Longevity Effect of Chromium Picolinate – ‘Rejuvenation’ of Hypothalamic Function?

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Abstract — The first rodent longevity study with the insulin-sensitizing nutrient chromium picolinate has reported a dramatic increase in both median and maximal lifespan. Although the observed moderate reductions in serum glucose imply a decreased rate of tissue glycation reactions, it is unlikely that this alone can account for the substantial impact on lifespan; an effect on central neurohormonal regulation can reasonably be suspected. Recent studies highlight the physiological role of insulin as a modulator of brain function. I postulate that aging is associated with a reduction of effective insulin activity in the brain, and this contributes to age-related alterations of hypothalamic functions that result in an ‘older’ neurohormonal milieu; consistent with this possibility, diabetes leads to changes of hypothalamic regulation analogous to those seen in normal aging. Conversely, promoting brain insulin activity with chromium picolinate may help to maintain the hypothalamus in a more functionally youthful state; increased hypothalamic catecholamine activity, sensitization of insulin-responsive central mechanisms regulating appetite and thermogenesis, and perhaps trophic effects on brain neurons may play a role in this regard. Since both the pineal gland and thymus are dependent on insulin activity, chromium may aid their function as well. Thus, the longevity effect of chromium picolinate may depend primarily on delay or reversal of various age-related changes in the body’s hormonal and neural milieu. A more general strategy of hypothalamic ‘rejuvenation’ is proposed for extending healthful lifespan.

Longevity effect of chromium picolinate

Recently, Evans and Meyer have reported a remarkable prolongation of both median and maximal lifespan in Long-Evans rats receiving food supplemented with the insulin-sensitizing nutrient chromium picolinate (1,2). Weanling rats were randomized to receive chow supplemented with 1 ppm chromium as either chromium picolinate, chromium dinicotinate, or chromic chloride. To assess glucose control, blood was drawn in mid-afternoon at 200 and 1000 days of age for assay of plasma glucose, and at 210 and 1010 days of age for assay of glycated hemoglobin. At 1100 days, plasma insulin was measured in surviving rats. The rats were fed ad libitum and allowed to live out their full lifespan.

The rats receiving chromium dinicotinate or chromic chloride did not differ significantly with respect to the measured clinical parameters or lifespan. Between 200 and 1000 days of age, glucose rose modestly, with a more substantial (~58%) increase in glycated hemoglobin, indicative of the expected age-related decline of insulin sensitivity and glucose tolerance. In contrast, there was no age-related rise in ei-
ther glucose or glycated hemoglobin in the chromium picolinate group, and already at 200 days, glucose was about 14% lower than in the other groups. At 1100 days, plasma insulin was nearly 50% lower in the chromium picolinate group as compared to the other two groups. These findings suggest that the chromium picolinate exerted a strong insulin-sensitizing effect, preventing the normal age-related decline of glucose tolerance.

The chromium dinicotinate and chromic chloride groups each had a median lifespan of 35 months and a maximum lifespan of 38 months — a good survival curve for rats fed ad libitum. Strikingly, the chromium picolinate group achieved a median lifespan of 44 months, and a 48-month maximum survival. Every rat in this group outlived every rat in the other two groups by over 2 months.

Although the chromium picolinate-fed rats weighed about 40 g less at death than the other groups, and appeared to have substantially less visceral fat on autopsy, this difference was by no means comparable to the marked disparity in size and weight seen in caloric restriction studies. Thus, although food consumption unfortunately was not measured in this study, it is unlikely that reduced food intake could account for the marked prolongation of lifespan in the chromium picolinate-fed rats.

This study also might be criticized because of its small size — only 10 rats per group. However, in the light of the exceptional lifespan achieved by the rats fed chromium picolinate — comparable to that achieved in caloric restriction studies or the celebrated deprenyl study of Knoll (3) — it is unlikely that these results merely represent a statistical fluke. Indeed, Knoll states (without citation) that 42 months is the maximum achievable lifespan of unmedicated ad-lib fed rats (3).

A chronic toxicity test with chromic picolinate run concurrently, provides some confirmatory data. In rats receiving 0 or 0.25 ppm dietary chromium, 9 of 20 were dead by 30 months of age; in contrast, only 1 of the 30 rats receiving 0.5 ppm or more (up to 5 ppm) had died by this age (4).

