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Research Article

Physical Dependence on a Substance Occurs When the Effect of This Substance Rapidly Decreases after Withdrawal

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Abstract

Using ants as models, we examined the effects of drugs, food additives and sweeteners on several physiological and ethological traits, including physical dependence. Seven drugs and a sweetener appeared to induce physical dependence. Each time, the effects of the product rapidly vanished after withdrawal, at least during a given time period. In contrast, fourteen other substances did not lead to dependence and, each time, the effects of these substances decreased slowly over time after withdrawal. The essential cause of physical dependence on a substance is thus a rapid decrease in its effect after withdrawal. This rapid decrease, even if short lasting, is perceived by the organism, which then wants to again consume the product. Humans must be aware that dependence will occur and must know the exact time period during which dependence may appear, i.e., the time period during which the effect of the substance will rapidly decrease after withdrawal. Caring of patients during that critical time period may help avoiding dependence as well as weaning patients. The critical time period can be defined through experiments on biological models; ants can be such models. The present paper shows the slow decrease of the effects of 14 substances that do not produce dependence, as well as the rapid decrease of the effects of 8 substances that lead to dependence. Moreover, the critical time period for the substances leading to dependence is each time defined. All this may interest readers and practitioners. For example, they may be interested in knowing the critical time period for nicotine, the difference between fluoxetine (the previously most consumed antidepressant, very toxic, inducing no dependence) and paroxetine (the currently most consumed antidepressant, less toxic but inducing dependence), the fact that sucralose leads to dependence, the difference between the analgesics paracetamol (inducing dependence) and ibuprofen (inducing no dependence), as well as the true action of glutathione.

INTRODUCTION

The occurrence of strong physical dependence on a drug after having consumed it for a time is a current problem for numerous patients. Even if patients are using the drug correctly as a treatment for their illness, they may still feel ill because they suffer from an uncomfortable dependence, and should receive care to ameliorate this new heath problem. We are studying ants since 1969, and have ultimately used them as models for examining the potential effects of products consumed by humans, being among others attentive to the appearance of some dependence on these substances. Ants were effectively good models for dependence detection. They were not aware that they consumed drugs and had no reason for becoming dependent on these drugs. If they nevertheless became so, they obviously preferred food containing the drug than food free of it. Moreover, these insects allowed defining the decrease of the effects of a substance after withdrawal, and we identified an important relation between dependence and the type of decrease. Indeed, we studied the effects of 22 substances, and discovered that when a substance led to dependence, its effects rapidly decreased within at least a few hours after withdrawal. Similarly, we did not observe dependence when the effects of the substance slowly decreased over time after withdrawal. Consequently, physical dependence developed when the effects of the previously consumed drug rapidly decreased. If dependent persons could be cared during that critical time period by receiving palliatives or alternatives (see the discussion section), these persons could be more easily weaned from the substance causing dependence.

In the present paper, we successively show that physical dependence is a social and medical problem, explain how ants' potential dependence on a substance was assessed, and relate the decrease of the effects of 22 substances after weaning together with the presence or absence of dependence on these substances, defining at the same time the critical time periods of 8 frequently products consumed by humns that lead to dependence.

Why is addiction a medical and a social problem? The dependence of a large proportion of the global population on a given substance or a behavior produces health, social, security, and economic problems. Dependent persons are ill, suffer continuously, and several of them die. For example, more than 100,000 dependent persons in France die each year. Dependent persons may become 'lost' to the economy of a country. They can become dangerous when suffering from withdrawal of their drug; they can behave aggressively toward anyone by threatening, frightening, injuring or even killing them to obtain their drug. Dependent persons must thus be cared by practitioners and medical assistants. The process of weaning these individuals is also a social, economic and perturbing problem. Persons living in the environment of a dependent individual are also impacted. Their lives are difficult and they often also suffer from hopelessness due to their inability to provide the proper assistance to the dependent person. Several organisms, institutions and groups are devoted to help not only dependent persons but also any individual caring for these dependent persons, and this requires time and money. More information on this important universal problem is found on Internet at the following links: www.reseau-addictions-rap.fr/.../addiction%20en%20medecine%20generale.pdf; https://fr.wikipedia.org/wiki/Addiction; http://intervenir-addictions.fr/.

Having identified the (or at least an important) physiological cause of the occurrence of dependence, we are able to propose a valuable strategy for caring of dependent persons during their withdrawal process. We here below explain our finding and the strategy we propose.

MATERIAL AND METHODS

Collection and maintenance of ants, their feeding with a substance to be examined

Ants were collected from different sites in Belgium (Ardenne), France and Gd Duché of Luxembourg. Ants were maintained in rooms under conditions described in numerous previous papers, such as [1]. The ants lived in nest tubes (containing water) deposited in foraging trays. They were fed with an aqueous solution of sugar and pieces of *Tenebrio molitor* larvae by *molitor* (Linnaeus, 1758) larvae.

The concentration of each examined substance was established based on the amount generally consumed by humans and on the fact that insects drink ten times less liquid than mammals per unit body weight. The amount of the substance consumed by humans per day (i.e., in one liter of water) was dissolved in 100 ml of sugar water and a stock solution was stored at -25°C. Ants received each tested substance in the same manner as their usual sugar water, i.e., in small tubes plugged with cotton. The latter was refreshed every two days, and the entire solution was replaced weekly. Regular observations confirmed that the ants consumed the provided solution.

