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CONCEPTS & THEORY

Is doping of cognitive performance an anti-herbivore adaptation? Alkaloids inhibiting acetylcholinesterase as a case

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Abstract. Historically, people who study interactions between plants and herbivores focused on the ecological costs and benefits of synthesizing secondary metabolites. These compounds have diverse functions including defenses against herbivores. Some plants produce alkaloids that act as acetylcholinesterase inhibitors, increasing both the level and duration of action of the neurotransmitter acetylcholine with potential toxic effects in insects and mammals. Yet, among a number of neuroactive plant chemicals, alkaloids that inhibit acetylcholinesterase (AIA) display nootropic activities, that is, positively affect cognition, learning, and memory in mammals. This creates a paradox: Neuroactive AIA, expected to punish herbivores, enhance cognition, learning, and memory. A prevailing view is AIA are pesticides that adversely affecting the nervous systems of herbivorous insects, and the positive influences in mammals are merely a by-product of other functions. We review literature on the behavioral ecology of diet choice, food-aversion learning, and neurophysiological actions of AIA in mammals to provide a more comprehensive view of the adaptive significance of AIA. These compounds act as anti-herbivory defenses that influence flavor (taste plus odor) preference/aversion, the formation of memories, and the feeding behavior of mammalian herbivores. Thus, what appears from an insect standpoint to be an enigma makes sense for mammals: AIA enable mammalian herbivores to quickly learn and remember specific plant(s) and the locations where they ate those plant(s). We provide examples of AIA, synthesized by over 200 plant species in 16 families, which affect learning and memory in mammals. Using 36 examples of acetylcholinesterase inhibitors synthesized by plants in 58 families, we also show that acetylcholinesterase blockers contribute to anti-herbivore chemical defense by affecting food-aversion learning and memory in mammalian herbivores. We provide an evolutionary rationale for why natural selection may favor synthesis of chemicals that positively affect mental functions of herbivores. Our hypothesis, which challenges the current view that plant chemical defenses are aimed solely at destabilizing herbivore physiology, facilitates a broader understanding of diet preferences and feeding behavior in mammalian herbivores.

Key words: acetylcholinesterase inhibitors; alkaloids; anti-herbivory chemical defense; aversion; cognition and memory; diet choice; feeding behavior; learning; nootropics; plant secondary metabolites; plant-herbivore interactions; taste.

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Introduction

The arms-race between plants and herbivores has contributed to the enormous diversity of plant secondary metabolites with a variety of functions (Foley and Moore 2005, McCall and Fordyce 2010). Alkaloids are a diverse and costly class of defensive chemicals. Their synthesis can reduce plant growth rate and competitive ability, but enhance plant survival in the presence of herbivores (Coley et al. 1985, Vrieling and Vanwijk 1994, Strauss et al. 2002). Here, we focus on neuroactive alkaloids that affect behavior of mammalian herbivores by inhibiting acetylcholinesterase (AChE), a key enzyme that catalyzes the breakdown of the neurotransmitter acetylcholine (Fig. 1; Wink 2000). Alkaloids that inhibit acetylcholinesterase (AIA) slow the breakdown of acetylcholine and boost cholinergic neurotransmission. In high doses, these compounds can disrupt neuronal signaling and cause toxicity. Intriguingly, at lower doses AIA display nootropic activity, positively affecting cognition, learning, and memory in mammals (Houghton et al. 2006, Murray et al. 2013). Indeed, AIA have become valuable medicines targeting Alzheimer's diseases, schizophrenia, and other mental illnesses (Oh et al. 2004, Houghton and Howes 2005, Adsersen et al. 2006, Houghton et al. 2006, Williams et al. 2011). Galantamine (nivalin, razadyne, reminyl), which boosts cholinergic neurotransmission with only mild adverse effects at low doses, is used to enhance cognitive performance in people with Alzheimer's disease and dementia (Heinrich and Teoh 2004). These dual roles create a paradox: Neuroactive AIA, expected to punish herbivores, beneficially affect cognition, learning, and memory in mammals.

