

Glucose aversion: a behavioral resistance mechanism in the German cockroach

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The German cockroach is a valuable model for research on indoor pest management strategies and for understanding mechanisms of adaptive evolution under intense anthropogenic selection. Under the selection pressure of toxic baits, populations of the German cockroach have evolved a variety of physiological and behavioral resistance mechanisms. In this review, we focus on glucose aversion, an adaptive trait that underlies a behavioral resistance to baits. Taste polymorphism, a change in taste quality of glucose from sweet to bitter, causes cockroaches to avoid glucose-containing baits. We summarize recent findings, including the contribution of glucose aversion to olfactory learning-based avoidance of baits, aversion to other sugars, and assortative mating under sexual selection, which underscores the behavioral phenotype to all oligosaccharides that contain glucose. It is a remarkable example of how anthropogenic selection drove the evolution of an altered gustatory trait that reshapes the foraging ecology and sexual communication.

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Introduction

Anthropogenic selection, particularly with insecticides, can lead to rapid evolution of adaptive responses in pest populations [1–3]. The German cockroach, *Blattella germanica*, has a global distribution, but is obligately associated with human-built structures [4]. It has served as an excellent model to understand the arms-race with humans, which includes recurrent rounds of innovative

pest control tactics and the rapid emergence of adaptive traits that counteract the new tactics [5]. In the past century, many types of mechanical, physical, chemical, and biological control tactics have been implemented to suppress German cockroach populations. Insecticide-containing baits are formulated by combining non-deterrent active ingredients (AIs) (e.g. abamectin, boric acid, clothianidin, dinotefuran, emamectin benzoate, fipronil, imidacloprid, indoxacarb, and thiamethoxam) with phagostimulants, which are typically common sugars that stimulate the sweet taste modality in animals [6,7]. The use of homemade generic insecticide baits (prepared by mixing peanut butter, jelly, and other phagostimulatory food items including sugars) dates back to the 18th century. However, the commercial insecticide baits that were introduced in the mid-1980s transformed German cockroach control because they were highly effective, easy to apply, and readily available to both pest professionals and consumers. Because all nymphal stages of the cockroach must feed to develop and grow, and adults must feed to reproduce, the AIs in palatable baits are readily bioavailable, making baits highly effective insecticide formulations.

However, under persistent selection with baits, their performance can be compromised through the emergence of physiological and behavioral resistance [8••–11••]. Physiological resistance is common and has been reported to > 40 AIs, usually within just a few years of their commercial use [12,13]. A most interesting resistance was found in a cockroach population collected in Florida in 1989 that behaviorally shunned toxic baits; these field-collected cockroaches rejected glucose, a nutrient sugar in baits that served to stimulate bait acceptance and ingestion [8••]. Subsequently, glucose-averse (GA) cockroaches have been found in multiple field populations in the United States and other countries [9••,10••,14••,15••]. The latest survey [15••] indicated that 37% of the 19 tested field populations contained GA cockroaches with a variable frequency in each population of GA individuals relative to glucose-accepting cockroaches, ranging from 0.5% in a Moscow strain to 30% in a Puerto Rico strain. The origins of glucose aversion are not known. Silverman and Ross [14••] speculated that glucose aversion may have evolved in ancestral lineages of the German cockroach under ecological selection imposed by allelochemicals such as glucosinolates or cyanogenic glycosides, which contain glucose. At the same time, however, these

researchers showed a clear correlation between a history of treatments with toxic baits and bait avoidance, which was not evident in field strains with no history of prior exposure to baits. Overall, these limited surveys suggest that regardless of its evolutionary origin, the glucose aversion trait is being selected independently in multiple isolated populations by different levels of selection pressures with toxic baits. Since baits have been broadly adopted by the pest management industry and cockroach populations have been persistently exposed to toxic baits for nearly four decades, a contemporary global assessment is needed of the distribution and frequency of sugar-averse cockroach populations.

