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The glucocorticoid paradox of caloric restriction in slowing brain aging

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Abstract

Glucocorticoids have a bimodal effect on cognition, hippocampal pyramidal neurons and long-term potentiation (LTP). Transient increases in glucocorticoids improve performance at spatial memory tasks and facilitate synaptic efficacy, depending on the context. On the other hand, long-term elevations of glucocorticoids are associated with decreased cognitive performance, attenuated synaptic efficacy and neuronal atrophy. Elevation of glucocorticoids during aging is also associated with mild cognitive impairment and hippocampal atrophy.

Caloric restriction (CR), a dietary manipulation which extends life-span in rodents, also increases free plasma corticosterone. Recent data suggests that CR attenuates many brain aging changes and increases resistance of neurons to toxins and injury. Thus, a paradox may be considered: if CR causes chronic elevation of glucocorticoids, and if glucocorticoids can increase the risk of neurodegeneration, how can CR be neuroprotective. We suggest that the neuroprotective effects of CR outweigh the deleterious effects of glucocorticoids. The neuroprotective effects of CR that are discussed here include decreased plasma glucose, attenuated free radical generation, alterations of the vasculature, increased expression of heat shock proteins and neurotrophic factors, and attenuation of age-related glial activation.

Keywords: Caloric restriction; Hippocampal atrophy; CORT; Neurons; Astrocytes; Microglia; Aging; Cognition; Spatial learning; GFAP; Glucose metabolism

1. Introduction

Chronic caloric restriction (CR) is well established to increase the life-span and protect hippocampal functions during aging in rodents. CR, however, also elevates blood corticosterone. Elevations of blood glucocorticoids (CORT; cortisol in humans and corticosterone in rodents) during chronic stressful conditions are associated with cognitive impairment and hippocampal atrophy in both humans and rodents. Thus, a paradox may be considered: if CR causes chronic elevation of CORT, and if CORT can increase the risk of neurodegeneration, how can CR be neuroprotective.

This review focuses on how CR may protect hippocampal function despite the elevated CORT. In parallel, we briefly summarize the evidence suggesting that elevation in CORT during aging and stress contributes to cognitive impairment and hippocampal damage.

2. Brief review of CR

CR slows many aging processes and extends the life-span of laboratory rodents. More than 100 studies show that a reduction of ad libitum (AL) caloric intake by 10–40% in adult rodents, without deficiencies of micronutrients, proportionately extends their life-span [18,59,101,110]. The increased life-span is due to a slower onset of many pathological conditions throughout the body that are associated with morbidity. The particular chronic and degenerative diseases that are attenuated by CR differ by species and genotype [50]. The positive effects of CR on health and life-span can be initiated even relatively late in life and do not depend on delayed sexual maturation [18,110]. The overall metabolic rate is not considered to be changed during CR because body mass becomes scaled down in proportion to food availability [31,63].

Mechanisms at work in CR are complex and appear to act at many levels. The most widely discussed mechanisms involve reduced oxidative damage [101] and lowered blood glucose [60]. CR also lowers secretion of numerous hormones, including growth hormone, insulin and insulin-like growth factors [102]. Reduction of these growth hormones,

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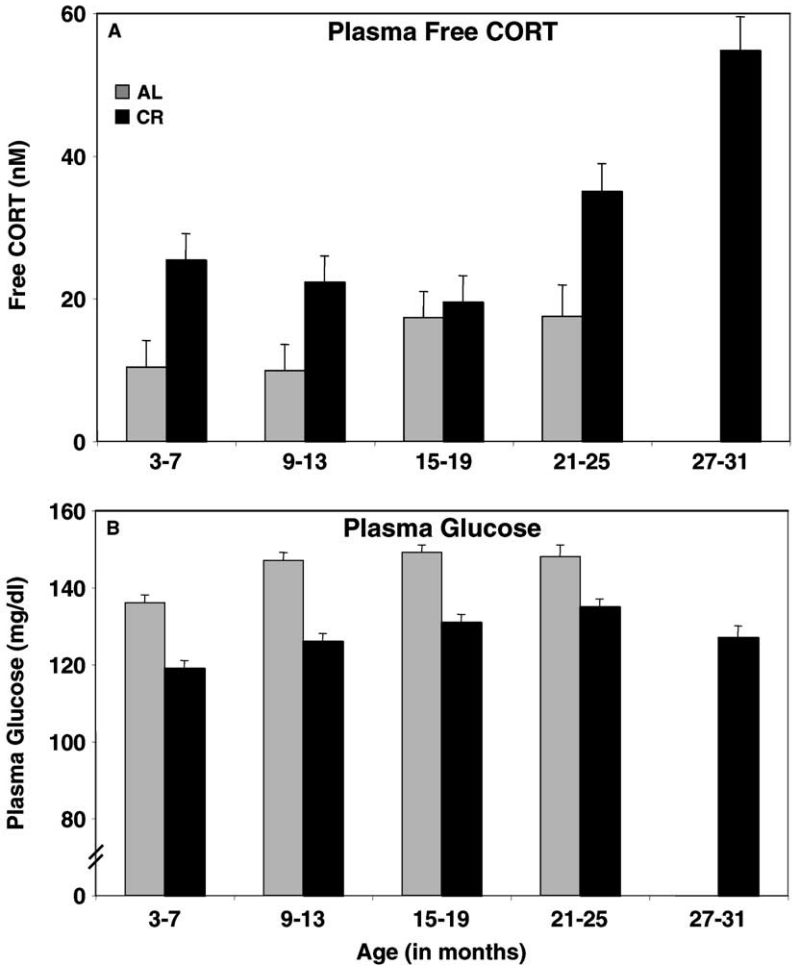