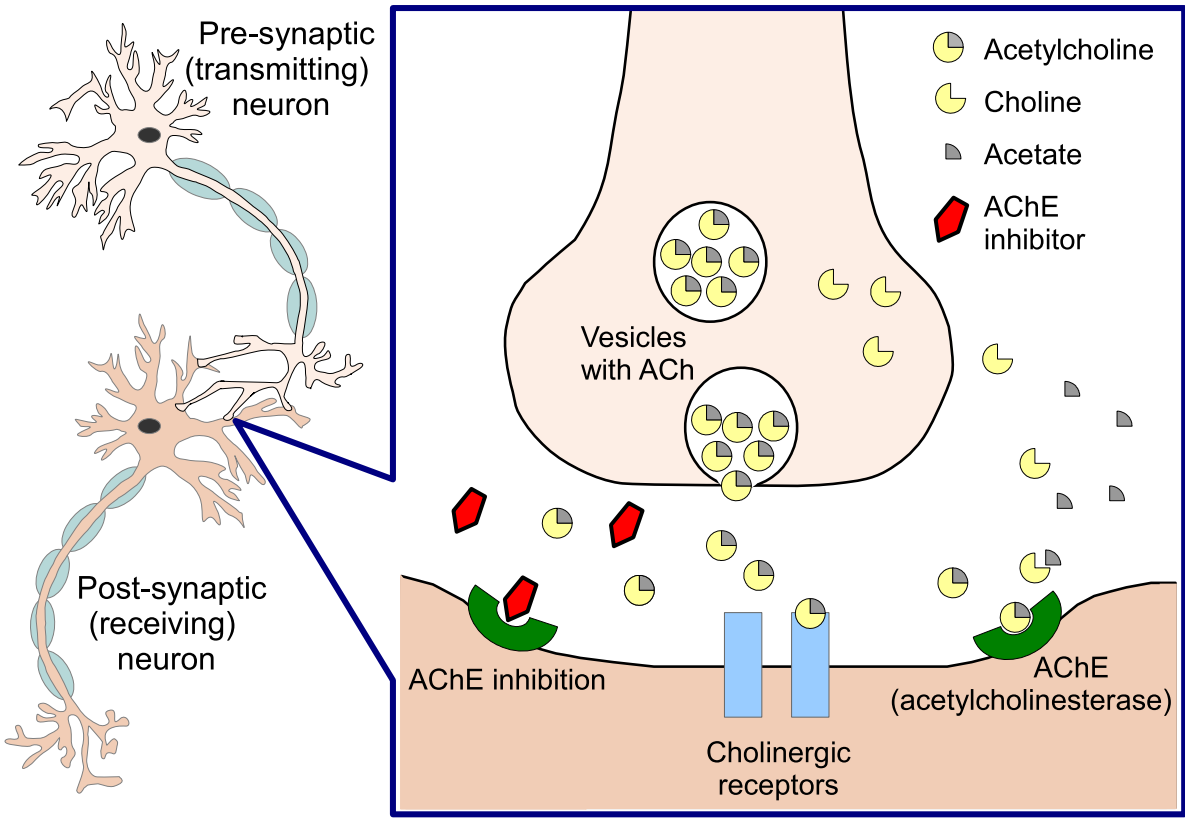

Fig. 1. Schematic representation of cholinergic neurotransmission mediated by the neurotransmitter acetylcholine and boosted by reversible inhibitors of acetylcholinesterase (AChE). Alkaloids that inhibit acetylcholinesterase enhance the cholinergic neurotransmission by preventing the acetylcholine breakdown by AChE.

In this paper, we present an ecological context and evolutionary rationale for why natural selection can favor synthesis of AIA that positively affect mental functions of mammalian herbivores. Our hypothesis is that the beneficial effects exerted by AIA on cognitive performance, learning, and memory are not a by-product of low-dose consumption. Rather, they are selected for as an anti-herbivory adaptation that can alter foraging behavior in mammalian herbivores. The prevailing view is that nootropic activity of AIA in mammals arises as a by-product of low-dose consumption: AIA are toxic to insects (Rattan 2010), and only coincidentally enhance memory when consumed in low doses by mammals (Houghton et al. 2006). Importantly, our hypothesis does not preclude the negative impacts of AIA on insects, but rather is a complementary view on the synthesis of AIA and their roles as anti-herbivore defenses of plants. Phytochemicals display manifold ecological roles, and the evolution of their synthesis is undoubtedly driven by multiple evolutionary advantages (Iason 2005).

