in metamaterials. This property doubles the values of the trapped charges and can mask their quantized fractional nature, so material candidates should be carefully selected. Detecting fractional charges would also require local probe techniques, such as scanning tunnelling spectroscopy, to be pushed to their resolution limits. The efforts will be huge, but the successes of the current studies make the observation of fractional charges at material defects more likely in the foreseeable future.

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Ageing

An anti-ageing mechanism for protein restriction

Cristal M. Hill & Matt Kaeberlein

Two animal studies show that restricting the dietary intake of branched-chain amino acids can extend lifespan by modulating the mTOR signalling pathway. But more research is needed before this diet should be recommended in people.

The idea that dietary restriction can be used as a tool to increase lifespan has been a centre-piece of ageing research for decades. But the mechanisms by which dietary restriction might act, and the specific nutritional components involved, remain unclear. Writing in *Nature Aging*, two groups demonstrate the importance of one type of nutrient, branched-chain amino acids (BCAAs), in the ageing of fruit flies[1] and mice[2]. Their work adds to our understanding of the effects of specific dietary components on ageing and connects previous observations into a coherent model.

BCAAs are the three essential amino acids leucine, isoleucine and valine, which cannot be synthesized by humans and so must come solely from dietary protein. Leucine is a potent activator of the 'mechanistic target of rapamycin' (mTOR) protein, which serves as a key regulator of cell growth and differentiation. Both dietary protein restriction (which results in low levels of leucine and other BCAAs) and inhibition of mTOR can extend lifespan in animals[3,4].

In the first of the current papers, Lu and colleagues[1] set out to better understand the mechanism by which dietary protein restriction extends lifespan in fruit flies. They focused on sestrin, an evolutionarily conserved stress-inducible protein that links amino-acid abundance to mTOR signalling[5]. Sestrin acts as part of a complex that inhibits mTOR — a brake that is released when sestrin senses and binds to leucine[5]. The authors found that flies deficient in sestrin fail to respond normally to dietary protein restriction. They identified a specific amino-acid residue in sestrin

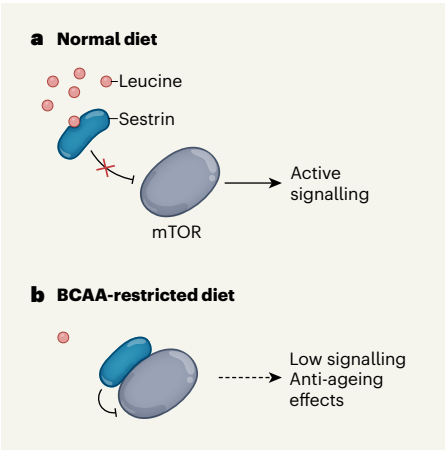

Figure 1 | Branched-chain amino acids (BCAAs) in ageing. a, The protein sestrin is thought to bind to the BCAA leucine. When sequestered by leucine, sestrin cannot exert its effects as part of a complex (not shown) that inhibits the protein mechanistic target of rapamycin (mTOR). **b**, Lu *et al.*[1] report that restricting dietary BCAAs in flies increases the inhibition of mTOR by sestrin. Reduced mTOR signalling produces anti-ageing effects. Richardson *et al.*[2] find that BCAA restriction also has anti-ageing effects in mice, supporting the idea that this pathway is common to multiple species.

(arginine 407) that senses amino acids. Flies that carry a mutation in this residue have lower mTOR activity than do controls. They are also longer-lived, and are protected against the negative lifespan-shortening effects of a high-protein diet.

In the second study, Richardson and colleagues[2] provide complementary data on the effects of a BCAA-restricted diet in mice. In contrast to a previous study[6], they observed a robust lifespan extension in male mice fed a BCAA-restricted diet throughout life, equal to the benefits of dietary protein restriction. Interestingly, female mice showed no lifespan extension from BCAA or dietary protein restriction, and if BCAA restriction was started during middle age, the benefits on males were greatly reduced. Thus, both studies collectively point to mTOR as a primary mediator of the benefits associated with BCAA restriction (Fig. 1).

Lu *et al.* go on to provide evidence that — at least in fruit flies — sestrin-mediated inhibition of mTOR improves gut function by activating an intracellular recycling process called autophagy in intestinal stem cells. These findings dovetail nicely with a large body of literature indicating that direct pharmacological inhibition of mTOR with the drug rapamycin can enhance autophagy and increase lifespan and the period of life spent in relatively good health (healthspan) in model organisms[3]. In mice, however, the effects of rapamycin seem to be more robust and less sex-dependent than those of BCAA restriction[7], suggesting that there are key differences between these interventions. There are several possible explanations for these differences. For instance, mTOR-independent effects of BCAA restriction might counteract some of the benefits of this dietary intervention, or the more-potent mTOR inhibition caused by rapamycin could affect downstream pathways differently[3].

Low-carbohydrate ketogenic diets, which are often lower in protein than control diets, can also increase lifespan and healthspan in mice[8,9]. The hormone fibroblast growth factor 21 (FGF21) is upregulated in animals subjected to either ketogenic diets or dietary protein restriction, and it has been implicated in the effects of dietary protein restriction on longevity[10]. Interestingly, Richardson *et al.* found preliminary evidence that lifelong BCAA restriction leads to FGF21 upregulation in the longer-lived male mice, but not in the shorter-lived females. The impact of FGF21 on mTOR signalling is complex, however, with evidence for both activating and inhibitory effects in different tissues. Future studies should address the overlapping and distinct mechanisms of action for these two dietary interventions, as well as for direct inhibition of mTOR by rapamycin.

