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Amino acid modulation of lifespan and reproduction in *Drosophila*

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Manipulating amino acid (AA) intake in *Drosophila* can profoundly affect lifespan and reproduction. Remarkably, AA manipulation can uncouple the commonly observed trade-off between these traits. This finding seems to challenge the idea that this trade-off is due to competitive resource allocation, but here we argue that this view might be too simplistic. We also discuss the mechanisms of the AA response, mediated by the IIS/TOR and GCN2 pathways. Elucidating how these pathways respond to specific AA will likely yield important insights into how AA modulate the reproduction-lifespan relationship. The *Drosophila* model offers powerful genetic tools, combined with options for precise diet manipulation, to address these fundamental questions.

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Introduction: dietary effects on lifespan and reproduction

Nutrition plays a primary role in shaping the physiology, life history and behavior of organisms, and nutritional interventions can have substantial health benefits [1]. Dietary restriction (DR), that is, the reduced intake of nutrients without malnutrition, has been the most widely studied nutritional intervention since the 1930s when it was first demonstrated that DR extends lifespan in rats. Since then, a large body of research has established positive effects of DR on longevity and age-related pathology in numerous organisms, ranging from yeast and worms to insects and mammals. At the same time, DR typically reduces reproductive output [2,3]. The fact that reduced food intake extends lifespan at the expense of reproduction makes the study of DR, and of dietary effects more generally, of key significance for our understanding of the commonly observed trade-off between reproduction and longevity [4,5].

Originally, reduced intake of calories was thought to be responsible for the lifespan-extending effects of DR, but this view began to shift when studies in *Drosophila* showed that lifespan extension under DR does not depend on caloric restriction [5,6]. By testing diets with different nutrient compositions ('nutritional geometry framework') [7], it was found that the ratio of proteins to carbohydrates (P:C ratio), not overall energetic content, affects lifespan and reproduction in *Drosophila* [8,9]. Today, there is growing evidence that especially dietary proteins play a major role in mediating the effects of DR [10,11] (but see [12]). Remarkably, beyond the effects of the proteins themselves, recent work suggests that the building blocks of proteins, that is, specific amino acids (AA), can profoundly impact lifespan and associated traits. For example, in both flies and mice, restriction of dietary methionine can extend lifespan to the same extent as DR [13–16].

Here, we give a brief review of how AA modulate lifespan and reproduction, and the trade-off between these traits. We also provide a short overview of the molecular mechanisms by which AA might control these two traits and their relationship. We focus on recent research in the *Drosophila* model, given that this system combines unrivaled genetic tools, a solid understanding of the effects of nutritional interventions, and the availability of holidic diets that now allow researchers to precisely control individual dietary components [14,17–19].

Amino acids significantly impact lifespan and reproduction

The finding that protein restriction can mediate the effects of DR opens up the possibility that specific AA might be responsible for the effects on lifespan and reproduction. Consistent with this idea, restriction of dietary methionine has been found to promote longevity in rats and mice [13,20]. Similarly, Troen *et al.* observed that reduced dietary levels of methionine optimize *Drosophila* lifespan, although too low levels were detrimental [14].

In one of the most comprehensive studies to date, Grandison and colleagues fed flies a lifespan-extending restricted diet (i.e. DR) and then added back specific nutrients to determine which nutrients would restore the

reduced lifespan and high fecundity of fully fed flies [15]. While adding back carbohydrates, lipids or vitamins had no effect, adding back all AA to the restricted diet shortened lifespan and restored fecundity to the level seen in fully fed flies. Further experiments showed that this lifespan-shortening and fecundity-increasing effect is mainly due to essential AA (EAA, i.e. those AA that cannot be synthesized by the body and must be supplied by the diet) and not due to non-essential AA. Next, the authors investigated the role of individual AA. While adding back all EAA (DR + EAA) shortened lifespan and restored fecundity, adding back all EAA minus methionine (DR + EAA − M) failed to shorten lifespan, indicating that methionine restriction can promote longevity. Remarkably, by manipulating each EAA individually Grandison and coauthors found that adding methionine alone to the restricted diet (DR + M) restores fecundity to normal levels but *without* reducing the long lifespan of DR flies (also see [21]). These findings suggest that methionine is — at least partly — responsible for the lifespan-shortening effect of full feeding, even though methionine alone (DR + M) might be insufficient to reduce longevity. In support of this idea, Lee and collaborators have recently found that the lifespan-extending effect of methionine restriction depends on the overall concentration of other AA and requires a low AA status [16]. Also, the effects of AA on lifespan in Queensland fruit flies depend on other nutrients, including vitamins, minerals and cholesterol [22].