Basic neurological mechanisms are highly conserved in various animal taxa, and a pesticide that destabilizes neural signaling in insects is also likely to be poisonous for mammals at high doses. While AIA produced by plants are used in the synthesis of new insecticides, they have not been used as insecticides per se (Houghton et al. 2006). That is because several properties of AIA significantly decrease their effectiveness as insecticides and paralyzing neurotoxins and make them well-tolerated and efficient enhancers of cognition, learning, and memory at low doses in mammals (Houghton et al. 2006). Many AIA modestly boost cholinergic neurotransmission and are rapidly reversible inhibitors of AChE. Hence, they are well tolerated by mammals in contrast to highly efficacious synthetic AChE blockers. Carbamate pesticides reversibly block AChE, with inactivation times up to dozens of minutes, whereas deadly poisonous organophosphates inactivate AChE irreversibly (Colovic et al. 2013). The trade-off between toxicity and tolerability of AChE inhibitors is also illustrated by the fact that AIA like galantamine can prevent lethality after exposure to organophosphate insecticides (Albuquerquet et al. 2006). AIA can cross the blood–brain barrier and boost neurotransmission in the central nervous system or display dual actions by altering signaling pathways. AIA, especially those considered promising candidates for treatment of neurological dysfunctions, display higher affinity for AChE than butyrylcholinesterase, a nonspecific esterase of acetylcholine found primarily in liver (Houghton and Howes 2005). In contrast, AChE is a key enzyme in neural signaling in the central nervous system.

In this paper, we merge knowledge of the neurophysiological actions of AIA and diet choice in mammalian herbivores within an ecological context to present evidence for our hypothesis on the nootropic properties of AIA. We first introduce the alkaloid galantamine, used as a medicine, to discuss neurophysiological action of AIA. Next, we explain how feeding behavior and diet selection are affected by the AIA in the context of neurophysiological processes underlying food learning. Third, we provide the ecological context and evolutionary rationale supporting our hypothesis. Finally, we provide an overview of different classes of plant-derived chemicals that inhibit AChE and enhance memory and learning as a way to discuss their role in plant chemical defense against mammalian herbivores.

AIA Boost Cholinergic Neurotransmission

Alkaloids that inhibit AChE are synthesized by a variety of plant species (Wink 2000). In Table 1, we provide 16 examples of AIA that affect cognition in mammals. The intensively studied alkaloid galantamine, used to treat mental dysfunctions, illustrates points regarding neurophysiological action of AIA (Heinrich and Teoh 2004). Galantamine (Proskurnina and Yakovleva 1952) boosts cholinergic neurotransmission in brain tissues by rapidly reversible inhibition of AChE (Sweeney et al. 1989, Geerts et al. 2002). The mentioned alkaloid also facilitates acetylcholine-mediated neurotransmission by binding to pre-synaptic nicotinic acetylcholine receptors and by increasing the number of open post-synaptic receptors during action potentials (Geerts et al. 2002). Galantamine efficiently enhances cholinergic neurotransmission in the central nervous system because it easily penetrates the blood–brain barrier (Harvey 1995), is rapidly absorbed, and has excellent bioavailability after oral administration (Yamboliev et al. 1993, Kewitz 1997). Consumed

Table 1. Alkaloids that inhibit acetylcholinesterase (AIA) and proven positive in vivo effects on cognitive processes or increased acetylcholine levels in the central nervous system of mammals (citations provided next to a compound name support AChE-inhibitory activity, and citations given at family names support information about synthesis of a given compound).