The glucose aversion trait is heritable and appears to be controlled by a single major gene that follows Mendelian inheritance patterns [8••]. All offspring from a cross of homozygous wild-type (WT, laboratory strain) and homozygous GA cockroaches avoid glucose. Crosses of these F1 offspring produce 75% GA and 25% WT progeny [16•,17]. The F2 GA offspring consist of 50% heterozygous GA and 25% homozygous GA cockroaches, and the latter exhibit 10-fold greater glucose deterrence than the heterozygous GA cockroaches [16•]. Injection of glucose into the hemocoel did not affect the physiology or behavior, including the feeding preference for glucose in WT cockroaches and deterrence in GA cockroaches, suggesting that glucose aversion requires processing of glucose through the chemosensory system [18•].

The glucose aversion trait renders all glucose-containing baits ineffective against GA cockroaches [19•] (Figure 1a), compelling bait manufacturers to reformulate bait products at considerable cost. However, soon after the discovery of GA cockroaches, researchers noticed behavioral aversions to other sugars in field-collected cockroaches [9••,10••].

Here, we review the mechanisms that underlie glucose aversion. We then discuss four processes that extend the glucose aversion phenotype well beyond the direct interaction of cockroaches with glucose-containing insecticide baits. First, olfactory learning during foraging can trigger avoidance before the cockroach even tastes the bait, extending the glucose aversion phenotype to baits that do not contain glucose. Second, salivary enzymes extend glucose aversion to oligosaccharides that contain glucose. Third, glucose aversion reduces the horizontal transfer of baits and coprophagy-mediated secondary kill, thus selecting for physiological resistance to insecticides. Finally, glucose aversion creates a mismatch between the male's sugary nuptial gift and the female's gustatory preferences, which interferes with courtship behavior and places the glucose aversion trait under sexual selection. Overall, glucose aversion is an outstanding example of how a single altered gustatory

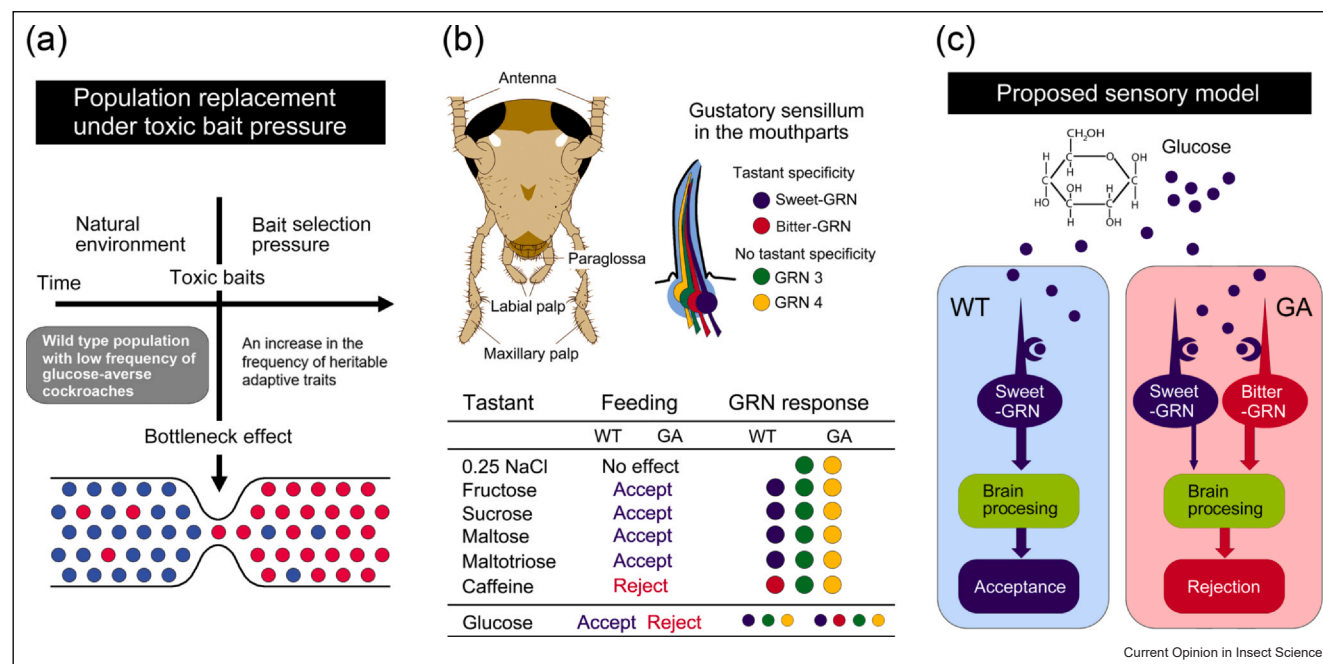
trait that evolved under anthropogenic selection shapes the foraging ecology, sexual communication, and population structure of insects.

