Are fibrils a consequence of the disease, merely correlated with it, or a cause? In the context of this question, Shi and colleagues' finding that the fibril type differs between diseases, but is largely reproducible in people with the same disease, is an intriguing result. It is difficult to imagine a scenario in which the 19 different neurodegenerative tauopathy diseases analysed so far lead to the misfolding of tau into reproducible fibrils in a total of 17 different ways (in the structural data from this new work and the previous studies). As such, it would seem highly unlikely that the variation in fibril type is a secondary consequence — that is, an indirect effect of events that occur downstream of the main disease-causing mechanisms.

Another possible interpretation of Shi and colleagues' findings is that healthy tau can form many different strains of fibril under normal conditions, but that specific tauopathies favour the formation and propagation of some of the fibril polymorphs in certain cell types. This type of adaptation was previously documented for prion diseases. In the presence of the drug swainsonine, a population of drug-resistant prion fibrils emerged, whereas after the drug was removed the swainsonine-sensitive prion fibrils reappeared[10]. These findings indicate that, in the case of the prion protein, the infectious material is composed of a pool of several fibril polymorphisms[10].

A third possible interpretation of Shi and co-workers' findings is that a certain fibril type causes intracellular damage in a particular way — for example, by exposing a certain fibril surface that is toxic for a certain function of a specific cell type. Indeed, each of the fibril polymorphs determined in Shi and colleagues' work has different exposed surfaces and varying flexibilities or stabilities. Therefore, it seems probable that the fibril types specific to each disease have a causative connection with the mechanism by which damage occurs in the cell[11]. Whatever the underlying reasons for the observed fibril patterns turn out to be, Shi and colleagues' findings are a milestone in our understanding of the broader family of amyloid diseases, which involve the build-up of proteins, and of tauopathies specifically.

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Ageing

How overnight fasting could extend lifespan

Stephen L. Helfand & Rafael de Cabo

A feeding schedule of prolonged overnight fasting periods extends healthy lifespan in fruit flies by promoting night-time autophagy, a process in which material in cells is degraded and recycled. **See p.353**

Timing is said to be the secret to comedy and to success in life, but it could also be one of the secrets to a longer, healthier life. The quest to extend healthy lifespan has been made seemingly attainable in humans through manipulations of calorie intake, such as caloric restriction[1,2]. However, restricting calories for more than a short time is difficult because the intense hunger is hard to withstand for most. Manipulations that focus not on the number of ingested calories, but on the timing of ingestion, such as time-restricted feeding (TRF) might be much more sustainable. Ulgherait *et al.*[3] show on page 353 that, in the fruit fly *Drosophila melanogaster*, a TRF schedule that includes prolonged periods of overnight fasting extends healthy lifespan. It does so by promoting an intracellular degradation and recycling process called autophagy, specifically at night[4,5].

"This intermittent time-restricted feeding schedule increased lifespan by 18% in females and 13% in males."

Studies of intermittent fasting — a type of TRF schedule that cycles between periods of fasting and eating — in various species have consistently reported improvements in many health indices, even without reductions in calorie intake. The benefits of intermittent fasting in humans include abdominal fat loss and improvements in glucose metabolism, blood pressure, heart-rate variability and physical endurance[6–8]. Moreover, several of the main positive effects of caloric restriction on metabolism, organ function and disease resistance that have been seen in humans are recapitulated with intermittent fasting, and can be dissociated from those of weight loss and total caloric intake[1,6].

TRF and other types of intermittent-fasting schedule are lifestyle interventions that can be applicable worldwide and thus benefit people in a truly egalitarian way. But how TRF schedules promote health and extend lifespan must first be understood. Intermittent fasting induces a change from metabolism of sugar and carbohydrates to metabolism of fatty acids and other nutrients — a process called metabolic shifting. The health contributions of this process must be distinguished from those of caloric restriction and weight loss, which could result from fasting, if we are to grasp more fully the responses to each of these dietary manipulations.

Ulgherait and colleagues modified a standard TRF schedule that alternated 12-hour fasts with 12-hour feeding periods to a regime in which 20-hour fasting periods that included the night (when fruit flies, like humans, are least active) were alternated with feeding periods of 28 hours (Fig. 1a). This intermittent time-restricted feeding (iTRF) schedule increased lifespan by 18% in females and 13% in males, compared with flies that had unrestricted access to food.

An extended lifespan is undesirable when health is not preserved — as in the Greek myth of Tithonus, who became immortal but was destined to age forever because he lacked eternal youth. However, the authors showed that iTRF not only improved lifespan, but also protected against declines in muscular, neuronal and intestinal function with age.