Of related interest are chronic toxicity studies in rats with orally administered sodium chromate (a well-absorbed but potentially toxic hexavalent chromium salt), reported by Byerrum in the 1930s and more recently cited by Mertz (5). When provided in the drinking water in a range of concentrations up to 7.7 ppm, the chromium not only did not exert discernible toxic effects, but actually resulted in consistent increases in lifespan. This provocative observation received little attention, perhaps because the nutritional role of chromium would not be established for another 25 years.

On the presumption that chromium picolinate can indeed increase both median and maximal lifespan in Long-Evans rats (other studies are in progress in an effort to confirm this effect in rats and mice), what mechanisms could account for this effect? Evans, noting the substantial reductions of glucose and glycated hemoglobin in aging rats receiving chromium picolinate, has suggested that a lessened frequency of spontaneous glycation and glucose-catalyzed free radical reactions may explain the life-prolonging activity (1,2), this 'glycation theory of aging' (6,7) has also been evoked as a possible explanation for the longevity effect of caloric restriction (8) — which also produces a moderate depression in serum glucose.

While elevated glucose levels clearly contribute to the increased collagen cross-linking and loss of tissue elasticity observed in diabetics, and while cross-linking by 'advanced glycation end products' (AGEs) undoubtedly plays a role in the comparable loss of elasticity observed during aging, it is questionable whether glucose levels per se are a major pacesetter for aging. The lifespans of mammals with roughly comparable serum glucose levels vary by over 20-fold. If the modest reduction of blood sugar achieved with caloric restriction (~10%) was responsible for the substantial observed increases in lifespan, one would expect that, conversely, diabetics would be fortunate to survive more than a few years. In fact, young diabetics, who often display a degree of collagen cross-linking typical of that seen in centenarians (9), can nevertheless survive for several decades with proper clinical management. The age-related increase of collagen cross-linking and AGEs may be more reflective of decreased efficiency of scavenging mechanisms for AGEs, than of modest age-related increases in serum glucose. It is also notable that, despite the availability of a tolerable drug — aminoguanidine — that reduces AGE formation, no reports have appeared demonstrating that this agent lengthens lifespan. Thus, while modest reduction in ambient glucose levels may mitigate the severity of certain specific changes associated with aging, it is unlikely that they can account for the full range of benefits and the substantial life prolongation achievable with caloric restriction. By analogy, if the life-extending action of chromium picolinate is a substantial and confirmable effect, it appears unlikely that reduced serum glucose is solely responsible for mediating this benefit.

A very reasonable alternative possibility is that the profoundest longevity benefits of both caloric restriction and chromium picolinate are mediated by alter-
Hypothalamic regulation of aging

Gerontologists have long speculated that centrally-directed alterations in hormone production and autonomic neural activity play a pace-setting role in the aging process. While it is undoubtedly true that most organs and tissues have a ‘built-in’ program of obsolescence, and would gradually lose functional capacity even if a ‘youthful’ hormonal milieu were maintained indefinitely (in analogy to the Hayflick limit in individual cells), it nevertheless is likely that age-related alterations in the neurohypothalamic milieu do indeed contribute to the aging of tissues, and moreover have an acute adverse effect on physiological function. Since the brain is the ultimate controller of the body’s hormonal environment, the brain is often posited to be the chief pacemaker of aging. The ‘central-direction’ theory of aging is supported by studies demonstrating life extension with the drug deprenyl (3,26,27) – the monoamine oxidase-inhibitory action of this drug is specific to monoamine oxidase B, found primarily in the brain.

This view inevitably focuses attention on the hypothalamus, which regulates production of anterior pituitary hormones by means of various inhibitory or stimulatory peptides (and dopamine) released into the portal vessels that supply the anterior pituitary (28). Moreover, the hypothalamus plays an important role in modulating activity of the autonomic nervous system. Since the pineal gland, thymus, and pancreas receive functionally significant autonomic innervation (29-32), the hypothalamus influences hormone production in these glands as well; the thymus is also dependent on hormones (growth hormone, thyroxine) regulated by the hypothalamus (33).