Mechanisms of glucose aversion

Taste recognition of nutrients and noxious substances in food is essential for the survival of animals, including cockroaches. As in humans, the peripheral gustatory system of insects is mainly localized in the mouthparts. *Drosophila melanogaster* has been extensively investigated as a model system of gustation: it has two or four different gustatory receptor neurons (GRNs) housed within hair-like cuticle-lined sensilla with a pore at the tip [20]. Each GRN expresses a specific taste modality and is thus denoted sweet-, bitter-, water-, or salt-GRN. The axons of GRNs with the same modal specificity (taste quality) project directly to the same region in the central nervous system (brain). Quality, strength, and duration of stimuli are represented as neuronal impulses by GRNs [21,22]. The sweet-GRNs mediate appetitive behavior via central nervous system processing, and the responses of bitter-GRNs mediate rejection behavior because bitter compounds often denote toxins. Thus, modifications in tastant discrimination by GRNs, which represent the peripheral first stage in gustatory information processing, can critically impact the expression of gustatory behavior [23].

As in *Drosophila*, each sensillum on the mouthparts of the German cockroach contains at least four types of GRNs [15••,18•,24•] (Figure 1b). Two of them show ligand specificity and are denoted sweet-GRN and bitter-GRN. In WT cockroaches, positive correlations are observed among feeding responses, GRN chemosensation, and the concentration of tastants, suggesting that activation of the sweet-GRNs mediates appetitive feeding responses to nutrient sugars such as glucose and fructose. Bitter-GRNs mediate aversive feeding responses to noxious substances such as caffeine [15••]. Comparative electrophysiological analyses using homozygous WT, homozygous GA [8••], backcrosses of WT and GA, and two field-collected GA populations revealed that a polymorphism in GRN sensitivity drives glucose aversion [15••]. In both WT and GA cockroaches, phagostimulants (e.g. fructose, sucrose, maltose, trehalose, and maltotriose) stimulate sweet-GRNs, guiding acceptance of the sweet tastant, whereas deterrents (e.g. caffeine) stimulate bitter-GRNs and rejection of the bitter tastant. Although glucose is detected only by sweet-GRNs in WT cockroaches, the bitter-GRNs of GA cockroaches respond to glucose in a concentration-dependent manner and the electrophysiological responses of the sweet-GRNs to glucose are attenuated in GA cockroaches. The responses of bitter-GRNs correspond to aversive behavior. These results suggest that in GA cockroaches, the bitter-GRNs acquired sensitivity to glucose, and this change is responsible for glucose-driven aversions (Figure 1c).

Figure 1



Population dynamics of glucose aversion, and sensillar mechanisms that underlie this behavior. **(a)** Model of population replacement from WT to GA cockroaches after exposure to glucose-containing toxic bait. GA cockroaches replace WT cockroaches in the presence of glucose-containing insecticide baits. **(b)** Gustatory neural mechanism of glucose aversion. Top, Head of male German cockroach showing the four sensory appendages (antennae, maxillary palps, labial palps, and paraglossae) and schematic of a sensillum containing four GRNs. Bottom, Summary of behavioral and GRN sensitivities of WT and GA cockroaches to sugars and caffeine. Bitter-GRNs of GA cockroaches respond to glucose, whereas in WT cockroaches, the bitter-GRNs never respond to glucose. **(c)** Mechanism of glucose aversion. Sweet-GRNs detect glucose in WT cockroaches, resulting in its acceptance. However, in GA cockroaches, both sweet- and bitter-GRNs detect glucose. Additionally, the response of the bitter-GRNs to glucose is stronger than that of the sweet-GRNs, resulting in brain processing of misinformation and rejection of glucose. The glucose-binding site in the bitter-GRN is unknown.

