

Side effects of five products largely used by humans and studied on ants as models: a mini review

Abstract

Here we summarize our recent studies on the physiological and behavior effects of five products widely used by humans, using an ant, having received these substances in their usual diet, as a biological model. Nutmeg is a spice which decrease the activity and movement speed of the ants, leading to further motor-linked impairments, but not impairing other behavioral traits as well as learning and memory. Vortioxetine (Brintellix) is an antidepressant recently appearing reducing obesity and having moderate adverse effects in humans. It negatively affected the ants' food intake, general activity, tactile sensitivity, state of stress and cognition. Berberine is a supplementary dietary regulating, in humans, glucosemia and several parameters. In ants, food intake, general activity, tactile sensitivity, were also negatively impacted, but not their state of stress and cognition. Cashew nuts and mangoes may have similar allergenic effects in humans. In ants, cashew consumption induces sinuosity of movement, stress and nervousness while mango consumption reduces their general activity and behaviors related to motor activity. The correspondence between dependence to a substance, short duration of its effect after withdrawal and abrupt loss of its effect is discussed.

Keywords: nutmeg, brintellix, berberine, cashew nuts, mangoes

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Abbreviations: ang.deg./cm, angular degrees per cm; mm/s, millimeter per second; n°, number; h, hours; t, time; %, percentage

Introduction

Study context

Products largely used by humans, depending on their dosage, low or high, can have moderate or severe adverse effects. The side effects reported in the literature are physiological ones, acting on the humans' health, causing for instance digestive disorders, nausea, headache, dermatitis, or liver and kidney problems. Generally, nothing is reported about potential side effects on behavior such as moving performance, sensory perception, stress and cognition. Our approach was to test the effect of products or substances used as food or medicine by humans, on various behavioral traits of an ant used as a biological model.

Accustomed to test these possible side effects on the ant *Myrmica sabuleti* Meinert, 1861, we went on working in the same way as for some 68 substances we have already studied, e.g.¹⁻⁷ We here summarize the effects of our last studied substances; namely a spice (nutmeg), an antidepressant (vortioxetine, commercialized as Brintellix®), a dietary supplement (berberine) and two fruits (cashew nuts and mangoes).

The effect of these substances, included in the usual liquid diet of ants which is 15% sugar water, in a proportion corresponding to that taken by humans, was therefore tested on several behavioral traits of *Myrmica sabuleti* workers. These included their consumption of sweet and meaty foods, their general activity, their linear and angular speed on smooth and rough ground, their orientation towards a source of alarm pheromone, their boldness or exploratory behavior, their care of larvae (transport of larvae away from the nest), social (agonistic) relationships between workers, their ability to leave an enclosure, the degree of physiological adaptation of the individual's speed of movement after a long period spent under the influence of the tested product, any dependence on the consumption of this product and the

decrease in speed of movement after consumption of the product had been stopped.

We would like we take the opportunity to adapt the titles of some of the behaviors listed in our previous publications in order to make them more neutral in terms of interpretation. For example, "tactile perception" as quantified by the speed of movement on a rough substrate has been renamed "speed on a rough surface" in our last publication (the one on mangoes), because the difference in speed of movement on a rough substrate may depend not only on a nociceptive sensation but also on the physical difficulty of walking on such a surface. As for the state of "stress and cognition" measured by the ability or ease with which an ant manages to get out of an enclosure, a more neutral title such as "escaping ability" is to be preferred before any interpretation. Concerning the degree to which an ant is able to cross a course of chicanes, this is not a simple measure of cognition, but rather a measure of ease of movement. It's thus more neutrally called a "twists and turns test".

