

Dispatches

Sexual Behavior: Dietary Food Switch Induced by Sex

Pregnancy in humans induces cravings for special food: the same occurs in *Drosophila* females. New work now shows that mating throws a nutritional switch in favor of a high-protein diet and that modulation of nutritional balance depends on the sex peptide receptor and involves neuronal TOR–S6 kinase signaling.

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Mating elicits drastic physiological and behavioral changes in most insects [1]. These post-mating responses are male-induced and have been intensely studied in the fruitfly *Drosophila melanogaster* [2]. The seminal fluid contains many components that elicit these responses [3]. In *Drosophila*, a single male peptide, dubbed sex peptide (SP, or Acp70A for Accessory gland protein cytoplasmic localization 70A) induces nearly a dozen diverse post-mating responses [4] (Figure 1). SP also affects food intake [5]. After mating, *Drosophila* females need to ingest considerable amounts of food to produce eggs. Enhanced food intake after mating is dependent upon SP transfer during copulation as SP⁰-males do not induce this change [5]. New studies now show that mated females are not only busier eating, but also change their tastes. Two papers published in this issue of *Current Biology* [6,7] report that virgin females like carbohydrates, whereas, after mating, females choose food containing protein-rich yeast: again, SP and its receptor SPR are involved.

A dietary switch to optimize the nutritional requirements of an organism after developmental or environmental changes has been observed in many species [8]. Food preferences in both sexes of *D. melanogaster* were studied by Vargas *et al.* [6] and Ribeiro and Dickson [7] using nutritional assays with radio-labeled [6] or colored food [7], respectively. After conditioning on food lacking either carbohydrates or protein (yeast), *Drosophila* shows a strong preference for the deficient nutrient when subsequently allowed to choose its diet [6,7]. The quality of the choice is independent of the sex of the fly, but males and females show different dynamics. Males require a much longer period of yeast

deprivation to show a switch in food choice [7]. Females eat a much larger amount of yeast than males and males consume more carbohydrates relative to females [6]. The choice depends on the nutritional needs of males and females, not age, since for all well-fed flies yeast is not attractive [7]. Virgin females seem to have a sweet tooth, but after mating they prefer protein-rich yeast. This makes biological sense, since mating-induced oogenesis and egg laying demands high energy and amino acid input. In the first days after mating, a female lays up to 80 eggs per day. Thus, the value of yeast is assessed according to the physiological and nutritional status of the organism.

The conserved serine/threonine kinase TOR regulates growth and metabolism in many organisms in response to environmental cues [9]. The TOR gene has been found in

all eukaryotic genomes examined, including yeasts, plants, worms, flies and mammals. Four major inputs have been implicated in TOR signaling: growth factors, nutrients, energy, and stress (Figure 2). During development, TOR primarily controls growth, while in the adult TOR controls aging and other aspects of nutrient-related physiology [9]. In *Drosophila* deletion of the *dTOR* gene results in developmental arrest, with a phenotype resembling starved larvae [10]. TOR regulates many cellular processes — translation, transcription, ribosome biosynthesis, actin organization and autophagy [9] (Figure 2) — with the translational regulator ribosomal S6 kinase (S6K) being a well-studied target of TOR. S6K is also involved in a negative feedback loop, regulating the insulin signaling pathway that feeds into the TOR complex. So, how does the TOR signaling cascade fit into *Drosophila* food intake and choice?

Virgin transgenic fruit flies expressing an activated form of S6K or virgins fed with a serotonin precursor (5-hydroxy-L-tryptophan) show a

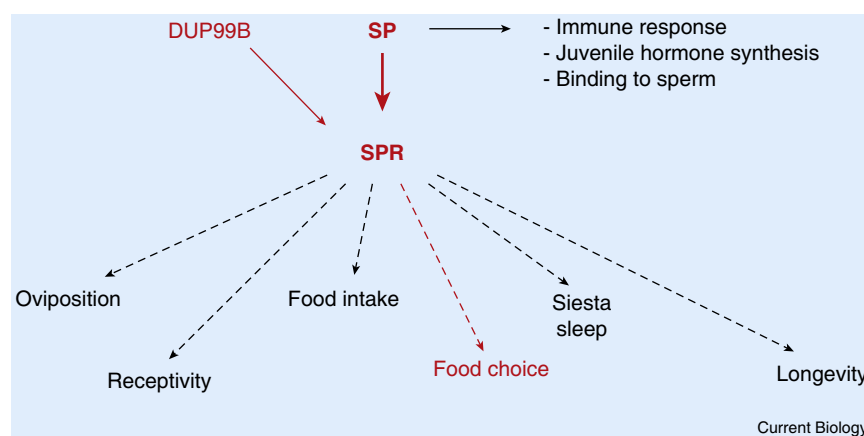


Figure 1. Post-mating responses elicited by sex peptide (SP) and DUP99B via the sex peptide receptor (SPR) in *D. melanogaster*.