It follows that age-related functional alterations in the hypothalamus can be expected to have far-reaching consequences for the body’s hormonal and neural milieu. These alterations are in fact profound, and gerontologists including Dilman, Everitt, and Meites have postulated that they play a crucial role in the aging process (24,34-40). In the rat, pituitary production of growth hormone and TSH fall with age, whereas prolactin and ACTH production increase; a loss of the mid-cycle LH surge results in ovulatory failure (37,39,41-46). These changes are largely attributable to altered production of the hypothalamic releasing/inhibiting factors (37). Dilman characterizes the fundamental alteration of hypothalamic function as an age-related reduction of feedback sensitivity to hormones (24,34-36), this formulation is not correct in every detail (feedback sensitivity to thyroid hormones appears to rise with age (24)), but is broadly consistent with considerable evidence.

With respect to steroid and thyroid hormones, the age-related changes in hypothalamic feedback sensitivity are of the most fundamental importance. While age-related changes in the responsiveness of the pituitary and peripheral endocrine organs do occur, these changes would have little impact on hormone levels if hypothalamic feedback set-points remained stable. By analogy, even an aging inefficient heater may be able to maintain a comfortable house temperature if the thermostat functions properly. An aging hypothalamus is analogous to a malfunctioning thermostat.

The neurochemical basis for the age-related alterations of hypothalamic function is obviously quite complex, but particular attention has been devoted to hypothalamic monoaminergic neurons (35,38,39). The hypothalamus is richly supplied with monoaminergic synapses, producing norepinephrine, dopamine, serotonin, and, to a more limited extent, epinephrine. These monoamine neurotransmitters play an important physiological role in regulating production of the hypothalamic releasing/inhibiting factors, as demonstrated by the many studies in which hypothalamic or pituitary hormone production is modulated by drugs that either stimulate, mimic, or inhibit monoaminergic function (38,39).

It is thus most intriguing that hypothalamic catecholamine levels and/or turnover have been reported
to fall precipitously with age. Riegle and colleagues (47) measured total hypothalamic catecholamine content in young (4 months) and old (24–26 months) rats, and found that both norepinephrine and dopamine were reduced by over 50% in the old rats. In rhesus monkeys, a substantial age-related reduction of hypothalamic dopamine was observed, while norepinephrine levels did not decrease. However, total hypothalamic catecholamine turnover (as indicated by L-dopa accumulation following aromatic amino acid decarboxylase inhibition) fell by 66%; since norepinephrine represented nearly 80% of total catecholamine content, this data implied a substantial reduction in norepinephrine turnover (48). Human studies are more difficult to interpret, since catecholamines are labile following death, and their levels thus vary as a function of the interval between death and autopsy; nevertheless, there is general agreement that both norepinephrine and dopamine fall with age in the human hypothalamus (49,50). In both norepinephrine and dopamine fall with age in the human hypothalamus (49,50). In contrast, serotonin levels show little age-related variation. It is not clear why there is a selective loss of catecholamine activity, but, by analogy to dopaminergic neurons in the substantia nigra (51), there may be accelerated cell death owing to free radicals generated by the interaction of catecholamines with monoamine oxidase (52,53). In humans, this reduction in hypothalamic catecholamines is probably exacerbated by an age-related rise in monoamine oxidase B activity, documented in many regions of the brain, including the hypothalamus (54–56).

Another factor contributing to reduced catecholaminergic activity is an age-dependent loss of beta adrenergic and dopamine receptors, which in rodents has been documented in the pineal gland, various brain regions, as well as several peripheral tissues (29,57,58), this deficit is accompanied by a marked delay in the ability to up-regulate receptor expression in response to diminished catecholamine release. It is not yet clear whether this phenomenon is prominent in the aging hypothalamus.

To evaluate the likely functional significance of the age-related loss of hypothalamic catecholamine activity, consider the following: norepinephrine and/or TSH, and gonadotropins, while suppressing release of prolactin, CRH, and ACTH (28). Aging in the rat has the opposite effect on production of each of these hormones.

Meites (38,39), as well as Dilman (24), draw particular attention to the decline in hypothalamic catecholamine activity as a crucial factor in the aging process and suggest that preservation of this activity may be a variable strategy for retarding aging and postponing age-related disease. In support of this view, Meites (39) cites several studies in which average rodent lifespan has been extended or age-related disease prevented by treatment with drugs that promote catecholamine activity (lergotrile mesylate, deprenyl, ibopamine, ephedrine) (3,4,59,60). Clinically, administration of deprenyl has been shown to prolong survival in L-dopa-treated Parkinsonian patients (61). While Knoll emphasizes deprenyl's impact on the striatal dopaminergic system, Meites suggests that the reported life-extending action of this drug is mediated by preservation or enhancement of hypothalamic catecholamine activity (38).

