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NEUROSCIENCE:

Love hangover

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Abstract

In many species, males have developed strategies to safeguard their genetic material from dilution by that of competing males. Fruitflies achieve this by altering the behaviour of their partners.

Sex can be transformative. Humans often romanticize the after-effects of copulation, but for most organisms there are real biological consequences to mating that go beyond the transfer of sperm. Most species have strategies for protecting their genetic investment that can involve alterations in both the biology and behaviour of the mating partners. For example, in the fruitfly *Drosophila melanogaster* a component of seminal fluid, known as sex peptide, leads to increased egg-laying by the mated female and behavioural changes that reduce the likelihood of her re-mating. How sex peptide triggers such a complex array of effects was unknown. On page 33 of this issue, Yapici *et al.*¹ identify the receptor for sex peptide and show that it is expressed in the reproductive tract and in a subset of female neurons believed to be involved in sexual behaviour.

Enhancing the survival of potential progeny is a common goal of males in many species. In mammals, intercourse changes the immunological environment of the female reproductive tract, increasing the probability of successful fertilization and implantation². This type of post-copulatory effect benefits both the male and female partner. For many species there are also other mating-associated events that apparently maximize the reproductive success of just one of the involved parties, often at the expense of the other. An obvious example of this is mate guarding. Males of many avian, reptile, rodent, primate and insect species remain close to a recent conquest to lower the probability of her re-mating with a more desirable male and so diluting or displacing their own sperm. The female may benefit in terms of decreased predation, but she loses any opportunity to better the genetic lot of her offspring. The success of this strategy for the male depends on his vigilance, and potentially decreases his chances of mating with other females, so is not without cost.

Nature has also come up with more subtle forms of mate guarding. In snakes³ and various insect species^{4–6}, mating can lead to changes in the female pheromone profile that decrease the attractiveness of mated females to subsequent suitors. Females' behaviour can also be modulated by mating. In rodents, exposure to dominant-male pheromones induces a female preference for dominant versus subordinate males that may involve introduction of new neurons into neural circuits⁷. Similarly, female jewel wasps change their response to male sex pheromones from attraction to aversion after mating⁸, and in *D. melanogaster* mated females will actively reject courtship, kicking and running away from a new male⁹. This type of 'mate guarding' does not require the continued presence of the successful male, maximizing his ability to mate with other females while still protecting his DNA investment. Many of these after-effects are generated by chemicals produced by the male and transferred to the female in his ejaculate.

The best-understood example of a behaviourally active seminal-fluid component is sex peptide in *D. melanogaster*⁹. It is produced in the male accessory gland, a prostate-like structure, and is absorbed into the female circulation from the vaginal tract. Behaviours resulting from sex-peptide absorption include increased egg-laying and reduced receptivity to male courtship. Previous studies indicated that there are binding sites for sex peptide in the brain⁹, but the nature of the receptor or receptors was unknown.

To identify the receptor, Yapici *et al.*¹ carried out an RNA-interference-based genome-wide screen for genes required in females for post-copulatory behaviours; they reasoned that genes whose reduced expression blocked mating-induced increases in egg-laying would be candidates. This approach identified a gene for a putative G-protein-coupled receptor. Reducing the expression of this gene did not affect the receptivity of virgin females or sperm storage in mated females, but it completely prevented the development of post-copulatory behaviours in either mated females or virgin females injected with sex peptide.

To determine whether their candidate gene was a bona fide sex-peptide receptor (SPR), the authors expressed it in mammalian cells maintained in culture. They found that sex peptide and DUP99B — a seminal-fluid component that can also mediate the switch to mated-female behaviour — activate SPR with nanomolar affinity. Other *Drosophila* neuroactive peptides whose receptors are closely related by sequence to SPR did not activate it. SPR homologues from other drosophilids, *Bombyx mori* and *Aedes aegypti*, also responded robustly to sex peptide and DUP99B, indicating that SPR is not unique to *D. melanogaster*.

The distribution of SPR provides some clues to how it might effect behavioural changes. The authors demonstrate that SPR is present both in the reproductive organs of the female and on the plasma membranes of neurons close to the surface of the central nervous system. Previous work by this group¹⁰ has suggested that *Drosophila* neurons that express a putative transcription factor encoded by the *fruitless* gene are required for suppressing mated-female-like rejection behaviours. Yapici *et al.* now find that a subset of these neurons also express SPR, implying that sex peptide modulates these neurons. They used RNA interference to decrease SPR expression in *fruitless*-expressing cells, and overexpressed SPR in mutant flies that could not express it, to demonstrate that expression of SPR in this subset of cells is both necessary and sufficient for the development of post-copulatory behaviour.

For students of neurobehaviour, the most interesting finding of Yapici and colleagues' study is that, in SPR, they now have another specific molecular tag for cells involved in an intriguing and 'plastic' behaviour, allowing them to perform a complete analysis of this behavioural circuit. The more global impact of the work, however, is that it provides a new target for the development of insect-control compounds. That SPR-like receptors exist in most sequenced insect genomes suggests that antagonists of this receptor could be used to reduce insect populations by blocking egg maturation and extrusion, or perhaps SPR agonists could be used to make virgin females reject mating. Although the irony of having their own weapon turned on them will doubtless be lost on the male insects, it is a satisfying and potentially specific approach.

Another question raised by this work is: how widespread is this type of 'mating-induced mind control'? At least one species of vertebrate, the red-sided garter snake, demonstrates mating-induced reductions in female receptivity³. Obvious homologues of sex peptide and SPR have not been identified in vertebrates, but this is not surprising given that genes involved in reproduction have a very fast rate of evolution — precisely because they are involved in reproductive behaviour — and this variation promotes the differentiation of species¹¹. Although sequence mining has not found much homology along the phylogenetic tree, using more subtle algorithms to analyse protein structure and function indicates that there are fairly

striking similarities between components of *Drosophila* and vertebrate seminal fluid¹². Perhaps there is yet another reason to use a condom, ladies.

References

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After mating, male fruitflies don't have to stand by and guard their transferred genetic material — sex peptide in their semen will do the job.

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