Fig. 1. Plasma free CORT (A) and glucose levels (B) in male F344 rats over the life-span (longitudinal study, initial $n = 21$). Data are means of CORT or glucose levels during the circadian cycle. Free CORT data are from Table 4 of Sabatino et al. [87]. Plasma glucose levels are from Table 1 of Masoro et al. [60].

along with the elevation of CORT, may extend life-span by reducing the rate of cell proliferation and tumor progression [94,108]. Experimental mutations in nematodes and flies that increase life-span through effects on insulin-like signaling pathways may also utilize mechanisms that are shared by CR [22].

However, CR also causes marked elevations of plasma CORT [87] (Fig. 1), a homeostatic response that is expected with the shift to below AL food intake and the need for increased gluconeogenesis. Masoro and Austad [59] suggest that CORT elevation in CR may be an evolutionarily conserved mechanism for adaptation to periods of food scarcity. Elevation of CORT in response to stress is also important for regulation of energy metabolism during life-threatening situations [92]. Utilization of CORT-mediated pathways in response to both CR and stress poses a physiological problem for understanding CR-mediated changes—does CORT elevation in CR signal as an energy regulator, a stressor, or both.

This review focuses on contrast between the effects of age-related and of CR-induced elevations of CORT on the hippocampus. Elevations of CORT during aging and CR have contrasting effects on other organs/systems as well. For example, long-term CORT treatment and chronic stress are known to suppress cell-mediated immunity. Similarly, there is an age-related reduction in T-cell-mediated toxicity, which is attenuated by CR [109].

3. Chronic CORT elevation is associated with cognitive impairment and hippocampal atrophy in humans

During aging, humans show an increasing risk of slow and progressive elevations of blood CORT, which is associated with a higher risk of cognitive impairments that range from severe changes in Alzheimer's disease to mild changes in the speed of information processing. Why individuals differ so widely during aging remains a mystery. Valuable information has come from several longitudinal studies. The MacArthur Foundation Study on Successful Aging examined three different groups of healthy community-living

elderly subjects in the eastern United States over a period of 2.5 years for CORT levels and cognitive performance. Urinary CORT increased progressively in 20% of the women, while 15% showed a decrease. In the sub-population of women with increasing CORT, 75% performed poorly at the delayed recall of a story task than their performance at the start of the study. Among the women with decreasing CORT levels, 70% showed an improvement at this task at the end of the study [95]. Similarly, a Canadian study reported that individuals with increasing CORT over a 5-year period and high CORT at the time of cognitive assessment ('increasing/high') showed a poor performance in delayed memory and spatial memory tests compared to those with lower CORT. The subjects with increasing/high profile also had 15% lower hippocampal volume without significant atrophy of the cerebral cortex. This selective loss of hippocampal volume was correlated with both the current CORT and with elevation of CORT over the 5-year period [51]. Deleterious effects of CORT elevation on the hippocampus are also shown in Cushing's syndrome, major depression, or post-traumatic stress disorder. In all three disorders, chronically elevated CORT was associated with hippocampal atrophy in the range of 5–25% [91].