The most fascinating implication of the work of Grandison *et al*. is that fine-tuning the levels of specific dietary AA can apparently increase lifespan without any loss of fecundity or fertility [15]. Lifespan extension might thus be realized without costs by providing an 'optimal' diet. To achieve such a diet, Piper *et al*. [23••] used information on the exome, that is, all protein-coding genes in the genome, to determine which proportions of AA an animal requires. The authors found that this exome-matched diet extends lifespan without costs in terms of growth or reproduction. Moreover, a comparison of the exome-based diet to a yeast-based diet revealed that methionine is the most limiting AA, which might explain why fecundity is particularly sensitive to this specific AA [23••]. However, in sterile workers of the Argentine ant (*Linepithema humile*) ant, an exome-based diet failed to increase lifespan [24••]. Whether this failure might somehow have to do with the fact that the workers were sterile, thus rendering nutrient allocation to reproduction impossible, remains an open question.

Dietary uncoupling of the reproduction-lifespan trade-off

The reproduction-lifespan trade-off associated with DR is often interpreted in terms of differential allocation of resources between the competing demands of reproduction versus somatic maintenance (the 'resource allocation' model). Since DR typically promotes adult survival at the cost of decreased fecundity or fertility, DR might represent an adaptive plastic response that allows organisms to survive poor dietary conditions by reallocating energy away from reproduction to somatic maintenance and survival until optimal conditions have returned [4,5,25,26]. Alternatively, the 'direct constraints' model postulates that reproductive processes cause direct damage or impair maintenance and survival [4,5].

The finding that a simple dietary intervention, that is, adjusting the levels of a single AA, can extend lifespan without apparent growth or reproductive costs clearly challenges both models [4,15,16,23••,27]. For example, Grandison *et al*. concluded that — since adding methionine back to a restricted diet can increase fecundity without reducing lifespan — the reduction of lifespan under full feeding does not result from nutrient reallocation away from survival and somatic maintenance to reproduction [15]. In support of this idea, DR can extend *Drosophila* lifespan even when flies are made sterile, suggesting that DR does not extend lifespan *because* it reduces reproduction [28] (but see conflicting evidence in *Caenorhabditis elegans* [29]).

While the above work clearly demonstrates that both lifespan and reproduction can be maximized under specific dietary conditions [15,16,23••], it might be premature to dismiss trade-offs as a proximate explanation for the effects of DR altogether. The fact that DR with methionine supplementation can restore high fecundity while lifespan remains extended does not logically imply that DR-induced lifespan extension is independent of resource reallocation. It rather suggests that methionine is a major limiting factor for egg production. Since on average methionine does not consistently affect lifespan across dietary conditions yet generally increases fecundity [16], allocation or reallocation of methionine seems to mainly influence reproduction, not lifespan. Methionine might thus not be directly subject to *competitive* resource allocation or reallocation between *reproduction* versus *lifespan* when conditions change from full feeding to DR, or vice versa. In fact, when methionine is raised to a level that does not limit egg production anymore, the lifespan-reproduction trade-off is once again observed: increasing EAA levels further enhance fecundity at the cost of reduced lifespan [15,16]. Together, these findings suggest that *on average* probably most EAA tend to negatively affect lifespan, while positively influencing fecundity. Reproduction and survival thus seem to have competing demands with regard to AA levels: reproduction requires high AA levels, but such high levels shorten lifespan.

However, one aspect of the reproduction-longevity trade-off that has often been overlooked is sex-specificity. Typically, effects of DR on this trade-off have been studied predominantly in females [8,9], presumably

due to the higher investment of females than males into reproduction. Interestingly, females and males differ substantially in their response to DR [30–32]; moreover, the two sexes exhibit a dramatically different genetic architecture of lifespan [33]. It will thus be interesting to see studies that contrast the physiological consequences of specific dietary AA manipulations between females and males.

Another open question is how manipulation of methionine or other AA affects fitness components other than lifespan and fecundity, for example stress resistance or immunity. At the level of fitness, trade-offs might be multidimensional and involve more than two traits. For example, previous evidence suggests that methionine is important for proper functionality of the immune system [34] — methionine might thus improve immunity at the expense of longevity.