Compound name	Species (family)	Effects exerted in vivo
19,20-dihydroervahanine 19,20-dihydrotabernamine (Ingkaninan et al. 2006)	*Tabernaemontana divaricata* (Apocynaceae) (Henriques et al. 1996, Ingkaninan et al. 2006)	Inhibit cortical AChE activity in rats (Chattipakorn et al. 2007)
Berberine (Kuznetsova et al. 2002)	80 species of eight families (Annonaceae, Berberidaceae, Buxaceae, Lauraceae, Menispermaceae, Papaveraceae, Ranunculaceae, Rutaceae) (Willaman and Schubert 1961, Villinski et al. 2003, Tang et al. 2009, Nechepurenko et al. 2010)	Reverse scopolamine-induced memory impairment in rats (Peng et al. 1997)
Coptisine (Shigeta et al. 2002)	Nine species (Papaveraceae) (Willaman and Schubert 1961, Preininger et al. 1976, Taborska et al. 1995, 1996); three species (Ranunculaceae) (Willaman and Schubert 1961, Shigeta et al. 2002)	Improve scopolamine-induced learning and reverse memory deficit in rats (Hsieh et al. 2000)
Dehydroevodiamine (Park et al. 1996)	*Evodia rutaecarpa* (Rutaceae) (Park et al. 1996)	Reverse scopolamine-induced memory impairment in rats (Park et al. 1996)
Desoxypeganine (Jalali et al. 2006)	*Peganum harmala* (Nitrariaceae) (Khashimov et al. 1969)	Improve learning abilities in rats (Jalali et al. 2006)
Geissospermine (Lima et al. 2009)	*Geissospermum vellosii, G. leave, G. sericeum* (Apocynaceae) (Willaman and Schubert 1961, Lima et al. 2009)	Reverse scopolamine-induced memory impairment in mice (Lima et al. 2009)
Harmaline (Zheng et al. 2009)	*Peganum nigellastrum* (Nitrariaceae) (Zheng et al. 2009); *Banisteriopsis caapi* (Malpighiaceae) (Wang et al. 2010)	Improve object recognition and short-term memory in mice (Moura et al. 2006)
Harmol (Zheng et al. 2009)	*Newbouldia laevis* (Bignoniaceae) (Oliver-Bever 1986); *Pauridiantha lyalli* (Rubiaceae) (Oliver-Bever 1986); *Banisteriopsis caapi* (Malpighiaceae) (Wang et al. 2010)	Improve object recognition and short-term memory in mice (Moura et al. 2006)
Huperzine (Small et al. 1997)	*Huperzia serrata* (Lycopodiaceae) (Houghton and Howes 2005)	Improve memory in cognitively impaired rats and gerbils (Lu et al. 1988, Zhou et al. 2001)
Palmatine (Shigeta et al. 2002)	37 species of six families (Annonaceae, Berberidaceae, Menispermaceae, Papaveraceae, Ranunculaceae, Rutaceae) (Willaman and Schubert 1961, Vasanthi and Kannan 2012)	Reverse scopolamine-induced memory impairment in mice (Dhingra and Kumar 2012)
Physostigmine (Houghton and Howes 2005)	Calabar bean *Physostigma venenosum, P. cylindrospermum, Dioclea macrocarpa, Mucuna cylindrosperma, Mucuna urens* (Fabaceae) (Willaman and Schubert 1961, Houghton and Howes 2005)	Improve cognition in healthy humans (Davis et al. 1978)
Piperine (Chonpathompikunlert et al. 2010)	Black pepper *Piper nigrum* and nine other species of *Piper* (Piperaceae) (Willaman and Schubert 1961, Rathnawathie and Buckle 1983); *Psilocaulon absimile* (Aizoaceae) (Willaman and Schubert 1961)	Reverse cognitive impairment (Chonpathompikunlert et al. 2010)
Protopine (Kim et al. 1999)	28 species of *Corydalis* and 40 other species (Papaveraceae) (Willaman and Schubert 1961, Su et al. 2011); *Nandina domestica* (Berberidaceae) (Willaman and Schubert 1961)	Alleviate scopolamine-induced memory impairment in mice (Kim et al. 1999)
Pseudoberberine (Hung et al. 2008*a*)	*Corydalis turtschaninovii* (Papaveraceae) (Hung et al. 2008*a*); *Thalictrum flavum* (Ranunculaceae) (Ropivia et al. 2010)	Reverse scopolamine-induced memory impairment in mice (Hung et al. 2008*a*)
Pseudocoptisine (Hung et al. 2008*b*)	*Corydalis tuber* (Papaveraceae) (Hung et al. 2008*b*)	Reverse scopolamine-induced memory impairment in mice (Hung et al. 2008*b*)

in high doses, galantamine is toxic, destabilizing neural signaling of mammals. However, in lower doses that improve cognitive performance, galantamine had no adverse long-term effects when tested on rodents or rabbits (Fulton and Benfield 1996, Heinrich and Teoh 2004, see Appendix S1 for discussion of dose-dependent effects of galantamine).