Similar effects of chronic CORT elevation are observed in other primates as well. Prolonged intense psychosocial stress in vervet monkeys caused dendritic atrophy and neuron loss in the hippocampus [105]. To determine whether elevated CORT, independent of stress, can lead to hippocampal damage, Sapolsky et al. [93] implanted cortisol pellets into the hippocampus of vervet monkeys. Examination after 12 months showed dendritic loss and other cytoarchitectonic abnormalities, but not the expected neuron loss. This result indicates that stress-mediated elevation of CORT contributed to hippocampal atrophy, but it was not sufficient for neuron death.

4. Rodent studies: effects of CORT, aging and CR

Chronic CORT elevation in rodents is also associated with hippocampal damage. Muhlen and Ockenfels were the first to report that chronic treatment with cortisone preferentially causes pyknosis (shrinkage) of cell bodies and nuclei of pyramidal neurons in guinea pigs [72]. Many subsequent experiments have established that elevation of CORT by either stress or pharmacological administration can endanger hippocampal neurons [90]. An age-related increase in CORT also decreases post-maturational neurogenesis in rodents (Section 4.5). Evidence discussed below implicates a role for CORT in age-related cognitive impairment, decreased synaptic efficacy and neuronal damage. In parallel with this, we review the paradoxical evidence that CR attenuates age-related deterioration of hippocampal function despite the CORT elevation.

4.1. CORT elevation during aging and CR

In numerous reports, laboratory rats show increases of plasma CORT at later ages that occur in both sexes and many genotypes (Fischer 344, Long Evans, and Sprague–Dawley) [89]. After excluding several studies where the baseline CORT levels were high, Sapolsky concluded that there was a generalized two- to three-fold increase of plasma CORT by the age of 20–28 months. In AL-fed Fischer 344 (F344) rats, a longitudinal study showed that the free CORT (calculated) increased by 70% between 9 and 19 months, without further increase at later ages [87] (Fig. 1). This increase in CORT during middle age was due to an elevation through most of the diurnal cycle. CR, in contrast, increased free CORT levels throughout the life-span, with a predominant increase at the diurnal peak. The free CORT levels (calculated) are two-fold higher in the young CR animals compared to age-matched AL rats (Fig. 1) [87]. Direct determination of free plasma CORT by ultrafiltration dialysis confirmed that the CR F344 rats have two-fold higher free CORT than AL rats at ages of 9, 15 and 21 months [27]. The elevated free CORT in the CR was due to 33% reduction in the plasma CORT binding globulin [87].

The rats used in the longitudinal study were also tested for restraint stress-induced CORT elevation. The peak levels of total CORT during 1 h of restraint stress in young rats was three times as high as that observed during the acrophase in the AL rats, 1.5 times as high as that in the CR rats, and 60-fold higher than CORT at the diurnal nadir [87]. The important point here is that CR increases total CORT throughout the adult life-span (see Section 4.3).

In contrast to the aging F344 rats, studies from this lab on C57BL/6J (B6) male mice gave quite different results: there was no elevation in CORT between the ages of 8 and 32 months [42]. Our study carefully excluded aged mice with gross pathological lesions or weight loss (~20% of the mice; for description of the necropsy findings, see [20,21]). Thus, the findings in aging F344 rats may reflect epiphenomenona of spontaneous diseases of aging, particularly kidney lesions [50]. By 18 months, the AL-fed F344 rats of both sexes presented about four gross organ lesions per individual, with a further increase to eight lesions/rat by 30 months. In contrast, CR cut the number of lesions by 50% in the age-matched rats. These data suggest a working hypothesis that a sub-population of laboratory rodents is at a higher risk for age-related elevation of CORT as a secondary consequence of gross pathological processes.

The possibility remains that primary aging changes in neuroendocrine brain centers contribute to the increased hypothalamic–pituitary–adrenal axis (HPA) activation. The release of corticotropin releasing hormone (CRH) and vasopressin from the paraventricular nucleus (PVN) of the hypothalamus induces secretion of adrenocorticotropin (ACTH) from the pituitary, and subsequently, release of CORT from the adrenal cortex. Elevated plasma CORT inhibits the release of CRH and ACTH by activation of

Table 1
Comparison of spatial learning: CR and AL animals of same age in Morris water maze

Species; strain	Ages compared (in months)	Effect of CR on escape latency	Effect of CR on probe trial[a]	Comments	Reference
Rat (COBS)	12, 24 and 30	12 and 30	30	Longitudinal study	[2]
Rat (COBS)	4, 12, and 24	12 and 24	24		[80]
Rat (F344)	6, 12, 18, and 24	No effect	No effect		[58]
Rat (Sprague–Dawley)	6	6	No effect	Alternate-day feeding starting at 3 months	[6]
Mice (C57/BL6)	12[b] and 22	No effect	N/A[c]	CR started at 14 months	[69]
Mice (C57/BL6)	3[b], 10 and 26	N/A	10 and 26 (on days 4–6)		[54]
Mice (C57/BL6)	3[b], 10 and 26	No effect	No effect		[55]
Mice (C57/BL6)	3[b], 15 and 27	27	27		[56]
Mice (C57/BL6)	3[b] and 24	No effect	No effect		[5]

The numbers indicated in the columns titled "Effect of CR. . ." are the ages at which CR animals performed better than AL animals. None of the studies report that CR impairs performance in Morris water maze.