Together, the current studies provide key insights into the mechanistic basis by

which dietary protein, and BCAAs in particular, enhance evolutionarily conserved pro-longevity mechanisms. A clear picture is emerging of how specific amino acids are sensed by sestrin to regulate mTOR signalling and autophagy and so preserve the function of intestinal stem cells during ageing. Although many details remain to be elucidated, and other downstream targets of mTOR are likely to be involved in mammalian ageing, these studies represent a key step forward.

The past decade has seen a growing trend in popular culture towards the idea that nutritional strategies that delay ageing in rodents should be adopted by people. Should we consider protein or BCAA restriction as a healthy lifestyle choice? Support for the idea that excessive protein intake is associated with poorer health outcomes and increased mortality in humans can be found in epidemiological data[11]. But even in people who have chronic kidney disease — for whom protein restriction is a favoured clinical intervention — it is unclear whether protein restriction has an effect on mortality[12]. It is also of note that most of the human evidence that points to the negative health impacts of high protein comes from populations that are probably eating too much altogether. Activity level is another factor that has not been addressed in animal studies. Although speculative, it seems plausible that protein or BCAA restriction could have quite different effects in people who have a sedentary lifestyle than in those who are active and exercise regularly.

There are other considerations, too. Genetic background is crucial in the response to dietary restriction, with an identical low-calorie regimen increasing lifespan in some mouse strains but shortening it in others[13]. It is not yet known how genetic variability might alter the effects of dietary protein or BCAA restriction in mice, although a study published last year found that protein restriction has detrimental effects in about one-quarter of the genetic backgrounds tested in fruit flies[14].

There is also evidence that dietary restriction initiated later in life might have reduced benefits in rodents and, in some cases, result in premature death[15]. Interestingly, there seems to be a hint of this in the data from Richardson and colleagues, who found that starting BCAA restriction at 16 months of age (perhaps equivalent to 50 years of age in humans) seems to cause about one-quarter of the female mice to die early. Perhaps of relevance, dietary protein intake in young people is associated with higher all-cause death rates, but this relationship inverts at around the age of 65, such that higher protein intake is associated with lower death rates in older adults[16].

Taken together, these observations suggest that although protein- and BCAA-restricted diets are a powerful research tool for exploring the fundamental mechanisms of ageing, it is premature to recommend adoption by the general population. This is especially true for those above the age of 65 or those who already have a healthy, active lifestyle.

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Drug discovery

Psychedelics revamped

Gabriela Manzano-Nieves & Conor Liston

An analogue of the psychedelic drug ibogaine has been developed. The analogue mirrors ibogaine's ability to treat addiction and depression in animal models, has fewer side effects and is much simpler to synthesize. **See p.474**

The discovery in the 1940s and 1950s that the drugs lysergic acid diethylamide (LSD) and psilocybin had psychoactive properties ignited intense interest in whether psychedelic compounds could be useful in the clinic[1]. But in the 1970s, increasing concerns about safety and the drugs' potential for abuse led to research becoming increasingly restricted. In the past decade, there has been a renewed interest in the therapeutic potential of psychedelic compounds, with preliminary findings indicating promise for drugs including LSD, psilocybin and ibogaine in combating treatment-resistant depression[2], post-traumatic stress disorder[3] and anxiety in people who have terminal cancer[4]. On page 474, Cameron *et al.*[5] report the synthesis of a non-hallucinogenic analogue of ibogaine that could have the potential to treat addiction and depression.

Ibogaine is a naturally occurring alkaloid found in the West African rainforest shrub *Tabernanthe iboga* (Fig. 1). Preclinical data and small-scale studies indicate that ibogaine might be useful for reducing drug cravings, withdrawal symptoms and the risk of relapse in opioid and alcohol addictions. This might be because of ibogaine's ability to modulate neuronal growth and maintenance and to alter the strength of the connections between neurons (synaptic plasticity)[6–9]. However, ibogaine has several undesirable properties[10]. First, it can cause dangerous irregularities in heartbeat and neurotoxicity. Second, the drug produces long-lasting hallucinations at therapeutic doses. Third, ibogaine is technically complicated to synthesize, limiting its production.

Cameron *et al.* set out to engineer an ibogaine analogue that retained its therapeutic potential but had less-severe side effects. The authors first systematically deleted key structural elements of the molecule, and found that ibogaine's tetrahydroazepine ring is crucial for promoting growth and branching of neurons in culture, as well as in the brains of mice. The group subsequently synthesized ibogaine analogues that retained their tetrahydroazepine ring and growth-promoting effects, but had more favourable toxicity profiles.

These efforts produced one particularly promising candidate for further study — a new compound called tabernanthalog (TBG), which can be easily synthesized in a single step from readily available starting materials. Cameron and colleagues used established assays in rodents and zebrafish to compare TBG and ibogaine. They showed that TBG had lower hallucinogenic potential than ibogaine, as measured by its propensity to elicit head-twitching behaviour in mice. It also showed less cardiac and developmental toxicity in zebrafish, especially at low doses. Together, these data indicate that TBG is