AIA Action in the Context of Neurophysiology of Food Learning

The diet choices of herbivores are based on nutritional requirements constrained by plant secondary metabolites (Freeland and Janzen 1974, Rosenthal and Berenbaum 1991). The relationships between plant secondary metabolites and nutrients are mediated by a comprehensive range of sensory receptors in organ systems throughout the body, including those for odorants, nutrients, and other chemicals (Furness et al. 2013). Diet selection is mediated by the flavor–feedback relationship—a palate in touch with abilities to meet nutritional needs and maintain intake of plant secondary metabolites within limits of tolerance (Provenza 1995). Mammals associate flavor (odor plus taste) cues with feedback from cells and organ systems, including the microbiome, in response to nutrients and plant secondary metabolites in foods in a meal (Provenza et al. 2015). Associating flavor cues with positive consequences due to needed nutrients and medicines causes conditioned food preferences, whereas digestive illness (malaise, nausea) due to excesses of nutrients or toxins conditions aversions (Welzl et al. 2001). The process of food selection is enabled by the abilities of animals to learn, remember, and associate past experiences with sensory cues that involve taste/odor recognition, as well as spatial orientation. On the neurophysiological level, cholinergic neurotransmission, a target of the AIA action, underlies the aforementioned crucial mechanisms involved in diet preference and feeding behavior. Below, we describe the effects AIA exert on taste recognition, odor recognition, and spatial learning.

Taste aversion, satiety, and satiation

Conditioned taste-aversion learning is one of the most important ways herbivores optimize food selection (Provenza 1996, Provenza et al. 2015). Compared with the tastes of familiar foods, animals readily form aversions to the tastes of novel foods (Kalat and Rozin 1973). In contrast to familiar tastes, exposure to novel or aversively conditioned tastes elevates extracellular acetylcholine in the nucleus accumbens and insular cortex, brain areas important in acquisition of conditioned taste aversions (Mark et al. 1995, Shimura et al. 1995, Miranda et al. 2000, Clark and Bernstein 2009). By increasing levels of extracellular acetylcholine, AChE inhibitors like neostigmine or carbachol, which are similar in action to galantamine and other AIA, induce a taste aversion for saccharin after administration to the nucleus accumbens and insular gustatory cortex (Clark and Bernstein 2009, Robinson et al. 2011, Taylor et al. 2011). Galantamine facilitates the formation of taste aversions, not only due to its AChE-inhibitory properties, but also through allosteric potentiation of nicotinic receptors of acetylcholine in the gustatory cortex (Hasegawa and Ogawa 2007).

The neurobiological processes responsible for learning and memory of flavors are being intensively studied, and researchers are far from understanding the full network of interactions between brain regions and neural systems (Avena and Rada 2012, Nunes et al. 2013). Behavioral effects triggered by a change in acetylcholine levels in one brain region do not necessarily occur when cholinergic neurotransmission is boosted in several brain regions at the same time following central infusion of an AChE inhibitor. However, dozens of studies show that taste-aversion learning is impaired after downregulation of cholinergic neurotransmission by scopolamine, an antagonist of acetylcholine muscarinic receptors, administrated to the central nervous system (reviewed in Klinkenberg and Blokland 2010). In addition, systemic administration of cholinergic antagonists that downregulate cholinergic neurotransmission through muscarinic and nicotinic acetylcholine receptors eliminates taste preference and facilitates acquisition of conditioned taste avoidance (Rotella et al. 2015).

Whereas aversions due to digestive malaise and nausea cause animals to avoid a food, satiation (process that brings a meal to an end) and satiety (process that inhibits eating between meals) temporarily suppress appetite for particular foods (Provenza 1996, Moore et al. 2015, Provenza et al. 2015). The satiety hypothesis ascribes changes in preference within and among meals to transient aversions that arise as primary (energy, protein, minerals, vitamins) and secondary (tannins, saponins, alkaloids) metabolites interact to cause satiation and satiety (Provenza 1996). Satiety and taste aversion reside along a continuum influenced by the dose of a compound: Low to modest doses of a compound induce satiety, whereas higher doses

induce prolonged food aversion (Provenza 1996). That continuum can make discriminating between satiety and aversion challenging. Cholinergic activity of the mesolimbic system can influence satiation and satiety (Avena and Rada 2012). Reduced feeding in rats given neostigmine, an AChE inhibitor similar in action to galantamine and other AIA, was implicated in satiation rather than aversion (Mark et al. 2011). Acetylcholine synaptic accumulation in the nucleus accumbens, a key brain area responsible for taste learning, is associated with the cessation of feeding (Mark et al. 1992, Avena and Rada 2012).