[a] Time spent in the quadrant that used to have the hidden platform.

[b] No age-matched CR group.

[c] N/A: not tested.

glucocorticoid receptors in the pituitary, hypothalamus and hippocampus.

Age-related alteration of glucocorticoid and mineralocorticoid receptors in the brain appears to be strain-dependent. In the Brown–Norway rats, there is an age-related loss of glucocorticoid receptors in the pituitary (50%) and the hypothalamus (40%), but not in the hippocampus [106]. In contrast, there is an age-related reduction of glucocorticoid receptors in the hippocampus (>30%) of Long Evans rats, but not in the hypothalamus or pituitary [33] (also see [39,112]). However, both studies found a 30–45% reduction in hippocampal mineralocorticoid receptors [33,106]. Occupancy of the high-affinity mineralocorticoid receptor facilitates long-term potentiation (LTP) in the hippocampus, while occupancy of the low-affinity, more prevalent glucocorticoid receptor by stress-induced CORT elevation decreases synaptic efficacy (Section 4.3) [11]. CR for 3 months by alternate-day feeding causes a 20% reduction of glucocorticoid receptor mRNA in the CA1, without an effect on the mineralocorticoid receptors [46]. This may be a compensatory alteration to protect the hippocampal neurons from glucocorticoid receptor-mediated deleterious effects at the cost of elevated CORT levels.

4.2. Maze learning

CORT elevations are implicated in age-related deficits in spatial memory performance. Reduction of CORT by adrenalectomy of middle-aged adults [38] or by neonatal handling [68] improves performance in the Morris water maze at later ages; neonatal handling down-regulates CORT release by inhibition of the HPA in association with a higher density of glucocorticoid receptor in the hippocampus [68]. The effects of CORT may be due to intracellular CORT levels. Aged mice lacking 11β-hydroxysteroid dehydrogenase, an enzyme which regenerates CORT from circulating 11-dehydroxycorticosterone, had escape latencies in the Morris water maze which were similar to young wild-type mice, and twice as fast as the age-matched wild-type mice [113].

The available data suggest that CR may improve spatial memory performance despite the CORT elevation. Table 1 summarizes the effects of CR on performance in the Morris water maze. For example, in a longitudinal study, CR rats had faster escape latencies than AL rats at ages of 12 and 30 months. At age of 12 months, the CR rats found the hidden platform twice as fast as the AL group, and had a shorter path length from the start site to the platform (Table 1). By 24 months, both groups showed a mild cognitive impairment, which subsequently worsened by the age of 30 months in AL, but not in CR rats [2]. CR also attenuates age-related cognitive deficits in other spatial memory tasks. In a 14-unit T-maze, the aged AL mice ($C3B10RF_1$) made twice as many errors as the young AL, while the old CR mice made only 30% more errors than the young AL [32]. Furthermore, the old AL rats made six times more errors than the age-matched CR rats and the young AL rats in an eight-arm water maze [79].

The effect of age on maze learning in B6 mice was fairly small (10% increase in proximity to the platform location during probe trials [55]; Table 1), which might be due to the lack of age-related increase of CORT in this genotype (Section 4.1) [42]. Moreover, the lack of age-related cognitive decline in F344 rats is surprising, because this strain is particularly susceptible to kidney lesions and does show an age-related increase in CORT (Table 1, Fig. 1) [58]. These divergent findings caution against sweeping conclusions on CORT and learning during aging.

4.3. LTP

LTP of synaptic efficacy in the CA1 region of hippocampus following tetanic stimuli of the Schaffer collaterals

meets Hebb's criteria for molecular mechanism underlying memory and learning—associative, cooperative and specific. Potentiation of synaptic efficacy is also observed after a physiologically patterned, lower-threshold primed-burst stimulation. In contrast, low-frequency stimulation of the Schaffer collaterals can yield long-term depression (LTD). Both LTD and LTP require activation of the NMDA receptor and Ca^{2+} influx.