Interaction with the thymus and pineal gland

As is well known, the pineal gland and the thymus atrophy with age, and these glands have also been postulated to act as pacesetters for aging (33,62–64). The pineal gland is of particular interest, since its chief secretory product, melatonin, appears to exert its main effects on the hypothalamus (65). This makes good sense homeostatically, since the pineal's physiological function is to modify hormonal activity appropriately in line with day/night cycles and the season (determined by daylight duration). Since nocturnal melatonin secretion drops substantially with age (63,66), the impact of pineal replacement has been studied. Appropriately-timed administration of melatonin or pineal peptide extracts, as well as the transplantation of youthful pineals to aging animals, have been reported to increase average lifespan in rodents (24,62,67). This may represent another instance in which hypothalamic ‘rejuvenation’ results in life extension. Dilman and colleagues report that injections of a pineal polypeptide extract (Epitalamin) reverse the age-related decrease in hormonal feedback sensitivity of the hypothalamus (24); this suggests a beneficial effect on hypothalamic catecholamine activity, although I am unaware of any direct evidence in this regard.

The pineal may thus be important for ‘youthful’ hypothalamic function, but the converse may also be true. An age-related decrease in sympathetic input to the pineal (68) leads to reduced pineal function and may contribute to pineal atrophy; the hypothalamus regulates this input (30), as it does many other sympathetic functions.

The thymus and hypothalamus/pituitary also show an intriguing mutual dependence. Certain hypothalamic lesions, as well as hypophysectomy or congenital hypopituitarism (in dwarf mice) lead to progressive thymic involution and impaired cellular immu-
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nity; injections of growth hormone and thyroxine prevent this thymic atrophy (33). Curiously, dwarf mice experience accelerated aging with hair loss, greying, weakness, and death by 5 months of age; this also is prevented by joint administration of growth hormone and thyroxine.

Conversely, the thymus plays a role in maintaining pituitary function (33). Neonatally thymectomized mice, even if raised in a pathogen-free environment, experience a severe growth failure associated with degeneration of the pituitary acidophilic cells which manufacture growth hormone and prolactin, as well as a reduction in thyroid activity and excessive production of luteinizing hormone. Another effect of thymectomy is an acceleration of the age-related loss of beta-adrenoreceptor density throughout the body (33,69); this potentially could impair pineal function and exacerbate the loss of hypothalamic catecholamine activity. In old animals receiving thymus grafts, T3 levels and beta-adrenoreceptor density increase, while hyperinsulinemia is corrected (33).

Cardarelli (64) has recently summarized evidence demonstrating an interdependence of the thymus and pineal gland—a thesis first evolved in the early 20th century. Pinealectomy accelerates thymic involution, while injection of pineal extracts leads to thymus hyperplasia; pineal extracts as well as melatonin have been reported to aid cellular immune function and retard cancer development. Conversely, thymectomy impairs pineal structure and function.

The hypothalamus, pineal, and thymus can thus be viewed as a functionally-linked triad, each component of which experiences a profound age-linked functional derangement that contributes to the functional decline of the other components. Thus, a truly effective strategy for maintaining youthful hypothalamic function and a youthful hormonal milieu, must include measures which retard age-related pineal and thymic atrophy (or which compensate for loss of their activity by hormonal replacement).

Insulin as a modulator of brain function

How does any of this related to chromium picolinate? Within the last decade, research has begun to clarify the significant role of insulin as a modulator of brain function (70). Until recently, this avenue of research was neglected, owing to the fact that insulin does not influence neuronal glucose metabolism, and to the misimpression that the blood-brain barrier excludes insulin. However, it is now known that insulin receptors are found on neurons throughout the brain, with particularly dense concentrations in the hypothalamus and ophthalmic bulb, and on catecholaminergic synapses (70–72). These receptors, though smaller in size than the systemic receptor (apparently owing to altered post-translational processing), express typical tyrosine kinase activity when activated by insulin binding (72). Furthermore, it is now known that serum insulin can pass through the blood-brain barrier in a process known as 'retroendocytosis' (70,73,74), which apparently is a general property of capillary endothelia (75,76). Insulin binding to the insulin receptor on the luminal capillary surface is internalized, and the internalized insulin/receptor complex migrates to the anti-luminal surface, where the insulin can be released into the interstitial space.