The taste modality of GRNs is characterized by not only the projection pattern of axons to the brain but also the expression pattern of tastant-binding receptors in the GRNs. For example, *Drosophila* sweet-GRNs and bitter-GRNs express different types of multiple gustatory receptors (GRs) to detect nutrient sugars and aversive tastants, respectively. Subsets of GRs in bitter-GRNs never overlap with GRs expressed in sweet-GRNs. Although both sugar and bitter receptors are thought to be composed of multimeric GRs, the structure and ligand-binding specificity of multimeric GRs are not well-understood [25–27]. Genomic and bioinformatic analyses of GR organization in Diptera [28–31], Coleoptera [32], Lepidoptera [33], and Hymenoptera [34] suggest a positive correlation between the complexity of the insects' chemical ecology and the size of their chemosensory gene repertoire [35••]. The German cockroach is an extreme omnivore and its genome encodes 545 putatively functional GRs, the largest known for insects [35••,36]. Most of these GRs fall into the general clades of bitter receptors that detect bitter tastants, but BgerGr1–BgerGr14 and BgerGr431 have been identified by sequence homology as sugar-GRs. Although GRN response to tastants could also be supported by other

chemosensory proteins, such as ionotropic receptors, pickpocket ion channels, transient receptor potential ion channels, and odorant-binding proteins, functional analysis of the candidate sugar-GRs will be a first step toward understanding the molecular mechanisms of glucose aversion.

We discuss four processes that extend glucose aversion beyond the interaction of cockroaches with glucose, including (1) olfactory learning, (2) salivary digestion of oligosaccharides, (3) horizontal transfer and coprophagy-mediated secondary kill, and (4) courtship, sexual selection, and transmission of the glucose aversion trait (Figure 2 a)

Beyond glucose aversion: 1. Olfactory learning extends the glucose aversion phenotype

Associative learning can modulate innate odor preferences based on the memory of specific odors associated with appetitive or aversive tastes; this behavioral plasticity couples foraging strategy to local conditions, which increases foraging efficiency [37••]. In the operant conditioning paradigm using the complex food odors of chocolate and vanilla, WT cockroaches learn to associate

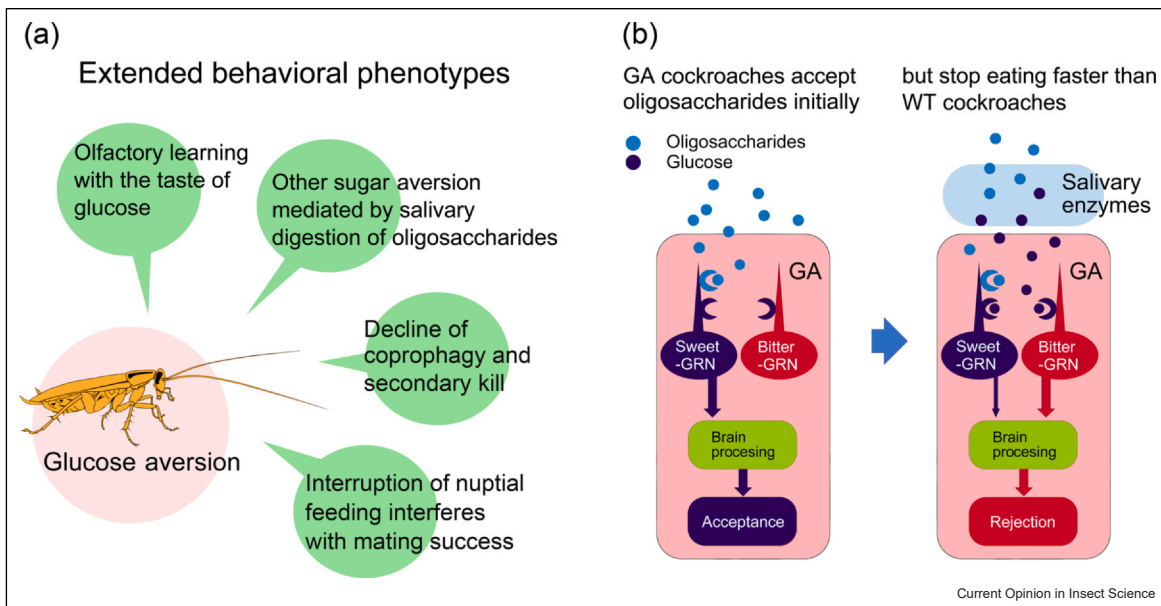
these food odors with fructose and glucose (sweet taste, reward) by <1 hour of training to enhance their odor preference. The association of these odors with caffeine (bitter taste, punishment) during three 1-hour training sessions causes a decline in preference of these odors. In GA cockroaches, odor preference was enhanced by training with fructose (reward) but declined by training with caffeine (punishment), as in WT cockroaches. However, GA cockroaches learn to avoid an innately attractive odor when it is associated with glucose. This olfactory memory is retained for at least 3 days. These results indicate that GA cockroaches can associate bait odors with punishment from glucose in the bait and learn to avoid the bait. After olfactory learning, GA cockroaches may generalize their olfactory learning to baits that contain the same or similar attractive odors even if they do not contain glucose. Associative olfactory learning can thus extend the aversion phenotype to various baits without even requiring that the cockroach tastes the bait, resulting in broader behavioral resistance (Figure 2a).