Olfactory recognition

Mammalian herbivores have higher rates of acquisition and retention of memory for olfactory than for visual stimuli and they learn olfactory cues rapidly (Slotnick and Katz 1974). In mammals, the olfactory system comprises several regions in the brain including the olfactory bulb and olfactory cortex (Gire et al. 2013). Acetylcholine plays a crucial role in olfactory learning and memory (Wilson et al. 2004, Linster and Cleland 2016). Cholinergic modulation of inputs from the olfactory bulb affects cortical odor processing and learning of odors (de Almeida et al. 2013). Increased efficacy of cholinergic neurotransmission in the olfactory bulb, due to localized infusion of the AChE inhibitor neostigmine, improves odor discrimination (Chaudhury et al. 2009). Likewise, scopolamine-induced impairment of cholinergic neurotransmission in the olfactory bulb decreases odor discrimination and performance in olfactory-dependent tasks (Chaudhury et al. 2009, Devore et al. 2012). When the cholinergic antagonist scopolamine is infused into the brain or administrated systemically, that impairs olfactory discrimination, habituation to novel odors, and short- and long-term olfactory memory formation (Miranda et al. 2009, Robinson et al. 2011). However, systemic administration of AChE inhibitors, including several AIA, reverses scopolamine-induced deficits in odor recognition and olfactory learning (Robinson et al. 2011). Galantamine and physostigmine, another example of AIA synthesized by the Calabar bean (*Physostigma venenosum*, Fabaceae), enhance discrimination of odorant mixtures, improve the accuracy, and shorten the time necessary for olfactory-based social recognition in mice and rats after systemic administration (Winslow and Camacho 1995, Doty et al. 1999).

Spatial orientation, learning, and memory

Learning requires processing multitude sensory cues linked with memory. Archival memories are encoded in long-term memory of enormous capacity, whereas transient memories are processed in short-term (working) memory with limited capacity (Cowan 2008, Luck and Vogel 2013). Long-term memory is involved in spatial orientation and allows for recollection of past experiences, whereas working memory holds and manipulates small amounts of information crucial for information about a selected goal, sensory processing, and attention (Klinkenberg et al. 2011, Lisman 2015). Both types of memory are involved in feeding behavior, diet choice, and food learning. For instance, associating past experiences with the place where a food was eaten requires not only reference to past experiences (long-term memory) but also attention, visual and olfactory recognition (working memory). Long-term memory and working memory are underlain by independent mechanisms. Long-term memory requires a consolidation period with protein synthesis and synaptic modification, whereas working memory involves persistent neurotransmission (Giovannini et al. 2015, Lisman 2015).

Despite involving separate mechanisms, scientists have long recognized the key role of the cholinergic system for learning as well as long-term and working memory (Hasselmo 2006, Robinson et al. 2011, Giovannini et al. 2015). Boosting cholinergic neurotransmission in the medial temporal lobe, a part of the brain crucial for learning and memory, improves long-term and working memory, whereas impairing acetylcholine-mediated neurotransmission causes deficits in these functions (Klinkenberg and Blokland 2010, Newman et al. 2012). Cholinergic neurotransmission by nicotinic and muscarinic receptors of acetylcholine in the hippocampus and cortex, regions within the medial temporal lobe, improves spatial learning (Ikonen et al. 2002) and spatial memory (Deiana et al. 2011). Hence, spatial learning, formation of long-term memories, and processing of working memory are improved after oral or systemic administration of AChE inhibitors (Robinson et al. 2011). Galantamine and other AIA positively affect memory,

spatial orientation, cognitive and learning abilities in mammals with drug- and lesion-induced cognitive deficits (see Table 1; Fulton and Benfield 1996, Williams et al. 2011). The same is true for animals with impaired cognitive function resulting from normal aging (Weible et al. 2004). Galantamine and other AIA also enhance cognitive function in young, healthy mammals (Davis et al. 1978, Winslow and Camacho 1995, Woodruff-Pak et al. 2001, 2010).

Ecological and Evolutionary Context of AIA Synthesis—Galantamine Synthesized by Amaryllidaceae as an Example

Insects are a major selective force for plant secondary metabolites (e.g., Hare 2012), but mammalian herbivores also influence the chemistry and growth rates of many plant populations. Grazing by wild ungulates, rabbits, and rodents can severely reduce population growth rate in several species of perennial herbs (reviewed in Maron and Crone 2006). Grazing can increases the likelihood of plants entering a non-reproductive stage or experiencing mortality in succeeding years (Hulme 1996, Piqueras 1999, Knight 2003). Fitness of perennial herbs drops in decelerating fashion along with grazing intensity (Knight et al. 2009), which means that even relatively rare episodes of mammalian herbivory can reduce plant population growth. Overall, the biomass loss due to repeated herbivory by mammals can significantly reduce fitness of perennial grasses, forbs, and shrubs (Teague et al. 2013). By altering food preferences and foraging behavior of mammalian herbivores, synthesis of secondary metabolites in concert with AIA is expected to reduce consumption of biomass in plant clones that allocate resources for synthesis of these compounds.