The physiological role of brain insulin is still largely obscure, but recent studies have begun to define it. In cultures of fetal chick neurons from the brain and sympathetic ganglia, as well as in human neuroblastoma cells, physiological concentrations of insulin promote survival and growth, enhance protein synthesis, and have a specific stimulatory effect on tubulin synthesis and neurite formation (77–81). These findings dovetail well with the discovery that neuronal insulin receptors are most densely expressed in amounts that do not provoke hypoglycemia, feeding is suppressed (70,83–88). This effect is likely to be of physiological significance, since intrahypothalamic injection of insulin antibodies triggers feeding (89). In addition, brain insulin can promote thermogenesis via action of the sympathetic nervous system (90,91), this is the basis of the facultative thermogenic response to carbohydrate ingestion. Also, the fact that serum free T3 levels rise with overfeeding, and fall with underfeeding, (92–94), suggests an alteration of the hypothalamic setpoint for thyroxine that may well be mediated, at least in part, by shifts in brain insulin activity. The fact that hypothalamic TRH content drops by 50% in streptozotocin-diabetic rats, accompanied by reduced thyroid function, is consistent with this formulation (95). T3 levels are also low in clinical diabetes, and rise when insulin therapy is instituted (96).
These findings suggest that insulin in the brain mediates a feedback mechanism whereby ample carbohydrate availability suppresses feeding while stimulating metabolism, thus moderating caloric balance and preventing excessive weight gain. This view is consistent with previous suggestions that insulin resistance is a risk factor for development of obesity. A variety of mechanisms have been suggested to mediate insulin's central satiety effect: activation of insulin-sensitive glucoreceptors in the ventromedial hypothalamus (the 'satiety center' (99–101)), suppression of neuropeptide Y release in the paraventricular nucleus (102–104) (where this peptide stimulates feeding and decreases thermogenesis), and sensitization to the central satiety effects of cholecystokinin (105).

The presence of insulin receptors on catecholaminergic synapses has motivated research into the impact of insulin on brain catecholamine function. In rats, systemic or intraventricular administration of insulin increases norepinephrine turnover in the hypothalamus, medulla, and forebrain, as well as dopamine turnover in the striatum (106–108). (Effects on insulin in individual hypothalamic nuclei are more complex (109, 110); for example, in the paraventricular nucleus, where norepinephrine acts to stimulate feeding, insulin has been reported to reduce norepinephrine turnover). In cultures of dissociated brain neurons or synaptosomes, physiological levels of insulin inhibit synaptic reuptake of norepinephrine (72,111) - an effect analogous to that of tricyclic antidepressants. Conversely, the effects of streptozotocin diabetes on central catecholamine metabolism have been studied. While findings have been inconsistent regarding the effects of diabetes on brain catecholamine levels, the data is reasonably consistent in demonstrating reduced turnover of norepinephrine and dopamine in the hypothalamus, striatum, and forebrain (107,112–114). Chu et al (115) did not measure turnover, but the substantial reductions of hypothalamic norepinephrine and dopamine levels (42% and 79%, respectively) in these diabetic rats would presumably be associated with reduced catecholamine activity. Thus, while the effects of insulin are somewhat variable dependent on brain region, the general impression is that insulin promotes catecholamine turnover and activity in the hypothalamus and elsewhere. This effect is likely to be of physiological significance, since diabetes impairs catecholamine turnover.

Hypothesis: chromium picolinate potentiates insulin's effects on hypothalamic function

In light of these considerations, I offer the following hypothesis regarding effects of chromium picolinate on hypothalamic function and the aging process:

1. Effective insulin activity in the brain declines in the aging process, concurrent with the systemic decrease of insulin sensitivity and glucose tolerance, and this reduced central insulin activity contributes to certain age-related alterations of hypothalamic and brain function that play a crucial role in the aging process. These age-related alterations may include reduced hypothalamic catecholamine activity, impaired function of insulin-dependent glucoreceptors, and increased neuropeptide Y activity. The reduction in the thermic response to carbohydrate (116,117) and the gain in body fat typically seen with aging could reflect, at least in part, this decreased brain responsiveness to insulin.