The scheme shows post-mating responses with SP and/or SPR involvement. Formally, DUP99B has only been shown to elicit enhanced oviposition and to reduce receptivity [19]. But, as DUP99B also interacts with SPR [11], it very likely also affects the other responses mediated via SPR. In addition, SP induces immune response, juvenile hormone synthesis, and binds to sperm (for details, see text and [4]). Red, signaling pathways leading to nutritional switch in mated *Drosophila* females; solid lines, direct interactions.

strong preference for yeast [6]. Thus, TOR signaling and serotonin may play important roles in enabling *Drosophila* to maintain an appropriate nutritional balance. However, mated females are insensitive to modulation of S6K activity or 5-hydroxy-L-tryptophan feeding [6]: they seem to have reached an optimal level of protein ingestion. Also, the TOR–S6K pathway does not seem to be activated through the insulin receptor (Figure 2), as food choice is not affected by manipulation of the pathway downstream of the insulin receptor [7].

To be effective, TOR–S6K function has to be neuronal [6,7]. Overexpression of S6K in the fat body has no effect [6]. Interestingly, inhibition and activation of TOR–S6K signaling stimulates yeast feeding [7]. Thus, the neuronal TOR–S6K pathway regulating nutritional balancing may be complex. These findings suggest that the brain obtains information about the internal physiological status of the organism that may then be used to assign value to sensory input about external food sources and direct the nutritional choices of the fly. Hence, *Drosophila* may be used as a genetically tractable model system to study nutritional homeostasis at molecular, cellular and neuronal levels and, thus, contribute to our understanding of human metabolic disorders, such as diabetes and obesity.

As mentioned above, SP induces enhanced food intake in mated *Drosophila* females [5]. Is SP also involved in food choice? The variety of responses elicited by SP in the mated female suggests that the peptide may interact with several proteins [4] (Figure 1). One of the proteins, SPR, a G-protein-coupled receptor that is well conserved in other insects, has been isolated and characterized by Yapici *et al.* [11]. Ribeiro and Dickson [7] show that SPR is not involved in the induction of yeast feeding itself, as yeast-deprived males still perform the switch to food containing yeast. However, yeast-deprived mated females lacking SPR do not perform the switch, behaving as if still virgin [7]. To perform the nutritional switch SPR expression is needed in SP-sensing neurons only in females after mating [7,12,13]. Signaling is not dependent on the presence of a functional ovary [7]. Hence, the switch is not due to a feedback mechanism involving egg

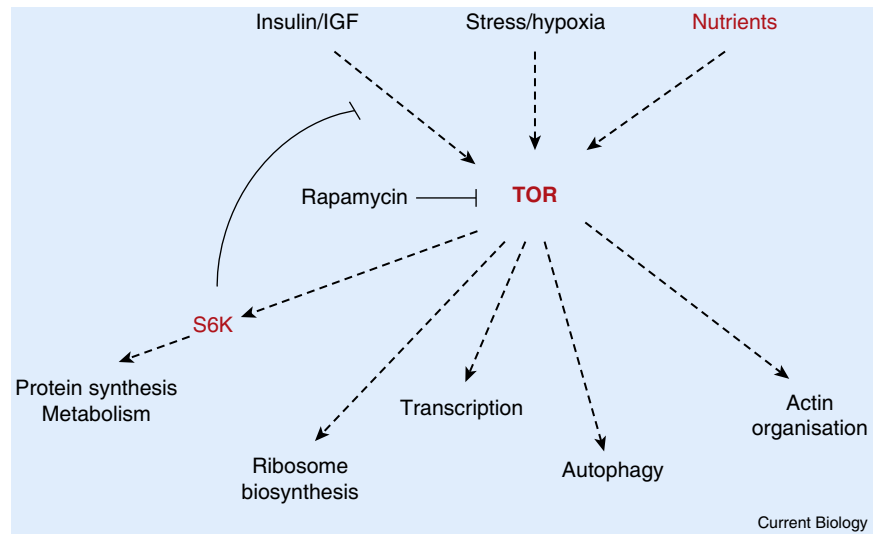


Figure 2. Food choice in *Drosophila* and the TOR–S6K pathway.