Ecological context is valuable for understanding the selective advantages of AIA for plants. Here, we use as an example the family Amaryllidaceae, whose members synthesize galantamine (Berkov et al. 2009). Species within Amaryllidaceae have similar life histories and morphologies: They are all perennial herbs that synthesize a range of plant secondary metabolites that deter foraging by herbivores. The majority of Amaryllidaceae, like the well-known snowdrops (*Galanthus* spp.), grow in moist deciduous woodlands and store resources in an underground bulb, the key organ that enables rapid growth and flowering in early spring (Orthen and Wehrmeyer 2004), before the leaves of deciduous trees overshadow the understory plants. For the numerous rodent species that inhabit deciduous forests, such as the bank vole (*Myodes glareolus*), yellow-necked mouse (*Apodemus flavicollis*), and wood mouse (*Apodemus sylvaticus*), a high-starch bulb is an attractive food resource in winter. Similarly, the fresh green biomass of leaves that emerge from melting snow early in spring attracts rodents and large mammalian herbivores such us European roe deer (*Capreolus capreolus*).

Snowdrops form impressive carpets with thousands of plants producing white blossoms in early spring. Though they appear to be quite uniform, patches of woodland herbs should be regarded as a mixture of competing, genetically diverse genets, with highly related ramets within a cluster, rather than a homogenous population of individuals that represent a single strategy for surviving and reproducing (Ziegenhagen et al. 2003, Jacquemyn et al. 2005). Individual *Galanthus elwesii* and *Galanthus nivalis* plants from different populations differ with respect to their alkaloid profiles and galantamine contents (Berkov et al. 2011). For small and large mammalian herbivores, such a mixture of genetically diverse genets is a heterogeneous chemical environment in which the choice of foraging sites and individual plants depends on spatial orientation, memory, and processing of taste and olfactory cues linked with feedback from primary and secondary metabolites.

Herbivores can recognize harmful foods even when negative post-ingestive effects occur many hours after food consumption, though the strength of a food aversion decreases as the delay between taste perception and digestive illness increases (Burritt and Provenza 1991). The more acute the post-ingestive illness, the more relevant the modulation of food-aversion learning by AIA. Thus, plants combining synthesis of AIA with production of a variety of secondary metabolites that affect physiology are expected to be most efficient in repelling herbivores. To further enhance aversive effects, members of the Amaryllidaceae accompany synthesis of cholinergic AIA with several other plant secondary metabolites that can be toxic in high doses (Selles

et al. 1999, Berkov et al. 2011). They include the following: Lycorine, which impairs muscle fiber tension by interfering with potassium channels (Quevedo et al. 1984), inhibits the synthesis of ascorbic acid in rodents, blocks protein synthesis, and can induce apoptosis (Lamoral-Theys et al. 2010); narciclasine, which has anti-mitotic activity and impairs ribosomal protein biosynthesis (Kornienko and Evidente 2008); ungeremine, which arrests cell cycles by inhibiting topoisomerases (Barthelmes et al. 2001); and tazettine and hemanthamine, which block protein synthesis and inhibit cell growth (Jimenez et al. 1976, Antoun et al. 1993).

Mammalian herbivores live in areas ranging from less than a hectare to home ranges of many hectares, and many of mammalian herbivores are territorial. AIA should enable them to quickly learn and remember specific plant(s) and the locations where they ate those plant(s). The dose-dependent nature of AIA consumed with other plant secondary metabolites, along with the abilities of herbivores to link flavor intensity with feedback intensity, causes mammalian herbivores to satiate, form aversion, and avoid individual plants at lower levels of plant consumption. Hence, plants synthesizing AIA are expected to have lesser biomass loss due to mammalian herbivory than plants that do not synthesize AIA. The response of herbivores to consumption of AIA and other secondary metabolites in plants should enable individual plants that synthesize AIA to produce less of other defensive chemicals, which means they can allocate fewer resources to defense and more to growth, reproduction, and competition with plant clones not synthesizing AIA. Defense strategy aimed at manipulating food learning is also less susceptible to toxin resistance in herbivores, as AIA enhance satiety and food aversions facilitated by consuming an array of different chemicals as opposed to just one compound. Plant clones synthesizing AIA in concert with other defensive secondary metabolites are expected to have higher fitness, and increase in number faster than clones that do not accompany synthesis of defensive chemicals with AIA. In asexually reproducing plant species growing in large patches like snowdrops, the natural selection is expected to promote AIA synthesis as genets consist of closely related ramets representing the same profile of defensive chemicals and bearing the same genes encoding their defensive strategy.