2. Conversely, promoting greater central insulin activity with chromium picolinate, and possibly other insulin-sensitizing modalities, may maintain the hypothalamus in a more 'youthful' functional state and thereby retard various aspects of the aging process. Sensitization of glucoreceptors and neuropeptide Y suppression should promote a more negative caloric balance and a leaner physique, while enhanced monoaminergic function may lead to a more 'youthful' hormonal milieu. If insulin's neurotrophic effects are significant in the mature brain, a deceleration of neuron or synapse loss may also play a role.

3. Improved function and delayed atrophy of the pineal gland and/or thymus may conceivably contribute to chromium picolinate's longevity effect. If so, this could reflect a direct effect of improved insulin action on these glands, or perhaps result from preservation of youthful hypothalamic function. Improved pineal and thymic function, in turn, should help to keep the hypothalamus and pituitary functionally youthful.

If this hypothesis is correct, one would expect that streptozotocin diabetes would lead to alterations of hypothalamic/pituitary hormone production compara-
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ble to those seen during normal aging. In fact, this is the case. In streptozotocin-diabetic rats, production of growth hormone, TRH, TSH, and pituitary gonadotropin declines (95,118-120). I am unaware of data regarding cortisol or prolactin in diabetic rats; however, clinically, dexamethasone suppressibility of cortisol production is diminished in diabetics (121), and hyperprolactinemia is commonly observed in male diabetics (122). In diabetic animals, an accelerated degeneration of neurons in key hypothalamic nuclei is observed (123,124). A reduction in estrogen receptor expression, noted in the hypothalamus and other brain regions (125-127), may contribute to reduced feedback sensitivity to estrogen and the absence of a mid-cycle GnRH surge responsible for ovulatory failure in diabetic animals (128). These findings are consistent with the thesis that central insulin deficiency results in impaired hypothalamic monoamine activity and an 'older' pattern of hormonal regulation. (However, it is also conceivable that a neurotoxic effect of hyperglycemia is responsible for some of these findings.)

Insulin might also influence the hypothalamus indirectly, via effects on the thymus or pineal gland. Streptozotocin diabetes decreases the production of thymulin by the thymus and of melatonin by the pineal gland (129,130), in humans, short-term fasting (which of course lowers insulin activity) reduces the nocturnal surge in melatonin production (131). Impaired thymus function may contribute to the reduced immune competence associated with clinical diabetes. The role of insulin in supporting the function of these glands may be direct or, alternatively, may be mediated by an effect on hypothalamic function. As noted earlier, both the thymus and the pineal influence hypothalamic/pituitary activity; thus, a functionally 'youthful' thymus and pineal gland may be necessary for 'youthful' hypothalamic function (and moreover are crucial for maintaining effective cellular immunity).

There has long been a clinical impression that diabetes results in accelerated aging (132). Although loss of tissue elasticity owing to glycation-induced crosslinking undoubtedly plays a role in this, the effects of diabetes on central hormone regulation and autonomic activity also merit attention in this regard.

The physiological role of chromium is to support the insulin sensitivity of tissues. Clinical and animal studies with chromium picolinate suggest that this nutrient does indeed enhance tissue insulin sensitivity (1,134-136), and attempts to confirm this clinically with the minimal-model technique are now underway. In cultured rat myoblasts, preincubation with chromium picolinate results in a substantial enhancement of insulin binding and internalization, and of insulin-stimulated glucose and leucine transport (137). The possibility that chromium picolinate can promote brain insulin activity, is suggested by demonstrations that this nutrient tends to reduce body fat content in pigs, rats, and humans (134,138-141). Since the peripheral effects of insulin would tend to promote the synthesis and retention of body fat, and since the increased insulin secretion of rats with lesions of the ventromedial hypothalamus tends to promote weight gain, it is logical to conclude that chromium picolinate's tendency to reduce body fat is mediated by a sensitization to insulin's actions as a central satiety signal (101). This concept is readily extended to yield the hypothesis that chromium picolinate has a general sensitizing effect on brain insulin activity, just as it presumably does on peripheral tissues. Such an effect might be mediated by a direct action on insulin-responsive neurons, or perhaps by an acceleration to the retroendocytosis mechanism of brain insulin uptake (in analogy to the increased insulin internalization reported in chromium picolinate-treated myoblasts) (137). Animal studies should examine the impact of supplemental chromium picolinate on blood-brain barrier transport of insulin and on physiological response to intracerebroventricular insulin.