Beyond glucose aversion: 2. Salivary enzymes extend the glucose aversion phenotype to other sugars

The saliva of animals contains enzymes that digest food components, potentially transforming the quality and taste of foods, and consequently altering feeding behavior,

including in humans [38,39]. Feeding behavior of the German cockroach is highly stimulated by mono- and oligosaccharides, resulting in their acceptance and the initiation of feeding [40]. As they ingest a sugar solution, salivary alpha-glucosidases hydrolyze oligosaccharides such as sucrose and maltose and release greater molar ratios of glucose (Figure 2b). Because the released glucose stimulates sweet-GRNs, WT cockroaches continue to ingest the sugars until they are satiated. GA cockroaches also initially accept all sugars (except glucose) because only sweet-GRNs respond to sugars. However, as salivary enzymes hydrolyze the oligosaccharides, the released glucose stimulates bitter-GRNs, causing the GA cockroach to cease feeding on the oligosaccharides. Fructose is not detected by the bitter-GRNs of both WT and GA cockroaches and there is no difference in its consumption by WT and GA cockroaches. The glucose aversion trait protects cockroaches from glucose-containing insecticide baits by causing the cockroaches to reject the bait before they ingest it. As bait formulations get modified with more complex sugars to overcome glucose aversion, the degradation of oligosaccharides by salivary enzymes decreases the suitability of these sugars and thus extends the impact of the glucose aversion trait to a broad array of sugars. Therefore, salivary enzymes extend the glucose aversion phenotype without altering the underlying molecular mechanism of glucose aversion.

Figure 2



Behavioral and physiological mechanisms extend the glucose aversion phenotype. (a) Extended behavioral phenotypes in GA cockroaches. The glucose aversion genotype impacts not only acceptance or rejection of glucose, but also (1) rejection of baits that do not contain sugars or insecticides based on olfactory associative learning, (2) rejection of other sugars that contain glucose, (3) decline in coprophagy that would impact the efficacy of secondary kill, and (4) interruption of courtship because of the mismatch between female gustatory preferences and the male’s sugary nuptial gift. (b) Oligosaccharide taste perception through GRNs in GA cockroaches. GA cockroaches initially accept oligosaccharide solutions because only the sweet-GRNs are stimulated, and the sugar is accepted. However, while drinking the sugar solution, salivary enzymes such as alpha-glucosidases hydrolyze the oligosaccharides, releasing glucose. Consequently, the bitter-GRNs start responding to glucose, resulting in shorter feeding than by WT cockroaches, and rejection of the oligosaccharide solution.