Short information on the products that were studied

Nutmeg

Beneficial in small doses to treat various aspects of health as listed in,⁸ this spice is toxic in high doses,⁹⁻¹³ acting notably as a hallucinogen. In one documented case, nutmeg intoxication caused a 20-year-old man to suffer neurological, cardiac and digestive disorders.¹⁴ Information on nutmeg toxicity should be known by users, but is not sufficiently publicized. This is why we have studied the effects of this substance on ant behavior.⁸

Vortioxetine (Brintellix)

Vortioxetine is a rather recent antidepressant which has, as the four previously used ones, the monoamine oxidase inhibitors (MAOI), the tricyclic antidepressants (TCA), the selective serotonin reuptake inhibitors (SSRI) and the noradrenaline and serotonin reuptake inhibitors (NaSRI), several adverse effects.¹⁵ Vortioxetine

is another SSRI, acting on different serotonin receptors than those of the previously existing SSRIs. Its side effects are less severe than the previous ones. They consist in nausea, vomiting, dizziness and headache.¹⁵ According to the authors who studied the efficacy and tolerability of this drug, it was either recommended or not considered because being no more active than previous antidepressants.¹⁶⁻²¹ Unexpectedly, these 'novel' SSRI antidepressant appeared to very efficiently decrease obesity, and was thus soon used for this therapy. The biological effects of Brintellix were examined on ants as models.¹⁵

Berberine

Plants containing berberine are used as a supplementary dietary for regulating glucosemia, lipid metabolism, as well as central nervous system disorders such as depression, schizophrenia, Alzheimer's and Parkinson's diseases.²² Berberine was also shown to lower the blood glucose in rats, and to reduce glucose, cholesterol and triglyceride in rats.²³⁻³² Some cases of cardiac, digestive and skin problems have been reported, but there is no information in the literature about possible on biological and behavioral effects. This is why we intended to fill this gap, and made a study of the effects of berberine, using ants as models.²²

Cashew nuts

Cashew nuts have several dietetic properties such as containing polyunsaturated fatty acids and vitamins K, B1, B6, and B9; moreover, they are rich in protein, calcium, potassium.³³ However, they also contain urushiol, a toxic substance which can cause severe dermatitis and health problems such as digestive disturbances, headache, tiredness, etc.³⁴⁻³⁷ No information on possible behavioral and biological problems having been published, we studied the effect of a cashew nuts diet on behavioral traits, using ants as models.³³

Mangoes

The tree *Mangifera indica* produces delicious fruits having many dietetic qualities, containing potassium, vitamin C and A, antioxidants, substance against cancer, allowing a reduction of the amount of glucose, etc.³⁸ However, the fruit of mangoes contain alkyl-resorcinol ('mangos') in the first half-centimeter under the peel, which may cause allergic reactions, due to cross-reactivity when having been previously sensitized to urushiol containing plants or to various respiratory allergens.³⁹⁻⁴³ Are there side effects other than those triggered by allergens? Since no information exists on possible behavioral consequences after consuming mangoes, this potential problem was investigated on ants as models.³⁸

Results

Nutmeg

Humans may consume about 1.5 g/day of nutmeg, a high dose they take together with one liter of water. Tested on ants at this dose, this spice affected their locomotion (Table 1) and general activity and, consequently, their number going onto food. It also affected their orientation, audacity, brood caring, escaping ability, but not their capability of crossing a twists and turns path and their learning and memory. The ants did not adapt themselves to the nutmeg side effects. They preferred to consume spiced sugar water than pure sugar water: faced with a choice, 77% of the ants chose the cashew-containing sugar water and 23% the pure sugar water. The effect of nutmeg as measured on the ants' linear speed vanished in about 24 hours after weaning (Figure 1). This relatively short duration, may suggest a dependence of the ants on cashew, as it has often been observed on

ants and humans in which a rapid decrease of an effect may lead to dependency.⁴⁴ This spice being appreciated, it is therefore suggested that nutmeg be consumed in moderation.