The effects of chromium picolinate on production of hypothalamic/pituitary hormone production in aging animals or humans have yet to be studied. However, Mowat and colleagues have reported that dietary supplementation with a chromium 'chelate' reduces cortisol production and reduces infectious morbidity in travel-stressed calves (142). This is consistent with improved suppressibility of CRH owing to increased hypothalamic catecholaminergic activity. In addition, we have received anecdotal reports of increased TSH production in thyrxine-treated thyroidectomized subjects during chromium picolinate supplementation — presumably indicative of reduced hypothalamic sensitivity to T3 feedback. (An increase in feedback sensitivity to T3 may be responsible for the age-related reduction in serum T3) (143).

Analogous actions of phenformin

It is instructive to draw an analogy to Dilman's work with the insulin-sensitizing drug phenformin (24,25). In addition to the expected beneficial effects on insulin sensitivity, cardiovascular risk factors, and atherogenesis, phenformin has been found to extend average lifespan in rats and mice, promote weight loss, aid dexamethasone suppressibility of cortisol production, decrease hypothalamic sensitivity to
T₄ inhibition, and stimulate cellular immunity. These effects are consistent with a more ‘youthful’ hypothalamic function, and Dilman proposes that phenformin enhances hypothalamic monoamine activity by inhibiting monoamine oxidase. As an alternative hypothesis, I suggest that phenformin does indeed promote hypothalamic monoamine activity, but that it accomplishes this by sensitizing the brain to insulin.

Dilman also reports (24) that phenformin enhances production of the fascinating adrenal hormone DHEA; a similar effect was reported for the insulin-sensitizing drug nitrendipine (144). In preliminary studies, Evans has observed increased serum levels of DHEA-sulfate during chromium picolinate supplementation (145). Although it is conceivable that correction of hyperinsulinemia (146) or a direct effect of these agents on adrenal function mediates this enhancement of DHEA production, an effect on hypothalamic function also should be considered. The pituitary contains a poorly-characterized peptide, known as cortical androgen stimulating hormone (CASH), which selectively stimulates DHEA production (147). A physiological role for this peptide is suggested by the fact that ACTH does not restore DHEA production to normal in hypophysectomized chimps. Whether reduced CASH production plays any role in the steady age-related drop in DHEA production (148), is unknown. In any case, DHEA is now believed to play a physiological role in promoting cellular immune function and in maintaining bone density in postmenopausal women (149–155); if chromium picolinate does indeed aid DHEA production, this would represent an additional avenue by which this nutrient promotes a more youthful hormonal milieu and thereby retards aspects of the aging process.

Using sensitive low-dose dexamethasone suppression tests, Dilman reports that the dexamethasone-suppressibility of cortisol production in humans declines with increasing age (24,156) – an effect which could well be indicative of reduced hypothalamic catecholamine activity. Dilman has coined the term ‘hyperadaptosis’ to describe this age-related loss of feedback suppressibility in the HPA axis, and posits that it plays a significant role in the aging process. This is likely to be the case in rats, in which age-induced hyperadaptosis leads to increased basal cortisol levels; however, basal cortisol shows little age-related variation in humans. In any case, Dilman uses pharmacological correction of hyperadaptosis as a screening technique for identifying aging-retardant drugs (24). For example, in rats and/or humans, he reports that dexamethasone suppressibility is aided by phenformin, diazepam, L-dopa, bromocryp-
may complement the efficacy of this approach. These agents all have minimal side effects in clinically effective doses, and thus would be appropriate for practical life extension purposes.

Since effective thymus activity may also be important to ‘youthful’ hypothalamic and pineal function (as well as cellular immunity!), it is interesting to note a recent report that thymulin production, both in aging mice and humans, can be substantially enhanced by joint administration of moderate doses of arginine and lysine (160); this same combination was earlier reported to promote growth hormone release in young men (161). Since this nutrient combination is safe, inexpensive and practical, its impact on production of both growth hormone and thymulin should receive further clinical study in elderly subjects.