It has been reported that field-collected cockroaches show aversions to other sugars, including sucrose and maltose ([9••,10••], Wada-Katsumata unpublished). Although multiple mechanisms might underlie aversions for various sugars in cockroaches, a parsimonious explanation for oligosaccharide aversion is that genetic changes in peripheral sensilla generate aversions to glucose, and salivary digestion of oligosaccharides releases glucose that stimulates bitter-GRNs of GA cockroaches. This mechanism would result in small amounts of oligosaccharide-containing toxic bait being consumed, and the small amounts of AI ingested may select for physiological resistance in the population. Aversion to fructose requires a molecular mechanism distinct from GA. This mechanism is under investigation in our lab.

Beyond glucose aversion: 3. Glucose aversion deters coprophagy and interferes with secondary kill

An advantage to the use of toxic baits in pest control is the lateral transfer of bait and AI within aggregations. AIs are translocated in cockroach residues such as feces and dead bodies within and near the cockroach aggregation, affecting early-instar nymphs that are relatively sedentary in aggregation sites and readily engage in coprophagy. Thus, insecticide residues excreted by cockroaches that ingested commercial baits effectively kill nymphs of the laboratory WT strain. However, secondary kill is less effective in field-collected German cockroaches exposed to baits containing hydramethylnon, fipronil, or indoxacarb because of varying levels of physiological resistance to the AIs [41]. Similar to what is observed with insecticide resistance, glucose aversion is a heritable trait that leads to reduced secondary kill [42••]. Ingestion of insecticide baits that contain glucose or disaccharides such as sucrose results in behaviorally relevant glucose levels in the feces. When feces from WT adult female cockroaches that ingested hydramethylnon baits rich in glucose, fructose, sucrose, or maltose were given to WT nymphs, they engaged in coprophagy and showed high mortality. However, GA nymphs rejected the feces of WT females that fed on glucose-containing bait because the feces contained glucose. Additionally, in the sucrose or maltose bait treatments, the disaccharides were hydrolyzed into glucose and excreted in feces. GA nymphs avoided eating these feces and only accepted the feces of females that fed on fructose bait, which did not contain any glucose; they experienced high secondary mortality.

Beyond glucose aversion: 4. Assortative mating promotes transmission of the glucose aversion trait

During courtship, the male cockroach attracts females to his highly palatable tergal gland secretion that serves as a nuptial gift, placing the female in the proper position for

copulation. However, the female must mount the male and feed on the nuptial secretion long enough for the male to extend his abdomen under the female and engage her genitalia [7]. Short nuptial feeding results in interrupted courtship and failure to mate. Thus, mating success is maximized by the convergence of the quality of the male's nuptial gift and the female's gustatory sensitivity to it. Glucose aversion is adaptive in a foraging context when glucose is coupled with an insecticide. However, GA females also reject the glucose- and maltose-rich nuptial gift of WT males, because maltose is quickly hydrolyzed by salivary enzymes into glucose that tastes bitter [43••]. Both glucose and maltose cause GA females to interrupt their nuptial feeding, resulting in lower mating success with WT males. Two-choice mating assays confirmed that GA females experienced lower mating success with WT males than with GA males. In no-choice mating assays, WT females paired with either WT male or GA male had >70% mating success, whereas GA females paired with WT male had around 50% mating success and >60% mating success when paired with a GA male. We found that GA males have adjusted the quality of their nuptial secretion to better match the GA female's taste preferences. The nuptial gift of GA males contains less glucose and maltose and more maltotriose than the secretion of WT males. Maltotriose is more resilient to salivary glucosidases than maltose [44••]. Thus, anthropogenic selection resulted in the emergence of glucose aversion, but GA males have evolved emergent traits that overcome their disadvantage under sexual selection.

Sex-biased dispersal of genes is influenced by various factors, including the mating system, sex ratio, costs of dispersal, local competition for mates and resources, inbreeding avoidance, habitat persistence, and dispersal timing. The German cockroach represents a polygynous mating system. The male-biased operational sex ratio may lead to male-biased migration of both WT and GA individuals. This male-biased gene dispersal system may enhance the transmission of the glucose aversion trait within and between populations, potentially causing the replacement of WT genotypes by GA genotypes. Concurrently, gene flow between WT males and emergent GA populations may be thwarted by the assortative mating of GA females. This hypothesis needs to be tested with gene flow simulations, empirical phenotyping, and use of molecular markers in field studies.