Scheme of TOR signaling in growth and development (for details see [9]). TOR and S6 kinase are involved in dietary switch in *D. melanogaster*. Red, proteins involved in nutritional switch in *Drosophila*.

production, but is a direct effect of SPR signaling. In accord with these results is the finding that the switch is partially dependent upon SP transfer [7]. But SP⁰-males still induce an intermediate level of nutritional switch [7]. Thus, SP is involved, but there must be other components that contribute. SPR interacts not only with SP, but also with the peptide DUP99B (for Ductus ejaculatory protein, cytological localization 99B) [4,11]. DUP99B also elicits egg laying and reduces receptivity, although only for one day and to a lower degree than SP [14]. Hence, this peptide may be the missing factor responsible for the intermediate level of switch induced by SP⁰-males. According to this model SP⁰/DUP99B⁰ double mutant males [15] should not induce the nutritional switch at all.

How does this fit into the other responses elicited by SP via SPR (Figure 1)? SPR has been shown to be involved in oviposition and reduction of receptivity [11]. Nutritional sensing is now added to the list of SP-induced post-mating responses mediated by SPR. Three further candidates for this signaling cascade may be ‘siesta sleep inhibition’ [16], enhanced food intake [5], and reduction of female longevity [17]. Males and virgin females indulge a siesta at lunchtime, often hiding from the burning sun, whereas mated females keep busy feeding. The signal

that throws this behavioral switch is SP and it is very likely transmitted via SPR [16]. Furthermore, SP transfer enhances food intake [5] and reduces the lifespan of mated females [17]. Given that food intake is intimately linked to aging in *Drosophila* [18], this aspect fits well into the nutritional aspects of SP action. Hence, SPR-expressing neurons may control at least six post-mating responses: oviposition, receptivity, food intake, food choice, siesta sleep and longevity [4] (Figure 1). It will be interesting to learn about the connections between the SP–SPR and the TOR–S6K signaling cascades that lead to the post-mating dietary switch, and additionally to determine how the brain interprets these signals and which neuronal circuitries are involved to produce the appropriate output.

References

1. Wolfner, M.R., Applebaum, S., and Heifetz, Y. (2005). Insect gonadal glands and their gene products. In *Comprehensive Insect Physiology, Biochemistry, Pharmacology and Molecular Biology*, L. Gilbert, K. Iatrou, and S. Gill, eds. (Amsterdam: Elsevier), pp. 179–212.
2. Sirot, L.K., LaFlamme, B.A., Sitnik, J.L., Rubinstein, C.D., Avila, F.W., Chow, Y., and Wolfner, M.F. (2009). Molecular social interactions: *Drosophila melanogaster* seminal fluid proteins as a case study. *Adv. Gene.* 68, 23–56.
3. Chapman, T. (2008). The soup in my fly: Evolution, form and function of seminal fluid proteins. *PLoS Biol.* 6, 1379–1382.
4. Kubli, E. (2008). Sexual behaviour: A receptor for sex control in *Drosophila* females. *Curr. Biol.* 18, R210–R212.
5. Carvalho, G.B., Kapahi, P., Anderson, D.H., and Benzer, S. (2006). Allochronic modulation of

- feeding behavior by the Sex Peptide of *Drosophila*. *Curr. Biol.* 16, 692–696.
6. Vargas, M.A., Luo, N., Yamaguchi, A., and Kapahi, P. (2010). A role for S6 kinase and serotonin in postmating dietary switch and balance of nutrients in *D. melanogaster*. *Curr. Biol.* 20, 1006–1011.
 7. Ribeiro, C., and Dickson, B.J. (2010). Sex peptide receptor and neuronal TOR/S6K signalling modulate nutrient balancing in *Drosophila*. *Curr. Biol.* 20, 1000–1005.
 8. Waldbauer, G.P., and Friedman, S. (1991). Self-selection of optimal diets by insects. *Annu. Rev. Entomol.* 36, 43–63.
 9. Wullschlegel, S., Loewith, R., and Hall, M.N. (2006). TOR signaling in growth and metabolism. *Cell* 124, 471–484.
 10. Oldham, S., Montagne, J., Radimerski, T., Thomas, G., and Hafen, E. (2000). Genetic and biochemical characterization of dTOR, the *Drosophila* homolog of the target of rapamycin. *Genes Dev.* 14, 2689–2694.
 11. Yapici, N., Kim, Y.-J., Ribeiro, C., and Dickson, B.J. (2008). A receptor that mediates the post-mating switch in *Drosophila* reproductive behaviour. *Nature* 451, 33–37.
 12. Hässemeyer, M., Yapici, N., Heberlein, U., and Dickson, B.J. (2009). Sensory neurons in the *Drosophila* genital tract regulate female reproductive behavior. *Neuron* 61, 511–518.
 13. Yang, C., Rumpf, S., Xiang, Y., Gordon, M., Song, W., Jan, L.Y., and Jan, Y.-N. (2009). Control of the postmating behavioral switch in *Drosophila* females by internal sensory neurons. *Neuron* 61, 519–526.
 14. Liu, H., and Kubli, E. (2003). Sex-peptide is the molecular basis of the sperm effect in *Drosophila melanogaster*. *Proc. Natl. Acad. Sci. USA* 100, 9929–9933.
 15. Chen, S. (2006). Molecular analysis of structure-function relationships of Sex-Peptide and DUP99B in *D. melanogaster*. Ph D. Thesis, University of Zurich, Zurich, Switzerland.
 16. Isaac, R.E., Li, C., Leedale, A.E., and Shirras, A.D. (2010). *Drosophila* male sex peptide inhibits siesta sleep and promotes locomotor activity in the post-mated female. *Proc. R. Soc. B.* 277, 65–70.
 17. Wigby, S., and Chapman, T. (2005). Sex peptide causes mating costs in female *Drosophila melanogaster*. *Curr. Biol.* 15, 316–321.
 18. Barnes, A.K., Wigby, S., Boone, J.M., Partridge, L., and Chapman, T. (2008). Feeding, fecundity and lifespan in female *Drosophila melanogaster*. *Proc. Biol. Sci.* 275, 1675–1683.
 19. Saudan, P., Hauck, K., Soller, M., Choffat, Y., Ottiger, M., Spörri, M., Ding, Z., Hess, D., Gehrig, P.M., Klauser, S., et al. (2002). Ductus ejaculatorius peptide 99B (DUP99B), a novel *Drosophila melanogaster* sex-peptide pheromone. *Eur. J. Biochem.* 269, 989–997.