CORT has a biphasic effect on synaptic efficacy. Occupancy of the high-affinity mineralocorticoid receptors at basal CORT levels is necessary for optimal LTP. However, activation of the lower affinity glucocorticoid receptors shifts the balance away from LTP [11]. The number of synapses that were potentiated following acute stress decreased inversely to the serum CORT [12,99]. Treatment of adrenalectomized rats with aldosterone (mineralocorticoid) enhanced synaptic efficacy, while RU-28362 (specific glucocorticoid receptor agonist) suppressed LTP [78]. Thus, the elevated CORT levels in both CR and in aged AL animals should shift the balance away from LTP.

The age-related impairment of synaptic efficacy was reduced by chronic CR in two studies. The number of potentiations observed after primed-burst stimulation in 24-month-old AL F344 rats was 60% lower than that observed in the 6-month-old rats. In addition, there was a 40% reduction in NMDA-mediated field excitatory post-synaptic potentials in the CA1 region with age. Chronic CR blocked both of these age-related reductions [17,29]. This effect of CR also contrasts the evidence that stress decreases both cognitive performance and LTP [65].

We note two important concerns in respect to the effects of stress and CR on LTP. First, whether or not CR-induced CORT elevation is comparable to that of restraint or psychosocial stress. Restraint stress for 1 h causes a 1.5-fold increase in total CORT levels compared to the acrophase in CR rats [87]. Second, experimental designs may not allow for a fair comparison. In most studies examining the effects of stress on cognition and LTP, the assessment was during stress and/or elevated CORT. However, studies examining the effects of CR on cognition were presumably done at times when plasma CORT was not elevated. During the time of CORT peak in CR animals the functional/biological responses may be very different. It remains to be tested whether these beneficial effects of CR on spatial memory and LTP also occur at the diurnal CORT peak.

The role of stress-mediated CORT elevation on learning and memory may be context-dependent. For example, rats subjected to cold water, a related stressor, in the Morris water maze task learned faster and retained the information longer [88]. In contrast, if rats trained for radial arm maze are placed in an unfamiliar environment, an unrelated stressor, half way through the test session, their recall capability was impaired [13]. Similarly, LTP was impaired in rats exposed to an inescapable low-intensity shock, but not in those that were allowed to escape the stressor after the initial shock [98]. de Kloet et al. conclude that CORT facilitates behavioral adaptation by a complex interaction between glucocorticoid and mineralocorticoid receptors [11]. Activation of the glucocorticoid receptor in an appropriate context promotes memory consolidation, while elevation of CORT by an unrelated or inescapable stressor decreases LTP in hippocampus, and behaviorally, consideration of other alternatives. A possible explanation for this opposing effect of CORT is that the process of synaptic efficacy itself is modulated by prior synaptic history, i.e. an active synapse would require much greater stimuli to induce LTP than a quiescent one [35]. Since both LTP and LTD are dependent on NMDA activation and Ca^{2+} signaling, CORT-mediated elevation in extracellular glutamate levels and intracellular calcium ($[Ca^{2+}]_i$) could non-specifically shift the balance away from LTP [64]. As discussed below, CR increases expression of the 70 kDa heat shock protein (HSP-70) which may improve $[Ca^{2+}]_i$ homeostasis [61], and thus could counteract the negative influence of CORT on LTP. Moreover, CR decreases the expression of glucocorticoid receptor in the hippocampus without altering the mineralocorticoid receptor levels [46]. This differential effect in itself could shift the balance in favor of LTP.

4.4. Neuronal endangerment and neurotoxicity in hippocampus

In humans, chronic elevation of CORT is associated with both cognitive impairment and loss of hippocampal volume (Section 3). The elevated CORT endangers neuronal survival in response to toxic agents possibly by reducing glucose uptake (see Section 5). However, short-term CR seems to protect hippocampal neurons against excitotoxins. CR attenuates kainate-induced damage to the hippocampal CA3 region in proportion to the CR duration [6]. Short-term CR also increased production of brain-derived neurotrophic factor (BDNF) in the hippocampus. Blockade of BDNF by intraventricular injection of anti-BDNF antibodies attenuated CR-mediated protection of hippocampal neurons against kainate [15].

Yet other mechanisms may also contribute to the neuroprotective effects of CR. For example, hyperglycemia increased and hypoglycemia decreased kainate-induced neurotoxicity in the non-pyramidal neurons of the hippocampus [34]. Since CR reduces plasma glucose levels (Fig. 1) [60], decreased glucose metabolism could also be a factor in the neuroprotective effects of CR [44].

