cardiovascular changes associated with aging/compromised heart function in normal rats were attenuated, including cardiomyocyte density and tachycardiac response to dobutamine (Ahmet et al., 2011). Consistent with these studies, we and others have demonstrated that dietary restriction is protective against ischemia when initiated in the weeks prior to ischemic injury. Short term CR (30% reduction of food intake) seven days prior to myocardial infarction was protective in C57BL6 mice (Noyan et al., 2015); this level of dietary restriction was also protective against renal ischemia/reperfusion when implemented 4 weeks prior to injury (Mitchell et al., 2010). Likewise, our group found that 30% reduction of food intake initiated four weeks prior to transient

MCAO significantly decreased stroke severity and improved histological and functional integrity of white matter tracts (Zhang et al., 2019). Neuroprotection against transient MCAO in rats was also observed in rats subjected to 40% reduction of food intake for four weeks prior to stroke (Ran et al., 2015).

Age is a significant risk factor for stroke and other conditions which might be improved by even acute dietary restriction. The question then can be posited whether dietary restriction-derived protection is a phenomenon that has greater conditioning impact if initiated in young adults and maintained for an extended timeframe, and do the mechanisms shift if initiated further along the aging continuum? Many older reports established that initiating dietary restriction in aged (1 year) mice improved survival in normal mice and mice with lymphoma development (Weindruch and Walford, 1982; Pugh et al., 1999) and improved cognitive function (Means et al., 1993) compared to normally fed aged mice. In mice with CR initiated at 14 months, the transcriptional profile of heart tissue was reprogrammed and reflected a state associated with healthier tissue (Lee et al., 2002). In even older mice, dietary restriction initiated at 23.5 months created changes in protein turnover in the liver, kidney, and brain that mimicked younger ages (Goto et al., 2002), suggesting that even an acute period of dietary restriction might be beneficial to extremely old mice.

The consideration of acute dietary restriction in older mice could be an attractive setting in which to study acute CR conditioning against stroke. Consistent with this, dietary restriction initiated in aged (and spontaneously obese) rats improved outcomes following transient cerebral ischemia (Ciobanu et al., 2017). Extrapolating from ischemic preconditioning studies, it is likely that the acute time window of dietary restriction is mechanistically distinct from longer term dietary conditioning.

Weight starting and ending points

The choice of starting weight for initiating dietary restriction could also have a variety of implications on outcomes, as the overweight or obese scenarios start with differences in hormones stores, likely receptor sensitivity, and basal metabolism. Since dietary restriction may act on these mechanisms in the normal weight context, initiating dietary restrictions in overweight or obese animals may lead to differential mechanisms or outcomes, particularly layered in the context of ischemic stroke. In non-obese healthy individuals, six months of 25% CR led to decreased estimated 10-year cardiovascular risk in humans (Lefevre et al., 2009), which is associated with stroke risk. Studies exist examining the effects of CR specifically in overweight or obese populations (Cui et al., 2013; Dungan et al., 2016). In human studies, six months of 12.5% CR in overweight (non-obese) adults decreased fasting insulin levels and decreased core body temp, as well as weight loss, compared to the control group (Heilbronn et al., 2006). Similar to some of the controversies of dietary restriction itself, the timing of dietary restriction intervention in obesity or the underlying pathology contributing to the obese state could grossly alter or limit the interpretive capacity. Because obesity can occur consequential to many clinical scenarios (e.g., high fat intake, metabolic alterations), these models will likely need to rigorously explore mechanism that may be universal or context-specific in the response of overweight or obese subjects to dietary restriction.

Excessive weight is another risk factor for stroke. Human data widely supports that increasing weight is associated with increasing risk for stroke (Strazzullo et al., 2010), although there may be a paradox in human stroke outcomes in obese patients (Oesch et al., 2017). However, in preclinical studies, prolonged exposure to high fat diets is readily associated with exacerbated injury outcomes in a variety of cerebral ischemic models (Nagai et al., 2007; Deutsch et al., 2009; Langdon et al., 2011; Li et al., 2013). In aged Sprague-Dawley rats that develop signs of spontaneous obesity, acute dietary restriction was beneficial in improving subsequent transient cerebral ischemia outcomes (Ciobanu et al., 2017). These reports suggest that dietary restriction may be a potential context to develop interventions specifically targeted to stroke with obesity as a co-morbidity, but further studies to more consistently model the intervention and identify mechanisms are needed.

Stroke-relevant co-morbidities

Hypertension

Chronic hypertension is another well-established risk factor for stroke (Brown and Haydock, 2000; Ninomiya et al., 2004). In humans, intervention using the Dietary Approaches to Stop Hypertension (DASH) regimen alone decreased systolic and diastolic blood pressure in mildly hypertensive overweight individuals that was not associated with losing weight (Smith et al., 2010). Likewise, in a group of individuals who practice long term dietary restriction, blood pressure steadily decreased across the initial two years of CR (reported from sourced personal physician documentation) and was relatively low compared to a non-restricted comparison group (Holloszy and Fontana, 2007). Preclinical studies have supported the association of dietary restriction and decreased blood pressure in hypertensive subjects. When subjected to a fairly extreme dietary restriction (50% intake of control diet), blood pressure was lowered (Young et al., 1978), the time of stroke onset was delayed, and expression levels of inflammatory markers was decreased (Chiba and Ezaki, 2010). Combined, these studies suggest that CR may be able to decrease a hypertensive state and delay stroke onset in the individuals prone to hypertension.