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Musical Consonance: The Importance of Harmonicity

A recent study suggests that musical consonance is based on harmonicity, a preference that reflects the central role of harmonicity in auditory perception.

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Musical notes can be played in a sequence to produce melodies, or they can be presented together to produce chords. Certain combinations of notes are *consonant* (sounding pleasant or resolved) while other combinations are *dissonant* (sounding unpleasant or unresolved). The perceptual distinction is exploited by composers to evoke feelings of tension and resolution. Explanations of consonance in terms of the physical characteristics of the sounds, and their physiological and psychological effects, have been debated for hundreds of years without a clear consensus [1]. In a new article, McDermott *et al.* [2] provide compelling evidence that consonance is based on how well the combined frequency components match a single harmonic series.

Harmonicity and Beating

A single note produced by a musical instrument is a *complex tone*, consisting of a series of harmonic frequency components. The frequency of each harmonic is an integer multiple of the fundamental frequency of vibration. For example, the A string on a guitar has a fundamental frequency of

110 Hz, and harmonic components with frequencies of 110 Hz, 220 Hz, 330 Hz, 440 Hz, 550 Hz and so on. When two or more such notes are presented simultaneously, the harmonics are combined. For certain musical intervals the combination can be described as a simple harmonic series with a single fundamental frequency (Figure 1A). These combinations have a pleasant (consonant) sound. For some ratios, however, the harmonics do not match well. For example, a tritone (the notorious “Diabolus in Musica”) corresponds to a ratio of 64:45. For this combination, the harmonics do not form a single series (Figure 1B). Such combinations evoke an unpleasant (dissonant) sound. Hence, our preference for consonance over dissonance may be related to the resemblance of the combination to a single harmonic series [3,4].

Acoustic vibrations are transduced into neural impulses in the cochlea. Running along the length of the cochlear spiral is the basilar membrane. Different places on the basilar membrane are tuned to different frequencies, and in this way the ear separates out the different frequency components of sounds. This allows us to identify sounds on the basis of their spectra, and to segregate sounds from

different sources. However, the frequency resolution is not perfect, and sounds with similar frequencies will produce patterns of excitation that overlap (Figure 1B). Two closely spaced frequency components interact on the basilar membrane to produce a ‘beating’ pattern, characterized by amplitude fluctuations at a rate equal to the frequency difference between the components. This leads to the unpleasant sensation of ‘roughness’. Because dissonant chords often contain harmonics that are closely spaced, it has been suggested that dissonance is related to the degree of beating between the harmonics [5].

The Basis of Consonance

Distinguishing between these two hypotheses is difficult, because inharmonic series tend to produce beats, and combinations of notes that produce beats tend to be inharmonic. The ingenious approach of McDermott *et al.* [2] was to use individual differences in preference ratings for beats and harmonicity using non-musical sounds to determine which factor correlates with the preference for consonance. The authors found that the measure of beating preference did not correlate well with the preference ratings for consonant and dissonant musical chords. In other words, individuals who found beating particularly unpleasant did not show an unusual dislike of dissonant intervals. In contrast, the measures of preference for harmonicity correlated well with the consonance