The exposure of neurons to agents that endanger survival is increased during aging (e.g. elevated levels of CORT, reactive oxygen species, and certain cytokines), while the cellular defense mechanisms (stress proteins) and production of several neurotrophic factors is decreased (Section 5). Such pathophysiological changes may set the stage for age-related hippocampal atrophy, and possibly neuronal death.

The extent of loss of hippocampal neurons during aging is difficult to evaluate because of opposite results from careful studies. In their classic studies, Landfield et al. [38],

showed extensive pyramidal neuron loss. Of great interest, adrenalectomy of 18-month-old F344 rats and supplementation with extremely low levels of CORT reduced the loss of pyramidal neurons at 27 months. However, many recent studies using stereological methods did not detect neuron loss in hippocampus of healthy humans, monkeys, rats and mice [8,49,82,83,111]. Moreover, age-related cognitive impairments in Long Evans or Wistar rats was not associated with neuron loss in the hippocampus [82,83]. These findings do not negate other reports of hippocampal neuron loss during aging [33,38,68]. One factor in these divergent findings is indicated by the remarkable observation that neonatal handling of Long Evans rats attenuated age-related cognitive impairment and also reduced age-related decline in neuronal density in the hippocampus [68]. Neonatal handling decreases the sensitivity of the HPA axis (Section 4.1) [67,68] and attenuates CORT elevation in response to stress [67]. Moreover, the HPA axis in the offspring is also sensitive to maternal CORT elevation during late gestation. Elevation of CORT in response to short-term starvation during pregnancy decreased expression of both mineralocorticoid and glucocorticoid receptors in the hippocampus of the offspring [48]. Thus, the age-related elevation of CORT, and the associated hippocampal impairment, may be dependent on experiences during development as well as adulthood.

4.5. Neurogenesis

During aging, the rate of neurogenesis in the rat dentate gyrus (DG) is decreased by 50% (5 versus 26 months) [9]. The rate of neurogenesis is also reduced by stress. Since these newly formed neurons do not express either glucocorticoid or mineralocorticoid receptors, McEwen has suggested that attenuation of neurogenesis in DG is possibly due to CORT-mediated elevation of extracellular glutamate [64]. The role of CORT in the age-related decline of neurogenesis in old rats was demonstrated by the increased neurogenesis in rats adrenalectomized at 16 months and examined at 26 months [9]. In light of this strong positive effect of lowered CORT, it is surprising that CR does not attenuate neurogenesis. Lee et al. [45] report that 3 months of CR by alternate-day feeding increased both the number of new neurons generated and the survival rate of these neurons. BDNF, nerve growth factor and neurotrophin-3 are robustly expressed in the adult hippocampus [57], and possibly contribute to the production and survival of the new neurons. Increased production of both BDNF and glia-derived neurotrophic factor in the hippocampus has been implicated in increased survival and generation of new neurons [117]. Thus, the observed increase in hippocampal BDNF production by CR may enhance the survival of newly generated neurons [45].

A recent report indicates that newly formed neurons in the DG are incorporated into memory circuits [97]. Since adrenalectomy increases both neurogenesis as well as cell death in the DG [9], and since enriched environment increases neurogenesis [117], it is possible that the rate of neurogenesis is dependent on cognitive demand. It remains to be examined what the "demand-related" signals are, and if these signals are differentially modulated by CORT during aging and in CR.

5. How does CR attenuate age-related hippocampal impairment?

The brain has a very high demand for glucose and is particularly vulnerable to alterations in energy supply. Regional glucose utilization in the hippocampus, prefrontal cortex, and medial septum was correlated with escape latency in the Morris water maze [24]. Aging decreases regional cerebral blood flow in rat [25,100], which may contribute to the age-related cognitive impairment. The reduction in cerebral blood flow in the aged AL rats is attributable to the combination of blood vessel constriction and a substantial loss of brain microvasculature [52]. CR blocks the age-related reduction in blood flow by maintaining the blood vessels in a dilated state and decreasing the loss of microvasculature. The subsequent reduction in nutrient supply could decrease the Na^+/K^+ ATPase activity and increase the cytoplasmic Na^+ ($[Na^+]_i$) in the astrocytes. Increased $[Na^+]_i$ was also observed after an increase in neuronal activity, and possibly signals for increased energy requirement by neurons [53]. Recovery from $[Na^+]_i$ is dependent on oxidative phosphorylation. Thus, the reduction in glucose availability in the aged brains may increase the time for recovery of optimal neuronal activity (see below) [24,84]. Elevated $[Na^+]_i$ also reduces glutamate and/or K^+ uptake by astrocytes. The resulting condition of elevated $[K^+]_o$ and glutamate along with increased $[Na^+]_i$ overlaps with characteristics of ischemia [84]. Elevation of intracellular Na^+ in astrocyte also increases the influx of water. The consequent swelling can increase the intracerebral pressure and further decrease vascular perfusion [41]. Thus, the reduced cerebral blood flow with age can have various implications for neuronal activity and hippocampal function.