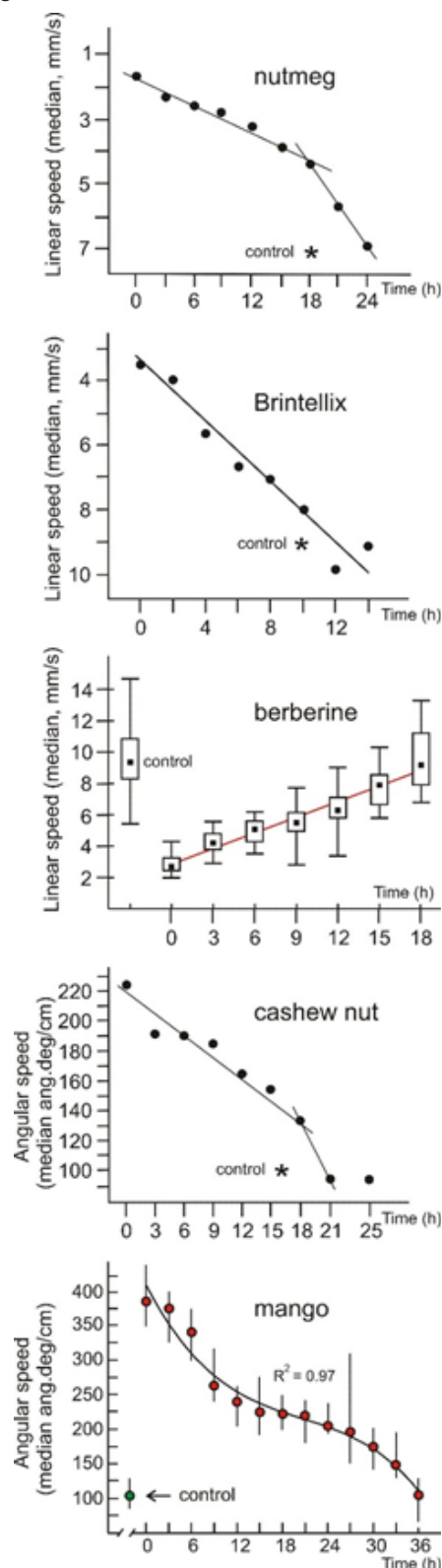


Figure 1 Ants' changes in moving speed in the course of time after withdrawal of a substance or product from their ordinary sugar water diet. Weaning starts at time = 0. Adapted from,^{8,15,22,33,38} with interquartile ranges and extremes added for berberine and interquartile ranges for mango.

Table 1 Some important results on studies made on ants and relative to a spice, an antidepressant, a drug regulating glycemia, cashew nut, and mango

	Examined traits	Experimental values		→ consequence
Nutmeg	Speed on smooth ground	control	+ nutmeg	→ decrease of speed what affect other traits
	linear speed (mm/s)	7.2 (6,8 – 8,0)	2,8 (2,3 – 3,1)	
Brintellix	Speed on rough ground	control	+ drug	→ less tactile perception
	linear speed (mm/s)	2.8 (2.4 – 3.2)	4.6 (4.1 – 4.9)	
	Dependence			
	n° ants on each solution	10	70	12.5% vs 87.5%
Berberine	Speed on rough ground	control	+ berberine	→ less tactile perception
	linear speed (mm/s)	2.4 (2.1 – 2.5)	4.8 (4.3 – 5.3)	
	General activity			
	mean n° of active ants	8.84	4.79	
Cashew nut	Dependence	control	+ cashew	→ possible dependence
	n° ants on each solution	24	84	
Mango	Dependence	control	+ mango	→ no dependence
	n° ants on each solution	78	28	

Brintellix

Brintellix is a useful antidepressant for humans, but it had several physiological and ethological biological activities when observed on ants as models. Indeed, it decreased the ants' food intake, locomotion, audacity, social relationships, capability of escaping, and learning. On the contrary, on a rough surface, the ants moved faster under a Brintellix diet than under a normal diet (Table 1), suggesting a less tactile sensitivity. The ants did not adapted themselves to the observed side effects of the drug, and they could habituate themselves to the effects of the drug. Moreover, the ants appeared to develop dependence on Brintellix consumption as 87.5% were seen on the drug solution and 12.5% on the drug-free solution (Table 1). Indeed, the effect of Brintellix on the ants' linear speed lasted only a short time (12 h) after weaning (Figure 1), which explains the dependence on the product. We suggest thus that Brintellix should be used, at a case-by-case, while monitoring the patients as for their health, and paying attention to the development of dependence.