Our hypothesis is founded on the premise that AIA synthesis reduces the loss of biomass in plants due to altered food preferences of mammalian herbivores. The alternative hypothesis states that AIA synthesized by plants are toxins aimed at invertebrate herbivores and any positive effects exerted on mammals are a by-product of low-dose consumption. These hypotheses lead to different predictions. The alternative hypothesis implies that plants with low AIA content and plants that do not synthesize AIA are expected to lose the same amount of biomass when exposed to mammalian herbivory. Alternatively, if AIA synthesis is an adaptation influenced by learning in mammalian herbivores, plant clones synthesizing low amounts of AIA are expected to lose less biomass when exposed to an experienced mammalian herbivore than to naïve individuals. However, such a test needs to control for the amount of biomass consumed by naïve and experienced herbivores because naïve individuals tend to be cautious while sampling novel foods (Provenza et al. 2015).

Synthesis of AChE Inhibitors as a Defense Strategy in Plants: A Complementary Hypothesis

Different classes of plant secondary metabolites, including neuroactive alkaloids, terpenes, and flavonoids, have multiple ecological roles, evolved in response to a diverse array of selection pressures (Iason 2005, Kennedy 2014). Hundreds of neuroactive plant chemicals show AChE-inhibitory activity (Wink 2000, Kennedy and Wightman 2011). Over 100 plant-derived AChE inhibitors hold promise for treating cognitive impairment (for review, see Williams et al. 2011). Within this group, at least 36 compounds penetrate the blood–brain barrier and improve cognition, memory, or levels of AChE in experiments in vivo on mammals (Table 1 and Appendix S2). These memory and aversion learning enhancers are synthesized by over 400 plant species in 58 families, including spices in everyday use (see Table 1 and Appendix S2).

Several herbs, including lemon balm (*Melissa officinalis*, Lamiaceae), Indian pennywort (*Bacopa monnieri*, Plantaginaceae), calamus (*Acorus calamus*,

Acoraceae), river red gum (*Eucalyptus camaldulensis*, Myrtaceae), and ginkgo (*Ginkgo billoba*, Ginkgoaceae), are "good for memory" or used in folk medicine to treat cognitive impairment due to the AChE-inhibitory activity of their extracts (for more examples, see Oh et al. 2004, Adsersen et al. 2006, Williams et al. 2011). Volatile terpenes, like eucalyptol (1,8-cineole) and α-pinene synthesized in sage (Salvia sp., Lamiaceae), rosemary (*Rosmarinus officinalis*, Lamiaceae), tansy (*Tanacetum vulgare*, Asteraceae), and several other common plants, affect cognitive performance through inhalation (Moss et al. 2003, Moss and Oliver 2012), as well as odor-driven food preferences in mammalian herbivores (Bedoya-Perez et al. 2014). This suggests plants may manipulate neurological processes of memory formation and aversion learning in mammalian herbivores not only through consumption, but also through exposure to plant odors of different intensity which can be used as pre-ingestive cues for food selection (see Provenza et al. 2000).

Based on the aforementioned evidence, we propose plants influence how mammals perceive food cues, a notion that contrasts with the prevailing view of plant chemical defenses aimed at destabilizing physiological facets of an herbivore's life. Doping of aversive learning and cognition—repelling mammals by altering their perceptions—may provide greater fitness benefits at less cost than synthesizing toxins aimed at acute harming. The effects exerted on food learning by AIA are expected to interact with the variety and toxicity of plant secondary metabolites animals consume. Hence, the hypothesis we present is the first step in discovering the ecological significance of AIA and other AChE inhibitors in modulating learning in mammalian herbivores. The fact that AIA, and perhaps other compounds, manipulate how herbivores recognize and interpret the environment (cf. Sullivan et al. 2008, Hagen et al. 2009) is an appealing aspect of plant–herbivore interactions that can bring us a step closer to better understanding diet choice and feeding behavior of mammals including humans.

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Supporting Information

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