CORT attenuates glucose uptake by both hippocampal neurons and astrocytes [30,107]. This reduction in glucose uptake increases susceptibility of hippocampal neurons and astrocytes, in vitro, to damage by hypoxia and hypoglycemia [103,104]. Treatment of hippocampal astrocytes with CORT for 24 h also reduces glycogen levels [104]. This is pertinent to energy metabolism in the aged brain since astrocytes play an important role in transport of glucose from the capillaries and supplying neurons with lactate. Uptake of glucose from the capillaries by the astrocyte is dependent on regional metabolic activity, and co-transport of glutamate and Na^+ into the astrocytes [53]. Expulsion of Na^+ from astrocytes by Na^+/K^+ ATPase promotes glycolysis and glucose transport from the capillaries. Reduction in glucose availability due to CORT may reduce uptake of extracellular glutamate and increase the threshold for

LTP (see Section 4.3). These conditions are also likely to deplete glycogen following increased neuronal activity and allow for accumulation of glutamate in the extracellular space during long-term CORT exposure. The consequent elevation of $[Ca^{2+}]_i$ in neurons for extended periods can compromise mitochondria permeability transition pore integrity, and affect neuronal survival by decreasing ATP production and increasing reactive oxygen species (ROS) generation [77]. CR attenuated the age-related increase in mitochondrial ROS production [23], suggesting that glutamate and $[Ca^{2+}]_i$-mediated mechanisms are attenuated in the old CR brain compared to the age-matched AL rats.

CR may protect the brain from some of these intra-cellular effects of the CORT-induced increase in extracellular glutamate by induction of stress-related proteins, e.g. young rats on short-term CR had increased expression of HSP-70 in the striatum [118]. Long-term CR induced several stress proteins in the hypothalamus which were normally at low levels in the AL rats [4]. Food deprivation of the AL rats for 48 h did induce HSPs in the hypothalamus, although, the expression was much lower than in CR [3]. Similarly, chronic CR attenuated the age-related loss of HSP-70 induction in hepatocytes in response to heat shock [28]. In a novel recent study, serum from CR rats, but not AL rats, induced stress responsive genes, including HSP-70 and glucose regulated protein 78 (GRP78), in hepatocytes [10]. This suggests that the endocrine changes associated with CR may be responsible for the expression of stress-related proteins. HSP-70 can confer neuronal protection by several different mechanisms including better regulation of $[Ca^{2+}]_i$, attenuation of ROS-mediated damage, and inhibition of necrosis and apoptosis [61,96,115]. Thus, CR may be adaptive to protect the brain against future stress, including CORT and toxins.

CR also increases expression of neurotrophic factors in the brain. As discussed above (Sections 4.4 and 4.5), elevated BDNF in CR promotes survival of hippocampal neurons. Gene array analysis of age- and CR-related changes in mRNA showed that 9% of the genes upregulated in old CR mice are neurotrophic factors, growth factors, and proteins involved in neuronal plasticity [81]. Most of these genes are not affected by the normal aging process. Thus, CR activates a distinct set of genes that promote neuronal survival and plasticity.

6. Role of astrocytes

The age-related increase in hippocampal hypertrophic astrocytes was positively correlated with CORT levels in middle-aged rats [40]. GFAP expression, which is a correlate of astrocytic activation, shows strong generalized increases with age in mice, rats, and humans [26,43,73]. This increase in GFAP expression and astrocytic fibrosis was associated with the rate of transcription [37] in sub-population of astrocytes [116]. In vitro, astrocytes expressing GFAP are inhibitory to neurites, whereas those deficient for GFAP are more permissive to neurite outgrowth [70]. Furthermore decreasing functional GFAP mRNA by either anti-sense GFAP mRNA [47] or by estrogen treatment [86] increased neurite outgrowth in an in vitro wounding model. This suggests that hypertrophic astrocytes may attenuate neurite outgrowth in adult animals. Atrophy of dendritic spines in CA3 region due to short-term stress or glucocorticoids can be reversed upon removal of the stressor or glucocorticoids [64]. If similar atrophy occurs during aging, then the regrowth of dendrites could be attenuated by the hypertrophic astrocytes in the aged animals. Since CR attenuates the age-related increase of GFAP expression and hypertrophic astrocytes in the rat hippocampus [71], the neuronal regeneration process may be facilitated by CR through effects on astrocytes.