Altogether, the observations that single dietary AA can have a profound impact on lifespan and reproduction, combined with the finding that DR is independent of caloric content itself [5,6], indicate that the field should revise simplistic notions of 'resource' or 'energy' allocation trade-offs. Further in-depth studies of how single dietary components affect various fitness traits, including reproduction and lifespan, would provide a more comprehensive understanding of commonly observed life-history trade-offs [15,16,23••].

Amino acids affect lifespan and reproduction via nutrient sensing

How, mechanistically, do AA affect reproduction and lifespan? A prime candidate is the insulin/insulin-like growth factor 1 (IIS)/target of rapamycin (TOR) signaling pathway, which is known to be a major regulator of longevity in worms, flies and rodents [35]. For example, the centrally important transcription factor *foxo* downstream of IIS modulates the DR response in flies [36,37], and the translational repressor 4E-BP downstream of TOR is functionally required for lifespan extension upon DR [38]. Moreover, given that insulin secretion in response to leucine and isoleucine uptake is controlled through a TOR-dependent mechanism [39], it is tempting to speculate that AA might act through TOR to affect lifespan and fecundity. The results of Grandison *et al.* and of Lee *et al.* corroborate this idea [15,16].

Grandison *et al.* found that adding back essential AA to restricted diet decreases lifespan, but only to a minor extent in flies carrying a dominant-negative (DN) form of the insulin-like receptor InR, showing that the negative effects of AA on longevity require a functional receptor [15]. Furthermore, dietary methionine supplementation is unable to promote fecundity in these mutants, suggesting that the fecundity-promoting effects of methionine also rely on InR function. Similarly, Lee and colleagues found that under conditions where methionine reduction extends lifespan of wildtype flies, restriction of methionine no longer extends lifespan in InR DN mutants or in flies that overexpress the TOR antagonist tuberous sclerosis complex 2 (TSC2) [16]. Moreover, a recent study by Emran and colleagues has reported that TOR signaling, but apparently not IIS, is required for the effects of EAA on fecundity and lifespan [40]. These findings are also interesting given the observation that methionine-deficient mice exhibit lowered levels of serum IGF-1 and insulin [13].

In addition to IIS/TOR, a number of other genes and pathways have been shown to play a role in AA signaling. For example, the general control nonderepressible 2 (GCN2) protein provides a conserved AA sensing mechanism that is independent of AA identity [11,41]. In *Drosophila* larvae, GCN2 signaling in a small subset of dopaminergic neurons is required for the avoidance of diets with unbalanced AA levels, a process that seems to be independent of TOR signaling [42]. It will be clearly of great interest to learn whether and how this mechanism contributes to the AA modulation of reproduction and lifespan.

Finally, it will be interesting to study how sensory perception of AA modulates lifespan and reproduction, given that olfactory perception and taste can affect the lifespan of flies independent of their actual food intake [43,44]. These findings raise the possibility that perception of AA alone might impact lifespan. The first gustatory receptor for AA in flies has recently been identified [45•]. In larvae, this receptor, *IR76B*, responds to a subset of AA, including methionine, and is required for the behavioral attraction to certain AA. These results demonstrate that flies can sense and respond to specific AA. Furthermore, internal AA status and reproductive state influence whether flies select or reject a particular diet [46,47•]. It is particularly noteworthy in this context that lifespan and fecundity have distinct optima at different dietary P:C ratios and that flies can self-regulate P:C intake in a way that maximizes lifetime fecundity at the expense of longevity [8]. An improved future understanding of the interplay of these mechanisms might explain how flies can maintain tight nutritional homeostasis and balance reproduction and lifespan in a way that optimizes fitness.

Concluding remarks

We end with a potentially important caveat for experiments designed to study the effects of AA on lifespan and reproduction. Dietary AA do not occur in isolation: most AA in natural diets are part of dietary proteins. As seen above, the effects of methionine on reproduction and lifespan depend critically on the background status of other AA and other nutrients. Moreover, recent research in ants suggests that directly providing free AA in a defined diet shortens lifespan considerably more than

supplying the equivalent amount of AA via whole proteins, potentially due to a difference in the uptake of AA versus proteins, or by bypassing protein digestion. In addition, providing free AA affects the chosen intake ratio of proteins to carbohydrates, suggesting that the perception of free AA and whole proteins differ [24••]. These findings thus indicate that results based on manipulating specific AA in chemically defined diets need to be interpreted with some caution. Nonetheless, there can be no doubt that the body of work we have reviewed here is greatly advancing our understanding of how diets and their components impact organismal reproduction and lifespan.

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