Metabolism

One of the earliest hypotheses addressing the beneficial outcomes by dietary restriction was that reduced metabolism was the most significant contributor. This theory was later cast into doubt by subsequent studies suggesting that the decreased metabolism is transient, and after longer periods of time, CR animals exhibit the same, if not increased, metabolic rate as control animals (Masoro, 2000; Sinclair, 2005). Although the potential role for reduced metabolism remains controversial, a recent paper has revived the concept that reduction in metabolism may contributed to the CR conditioned state in humans (Redman et al., 2018). Redman et al. reported that energy expenditure in humans, as measured by a metabolic chamber in both a 24h sedentary and a sleeping context, was significantly reduced in humans subjected to 15% CR compared to control subjects (Redman et al., 2018). This difference was observed even one and two years following initiation of the CR diet.

The role of metabolism or energy expenditure is not understood in predicting stroke. Metabolic inhibitors can contribute to a conditioned state in preclinical models, yet other models of preconditioning appear to increase metabolic activities (Gidday, 2006). In an interesting study that combined age with CR, CR was found to have a consistent and distinct effect on profiling adipose metabolism (Miller et al., 2017). These observed effects on adipose tissue has also been implicated in the protection afforded by acute CR against subsequent cerebral ischemic injury (Zhang et al., 2019). The controversy exists in ischemic protection concerning the impact of metabolic changes on outcomes due to conditioning as well.

Diabetes/insulin resistance

Diabetes is another well-established risk factor for stroke, and highly predictive of worsened stroke outcomes. Insulin resistance (indicated by higher plasma levels of glucose and

insulin) is correlated with increased risk for and more severe consequences to stroke (Ninomiya et al., 2004). In humans subjected to six months of a pharmacological mimetic of dietary restriction, predictive risk factors for diabetes declined (Roth et al., 2001). In a longer-term study of humans, plasma insulin concentrations decreased significantly in a CR group cohort at one year of maintaining the diet; by two years in the study, there was no longer a discernible decrease in plasma insulin concentration. A study in overweight human subjects found that six months of dietary restriction improved insulin sensitivity (Larson-Meyer et al., 2006). Preclinical studies also suggest that dietary restriction in the laboratory setting can consistently decrease indicators of insulin resistance. In two different rhesus monkey studies, the CR groups had less percent incidence of insulin resistance or diabetes (Mattison et al., 2017). In contrast to the human study that observed decreased plasma insulin levels only at one, but not two, years, long term dietary restriction in rhesus monkeys conferred long lasting effects at mitigating the development of insulin resistance (Bodkin et al., 1995). This could be an issue in long term diet adherence in human subjects. Adding on the layer of stroke protection at the preclinical level, acute (4 weeks) dietary restriction in mice did not lead to changes in plasma insulin concentration, but resistin was decreased and post-stroke glucose tolerance was improved in the dietary restricted mice. More research combining co-morbidities such as an insulin-resistant state and interventions such as dietary restriction will likely contribute to better understanding of the depth and potentially divergent mechanistic effects of dietary restriction-mediated protection against stroke. This need is further extended to sex-dependent variables, as the glucoregulatory response in rhesus monkeys may be influenced by sex in relation to adiposity (Mattison et al., 2017). Sex-dependency has not been well-explored at the preclinical level, unfortunately, despite females have a higher lifelong incidence rate of stroke compared to males (Girijala et al., 2017).

Can dietary restriction be a plausible intervention as a conditioning state?

With the wide variation in experimental paradigms of dietary restrictions and observed strain and substrain differences, more preclinical studies are warranted with rigorous design and interpretations. There are many avenues to explore and given the vast amount of literature that does point toward a positive effect of dietary restriction, particularly when well-defined and nutrient sufficient, it is all but certain that further exploration will yield fruitful targets and better understanding of the human conditioned state. The function and applicability of dietary restriction as a potential intervention in stroke susceptibility or outcomes are still under investigation. Obviously, if patient compliance were not a factor, suggesting a mild reduction in dietary intake would likely benefit those at most risk for stroke. However, this approach is likely to fail for multiple reasons. First and foremost, the success rate of adhering to a dietary restriction regimen in humans is very low (and a far cry from imposing it on laboratory mice!). Second, the individual state – age, weight, adiposity, hypertension, genetic background, and sex – of stroke-risk individuals will likely necessitate more targeted intervention than simple dietary restriction. Protein restriction, modulation of types of fats, and salt restrictions can all be a part of dietary restriction. Further identification of specific pathways necessary for protection in various contexts would likely lead to an intervention that can be more easily adhered. These studies will likely be forthcoming in the next decade.

Conflicts of interest:
None.

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