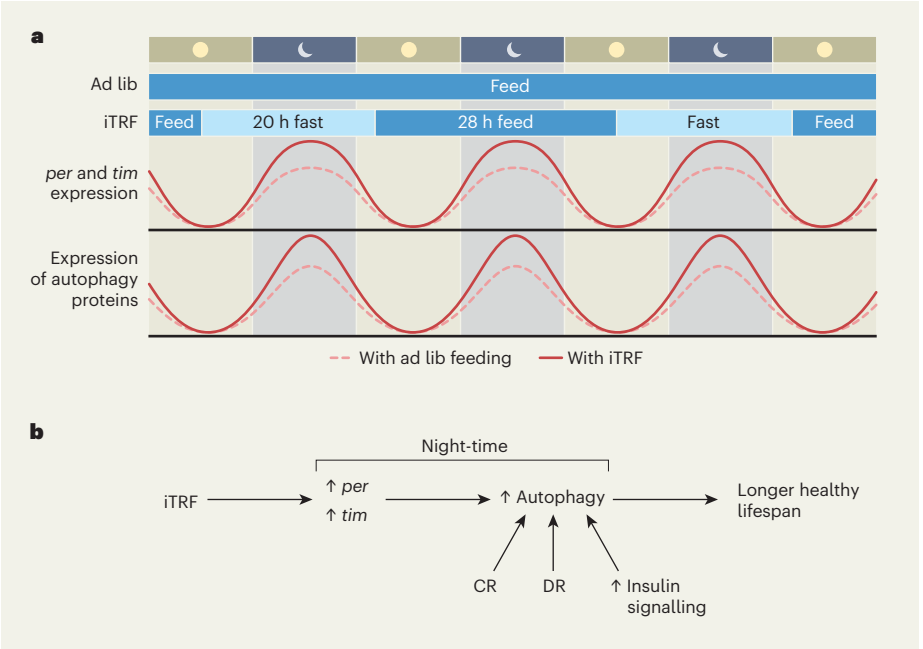

Figure 1 | Timing of eating without a change in diet composition substantially improves healthy longevity. a, Ulgherait *et al.*[3] found that, compared with fruit flies with continuous access to food (ad lib), flies on an intermittent time-restricted feeding schedule (iTRF), in which 20-hour fasting periods that ran overnight were alternated with 28-hour feeding periods, lived longer. The expression of genes that make up the internal 24-hour clock — including period (*per*) and timeless (*tim*) — oscillates during the day–night cycle, and iTRF enhanced night-time expression of *per* and *tim*. These changes in clock-gene expression resulted in higher night-time expression of proteins required for autophagy, a process in which intracellular material is degraded for recycling. **b**, Caloric restriction (CR), dietary restriction (DR) and changes in insulin signalling also promote autophagy, but the effect of iTRF on healthy lifespan is distinct from and additive to these other interventions.

The TRF and iTRF schedules optimally extended lifespan when initiated at day 10 of the flies' adulthood and terminated at day 40. Beyond day 40, the authors observed no clear lifespan benefit with iTRF, and a possible shortening of the remaining lifespan with TRF. The age range in which TRF or iTRF can be beneficial should be considered before translating such an intervention to the clinic.

As with studies of intermittent fasting in mice[1,9], the authors ruled out the possibility that iTRF was inadvertently inducing a restriction in food intake; indeed, flies on the iTRF regime ate more food than did those with continuous access to food. Furthermore, the combination of iTRF with caloric or dietary-protein restriction led to a greater lifespan extension than did either intervention alone, indicating that these manipulations extend lifespan through distinct mechanisms (Fig. 1b) — as has also been observed in mouse studies[1,7,8]. Altering signalling by the hormone insulin extends lifespan in many organisms, including fruit flies[10]. Ulgherait *et al.* found that flies with a lifespan-increasing alteration in insulin signalling lived even longer when the alteration was combined with iTRF. This again demonstrates that distinct mechanisms underlie the two interventions. These studies show that iTRF has the potential to be combined with either dietary or insulin-related interventions to achieve a greater improvement in health and lifespan than either type of intervention could bring about alone.

Feeding behaviour and metabolism in flies, rodents and humans are regulated by an internal 24-hour (circadian) clock — in which a set of genes interact to coordinate various cell functions according to the time of day[6,11]. In a series of experiments in mutant flies in which different clock genes (including *Clock*, *period* and *timeless*) were disabled, Ulgherait and colleagues demonstrated that the circadian clock is required for the health and lifespan benefits of iTRF to take effect (Fig. 1). In addition, flies that were put on an iTRF schedule that was shifted by 12 hours, so that the fasting period occurred mostly during the day instead of at night, lived no longer than those with unrestricted access to food — suggesting that iTRF might exert its effects through a mechanism that is regulated by the circadian clock.

Autophagy is regulated by the circadian clock such that it peaks at night, and it has previously been associated with longevity[4–6]. The authors show that genetic disruption of components of the intracellular machinery needed for autophagy prevents iTRF from extending lifespan. They also show that using a genetic technique to artificially drive autophagy above usual levels at night-time in flies with continuous access to food extends lifespan. Thus, the clock-driven boost in autophagy at night[4,5] is crucial for the effects of iTRF on healthy lifespan. Because Ulgherait and colleagues have revealed these underlying molecular mechanisms, and shown when they occur, it might be possible to identify drugs that can be used to mimic the effects of iTRF specifically on night-time autophagy.

The past decade has seen the convergence of research into nutrition and circadian rhythms, the possible synergies between them and their combined effects on human health and ageing. Emerging evidence suggests that the timing of meals and fasting periods with respect to circadian rhythms is crucial for reaping many of the health and longevity benefits that are provided by calorie restriction, without the need to restrict nutrient intake[9,12]. Further research into the potential of strategies that are based on the timing of food intake, calorie loads and diet quality should establish whether scheduling food intake according to circadian rhythms yields consistent and meaningful benefits across organs and species. These studies suggest the intriguing possibility that behavioural or lifestyle changes could be used worldwide to improve healthy longevity, without the need for expensive pharmacological agents.

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