Despite the intuitive appeal of hypothalamic ‘rejuvenation’ as an aging-retardant strategy, it must be admitted that there are broad gaps in our understanding of how such an approach could retard aging of the body’s organs. This may reflect the fact that the hypothalamus and pituitary, as well as the pineal gland and thymus, very likely produce a number of hormones which have not yet been characterized. The cortical androgen stimulating hormone (CASH) cited above, may be one such example. Denckla has presented evidence for a pituitary hormone (DECO) that diminishes tissue responsiveness to thyroid hormones in aging animals (162,163). Parabiosis studies suggest that the serum of old rats contains a factor which rapidly increases the glycation level of tissue proteins in young rats to that typical of older rats (164). The intriguing ability of the thymus to stimulate β-adrenergic receptor expression throughout the body (69), suggests an unknown hormone. Although pineal peptides can exert remarkable pharmacological effects (24,67), their physiological role is not yet clear. It will undoubtedly take many more decades of endocrinologic research to explain adequately how the aging hormonal/neural milieu contributes to tissue aging and the age-related onslaught of disease. This, however, does not invalidate the simple insight that preserving youthful function of the hypothalamus (and of its ‘allies’, the thymus and pineal gland) is likely to retard aging and extend longevity.

Conclusion

The dramatic life-extending effect of chromium picolinate reported in Long-Evans rats, very likely indicates that efficient insulin activity, both centrally and peripherally, is important for maintaining a youthful hormonal-neural milieu. This view is supported by the numerous normal derangements, comparable to those seen in senescence, reported in diabetic animals as well as clinical diabetes. It is also consistent with recent evidence that brain insulin promotes a leaner physique, aids monoaminergic activity, supports brain steroid receptor binding, and exerts a trophic effect on neurons. Reduced function of both the thymus and pineal gland in diabetic animals, suggests that appropriate insulin activity, directly or indirectly, promotes the activity of these crucial aging ‘pacesetters’. Preliminary evidence of increased DHEA production in middle-aged humans using chromium picolinate or insulin-sensitizing drugs, suggests an additional respect in which insulin-sensitization may ‘rejuvenate’ the body’s hormonal milieu. The common clinical perception of accelerated aging in diabetics, may reflect not only the adverse effects of hyperglycemia, but also a premature senescence of the body’s neurohormonal environment.

Future animal longevity studies with chromium picolinate should assess hypothalamic/pituitary function in a variety of respects, as well as monitoring pineal and thymus structure and function. Short-term supplementation studies can examine the impact of this nutrient on blood-brain barrier transport of insulin, and on physiological response to intracerebroventricular insulin. The effects of chromium picolinate on hormonal milieu and regulation should also be studied clinically, particularly in elderly insulin-resistant subjects. The battery of clinical endocrinological tests suggested by Dilman and Dean may be useful in this regard (24).

These considerations are not intended to slight the more direct systemic benefits of insulin sensitization, typically accompanied by correction of hyperinsulinemia and improved glycemic control. Insulin resistance is known to be an important clinical risk factor for atherogenesis, thrombosis, hypertension, and diabetes; it can therefore be anticipated that chromium picolinate and other safe insulin-sensitizing strategies (e.g. aerobic exercise, low-fat diet, weight control) will promote vascular health and increase average human longevity, independent of any more profound effects on hormonal regulation of aging. Nevertheless, these vascular benefits cannot explain the effect of chromium picolinate on the longevity of Long-Evans rats, which rarely die of atherosclerosis, diabetes, or hypertension. Nor is reduction of protein glycation likely to offer an adequate explanation for such a substantial effect on longevity. Thus, the impact of long-term supplemental chromium picolinate on the hypothalamic function and hormonal milieu of aging animals (including humans) deserves a thorough exploration.
References

2. Evans GW, Meyer LK. Lifespan is increased in rats supplemented with a chromium-pyridine 2 carboxylate complex. 1994; submitted.


34. Dillman VM. Age-associated elevation of hypothalamic threshold to feedback control, and its role in development, aging and disease. Lancet 1971; i: 1211-1219.


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118. Kirchick HJ, Keyes PL, Frye BE. Etiology of anovulation in the immature alloxan-diabetic rat treated with pregnant mare’s serum gonadotrophin: absence of the preovulating luteinizing