The role of CORT in GFAP expression is further complicated by the in vitro observation that CORT increases GFAP expression in monotypic astrocyte cultures and attenuates GFAP expression in neuron–glia co-cultures [85]. In vivo, short-term CORT treatment decreases GFAP levels in hippocampus and cortex [74,75]. Since GFAP expression in the hippocampus is increased with age but decreased with chronic CR, we hypothesize that neuronal dysfunction during aging relieves the inhibitory effect of CORT on GFAP expression.

7. Role of microglia

Several lines of evidence suggest that neuro-inflammatory processes promote neurodegeneration (e.g. [1]). With age, there was an increase in microglial activation in several brain regions including the hippocampus [71]. Possible mechanisms could include microglial reaction to glyco-oxidized proteins. Non-enzymatic reactions of glucose and other reducing sugars with proteins slowly proceeds through Amadori rearrangement to form Maillard products that are also referred to as advanced glycation end-products (AGEPs) [19]. AGEPs can activate NF-κB in cells of monocytic lineage [114] and induce transcription of pro-inflammatory cytokines which accentuate the inflammatory reaction [62]. Chronic CR decreases plasma glucose and attenuates AGEPs [19,60]. Thus, CR may attenuate the age-related microglial activation by modulation of several pathways. First, CR decreases blood glucose levels by 15% across the life-span which would decrease formation of AGEPs. Second, the anti-inflammatory effects of CORT are mediated by a direct interaction of the glucocorticoid receptor with the transactivation domain of NF-κB [66]. Furthermore, both of these transcription factors are redox sensitive. Oxidation of NF-κB modifies its interactions with specific DNA binding sites, while oxidation of the glucocorticoid receptor blocks its translocation to the nucleus [76]. With age, there is an exponential increase in oxidative stress markers which is attenuated by CR [16,101]. Thus, we hypothesize that CORT elevation in the aging AL brain preferentially

mediates the non-transcriptional effects, while in CR brain all the functions of glucocorticoid receptors are maintained.

The anti-inflammatory effects of CORT are well recognized, yet CR animals are more effective at pathogen clearance than AL animals. Nelson and coworkers have reported that carrageenin-induced edema of the foot-pad, a model of inflammation, was cleared faster in CR mice compared to the AL group [36]. Furthermore, alveolar macrophages isolated from CR mice are more efficient at reducing bacterial viability than macrophages from AL mice [14]. So, how does CR improve pathogen clearance, despite the anti-inflammatory effects of CORT on cells of monocytic lineage. It is possible that CORT activates pathway(s) near the infection site that are not inhibited by CORT. For example, CORT can induce migration inhibitory factor (MIF) in macrophages and T-lymphocytes, and MIF-induced pro-inflammatory cytokines are not inhibited by CORT [7]. Thus, the enhanced CORT response in CR animals may attenuate the inflammatory responses. This would protect the by-stander cells from the ROS produced by microglia/macrophage. Thus, CR may effectively defend the brain against infections/injury without causing a wide-spread damage to the surrounding neurons and by attenuating cytokine-mediated pro-inflammatory responses at distant sites.

8. Conclusion

Elevation of CORT during acute stress may be essential for immediate survival, but chronic elevation of CORT has multiple, slowly evolving deleterious effects. The age-related increase in CORT is associated with hippocampal atrophy, cognitive impairment, decreased LTP, and reduced neurogenesis. However, these effects are not observed in CR rodents despite the diurnal CORT elevation. CR improves the performance of aged rats at spatial memory tasks, protects the neurons from excitotoxins, facilitates LTP, and increases survival of the newly generated neurons. The neuroprotective effect of CR is most likely due to a combination of several different mechanisms. We have presented evidence supporting some of these mechanisms: (1) attenuation of age-related decline in cerebral microvasculature, (2) attenuation of oxidative damage and ROS generation, (3) promotion of neuronal survival by increasing neurotrophic factors and stress proteins, and (4) attenuation of glial activation. We suggest that CR protects the hippocampus by evoking several beneficial mechanisms that outweigh the deleterious effects of CORT. Furthermore, CORT itself maybe involved in activating some of these neuroprotective effects by modulating glial functions.

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