Berberine

Tested on ants, this drug had several side effects, such as a decrease of food intake, activity (Table 1) and locomotion on their ordinary smooth foraging area surface. However, it caused a more rapid movement speed on a rough surface (Table 1), what suggests a reduced sensitivity. However, it did not affect the social relationships, ability of escaping, learning and memory of the ants. The ants did develop some preference for a sugared solution with berberine than without it, although it was just significant (binomial test: $P = 0.0464$). Since the effect of this drug on the ants' linear speed rather rapidly decreased in 18 hours after weaning (Figure 1), we suggest a dependence on this product. We therefore suggest that the effect of berberine on behavioral and physiological human traits should be assessed.

Cashew nuts

The most observed effect on ants of cashew consumption was that it induced stress and excitation. A diet with cashew nuts lowered their

food consumption and activity, increased their sinuosity of movement, decreased their orientation capability, enhanced their audacity and nervousness, decreased their social relationships and their ability to escape from an enclosure. These fruits did not affect the ants' speed on a rough surface, brood caring, progression speed when crossing twists and turns and conditioning acquisition. The ants did not adapt themselves to the side effects of cashew nuts. They appeared to develop dependence on cashew consumption, 78% of them having preferred it to their normal diet (Table 1). The effect of cashew nuts on the ants' sinuosity of movement decreased in 20 hours after weaning, with two short but quick falls, one at the beginning and one at the end of the decrease (Figure 1). Two such rapid decreases could be perceived by consumers, and lead to increase their consumption, what finally could lead to some dependence (i.e. addiction) on cashew nuts.

Mangoes

Compared with an ordinary diet, a diet containing mango pulp reduced the ants' general activity, linear speed, audacity to explore a new situation, transport of brood, ability to escape from an enclosure and ability to cross a twists and turns path, while movement on a rough surface was somewhat faster, but at the limit of statistical significance. Traits not clearly depending on motor activity, such as orientation, social relationships and memory were not impacted by mango consumption. The result obtained with orientation and speed on a rough surface also suggest that tactile and sensory perception were intact under a mango diet. Some slight physiological adaptation (i.e., regulation at the individual level) occurred for linear speed. No dependence was observed in a choice experiment: around 16% of ants were observed on ordinary sugar water, compared with around 74% on sugar water containing mango juice (Table 1). The effect of a mango diet on ant angular velocity became null after 33 hours of withdrawal (Figure 1). While this decrease of angular speed showed two rapid falls, it was, on the whole, a rather slow one. Such a result is in line with our usual observation of a correspondence between a rapid versus slow decrease in the activity of a product and a dependence versus non-dependence on that product.⁴⁴

Discussion and conclusion

The use of ants tested as a biological model on 5 substances highlighted various secondary effects on the behavior and physiology of these insects, suggesting the monitoring of related traits in humans who consume these substances.

When tested on the ants' speed of movement, we found that the substances for which the ants showed a preference over their usual sweet diet were those with a short duration of effect, not exceeding 18 hours after weaning (Brintellix and berberine), or 24 hours with, in this case, a sudden drop in effect within 3 hours (cashew nuts) or 6 hours (nutmeg) before extinction (Figure 1). Dependence on these products may have arisen as a result of the brevity or abruptness of their action. In fact, the critical period is the one during which a substance rapidly loses its effect.⁴⁴

The ideal way to certify whether a product is addictive is to subject the ants to a choice between food with and food without the product when they are first exposed to it, and to repeat this test after several days of exposure. For paroxetine, paracetamol and glutathione tested on ants, we observed an exact correspondence between dependence certified by this double test, an abrupt loss of effect and the short duration of the effect.⁴⁴ This correspondence should be verified for other substances.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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