Conclusions

Glucose aversion is expressed as a reversal in the modal quality of glucose from sweet and appetitive to bitter and aversive. This gain-of-function change results from a modification of the peripheral gustatory system wherein glucose stimulates not only sweet-GRNs, but also bitter-GRNs. At present, the molecular mechanisms that

confer behavioral resistance in pest insects have not been delineated, in part due to limited genetic and genomic resources in nonmodel species. However, recent progress in genome sequencing, annotation of chemosensory gene families, and RNAi techniques should enable a deeper understanding of the molecular mechanisms of taste polymorphisms that affect food preference in German cockroaches under various selection pressures.

In this review, we highlighted how glucose aversion can profoundly affect food choice and bait acceptance. Additionally, this trait affects other traits that are under sexual selection, resulting in changes in sexual communication and mate choice and impacting gene flow of the glucose aversion trait (Figure 2b). To preserve the effectiveness of baits in indoor cockroach control, it is imperative that we consider not only physiological mechanisms of insecticide resistance and cross-resistance but also altered chemoreception traits that confer behavioral resistance, which in turn can affect a broad array of behaviors that affect foraging and sexual communication.

The origin of glucose aversion is unknown, and it is also unclear how it emerges and is maintained in various field populations. When no insecticide baits are deployed, this trait is maladaptive and probably maintained in heterozygotes as a low-frequency gustatory polymorphism. However, under the strong anthropogenic selection of glucose- or oligosaccharide-containing insecticide baits, this trait becomes highly adaptive. Nevertheless, it is unknown whether glucose aversion can reach homozygosity in field populations under typical selection pressure in residential and commercial environments. It is also unknown if the ramifications of glucose aversion on horizontal transfer of AI, mating behavior, and aversion to oligosaccharides that we observed under artificial selection in the laboratory will be found in field populations. To inform ecologically sound pest management, it is imperative to conduct comprehensive behavioral screens of global field populations to understand the evolution and spread of physiological and behavioral resistance in the German cockroach.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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This paper confirmed that GA cockroaches rejected glucose, but they accepted oligosaccharides, as shown in previous studies. However, whereas WT cockroaches that accepted glucose also satiated on oligosaccharides, GA cockroaches ceased ingesting the oligosaccharides within seconds, resulting in significantly lower consumption. Authors found that salivary enzymes hydrolyzed oligosaccharides, releasing glucose, which terminated feeding.

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Bait formulations are considered to be the most effective method for reducing German cockroach infestations. An important property of some bait formulations is secondary kill, whereby AI is translocated in

insect-produced residues throughout the cockroach population, especially affecting relatively sedentary early-instar nymphs. However, ingestion of insecticide baits that contain glucose or glucose-containing disaccharides resulted in behaviorally relevant glucose levels in the feces, deterring coprophagy by GA nymphs.

43. Wada-Katsumata A, Hatano E, McPherson S, Silverman J, Schal C: **Rapid evolution of an adaptive taste polymorphism disrupts courtship behavior.** *Commun Biol* 2022, **5**:450, <https://doi.org/10.1038/s42003-022-03415-8>.

Sugars are prominent components of the male's nuptial gift and play an essential role in courtship. Authors revealed that the saliva of GA females rapidly degrades nuptial gift sugars into glucose, and the inversion of a tasty nuptial gift to an aversive stimulus often causes GA females to reject courting males.

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During courtship, the German cockroach male offers the female a nuptial gift that contains maltose, which expedites copulation. However, the female's saliva rapidly hydrolyzes maltose into glucose, which causes GA females to dismount the courting male, thus reducing their mating success. However, the authors revealed two adaptive traits in GA males. They produce more maltotriose, which is more resilient to salivary glucosidases, and they initiate copulation faster than WT males before GA females interrupt their nuptial feeding and dismount the males.