Assessment of ants' preference for a studied substance

Ants were separately exposed to each studied substance. After they had consumed a given substance for 15-21 days, an experiment was conducted to determine if they had become dependent on that drug. As explained in previous papers, for instance in [2], for each colony, 15 ants were randomly selected and set in a small tray (15 cm × 7 cm × 5 cm), the borders of which had been covered with talc, and in which two tubes (h = 2.5 cm, diam. = 0.5 cm) were laid, one containing sugar water, the other a sugar solution containing the substance (the same solution as that used throughout the experiment); each tube was plugged with cotton at a depth of ca. 4 mm, and laid horizontally at a separation distance of ca. 2.5 cm. The tube containing the product was deposited on the right in one of the trays; it was deposited on the left in the other tray. The ants drinking each liquid were counted 15 times in 15 min, and the mean value was established for each liquid. The sums of the values obtained for each liquid were compared to the expected values if ants randomly drank each kind of liquid using the non-parametric goodness of fit χ^2 test.

Decreased effects of a substance over time after withdrawal

Weaning started when the sugar water containing the product was removed from the ants' foraging area and replaced with the standard, untreated sugar water. This acute withdrawal phase marked the onset of the study of the loss of the effects of the examined product over time. A previously examined trait that was obviously impacted by drug consumption, but did not lead to adaptation or habituation, could be assessed in a very short time (i.e., far less than half an hour), and causing no ant's death, was assessed over time using previously described methods. The results obtained for several colonies were summed, and results obtained at different times were compared to one another, to the control ones, and to the initial ones using appropriate non-parametric tests.

The physiological or ethological traits assessed to examine the decrease of the effects of a given substance after withdrawal differed according to the effects of the studied substance. These traits were the ants' linear and/or angular speeds, orientation to an alarm signal, aggressiveness toward nestmates, locomotion on a rough substrate (an indicator of tactile or pain perception), locomotor activity when ants were captive in an enclosure (an indicator of stress), and movement on a risky apparatus (an indicator of boldness). The methods used to assess these traits are detailed in papers devoted to the study of one to four substances. The reference to each of these papers are given in each subsection of the 'Results' section. The methods are nevertheless briefly outlined in the next subsection.

Assessment of seven physiological or ethological traits of ants

Linear and angular speeds of moving ants were assessed in the absence of a stimulus; their orientation towards an alarm signal was assessed in the presence of an isolated worker's head or a tied worker. Each time, the trajectories of 40 ants were recorded and analyzed using the software described in [3]. The recording technique and the calculation of the three variables are detailed in papers cited above. The distribution of each variable was reported as medians and quartiles. Note that a smaller orientation value indicated a better orientation of the ants.

The ants' aggressiveness toward nestmates was assessed during dyadic encounters conducted in small cylindrical arenas (diameter = 2 cm, height = 1.6 cm), each lasting for 5 minutes. The assessment consisted of recording the numbers of times a tested ant exhibited no behavior (level 0), touched the other ant with its antennae (level 1), opened its mandibles (level 2), gripped and/or pulled the other ant (level 3), and tried to sting or stung the opponent (level 4). An agonistic index 'a' was also computed using the formula: a = the number of obtained aggressiveness levels 2 + 3 + 4 divided by the number of levels 0 + 1.

The ants' tactile (pain) perception was evaluated by recording their linear and angular speeds on an uncomfortable substrate on which the ants walked with difficulty at a small linear speed and a large angular speed.

Stress was evaluated by imprisoning 5 or 6 ants under an upturned polyacetate glass (h = 8 cm, bottom diameter = 7 cm, ceiling diameter = 5 cm); the rim of the bottom had a small notch (3 mm height, 2 mm broad), allowing the ants to escape. The calmest, less stressed ants, as well as ants whose cognitive abilities were not impacted, could escape, moving calmly along the rim of the reversed glass. The stressed ants and those whose cognitive abilities were impacted walked erratically around the glass and could not discover the exit. The numbers of ants remaining under the glass and those that escaped were counted at the end of 10 successive minutes. Moreover, the ratio of escaped/captive ants by escaped ants/initial captive ones obtained after the 10 minute period was used to evaluate the ants' escape ability.

The ants' boldness was examined by counting, 10 times over 10 min, the number of ants present on a cylindrical tower made of strong white paper (Steinbach ®, height = 4 cm; diameter = 1.5 cm) set on their foraging area. The mean and extremes of the obtained values were established.

For each experiment, adequate statistical tests were made. Their results are not given in the present paper for avoiding plagiarism and writing heaviness, but can easily be found in the references to the original works.

RESULTS AND DISCUSSION

Caffeine, theophylline, and atropine

These alkaloids are frequently used by humans, and thus, their effects have been studied to some extent (f.i. [4]).

After having consumed caffeine for three weeks, ants presented neither a preference nor aversion for that alkaloid ([5], Figure 1). Indeed, when having the choice between sugar water + caffeine and sugar water, 80 ants drank the former liquid while 81 drank the latter liquid. After weaning, the effects of caffeine decreased slowly and regularly. Indeed, the ants' linear speed, increased by caffeine, equaled 20.3, 18.7, 16.9, and 13.8 mm/sec 1, 2½, 4½ and 8 hours after weaning, respectively. Ants consuming theophylline (which is structurally and pharmaceutically similar to caffeine) also did not develop dependence on this alkaloid ([5], Figure 1). Upon exposure to sugar water + theophylline and sugar water, 37 ants preferred the former liquid, whereas 40 preferred the latter. The effect of theophylline slowly dissipated after its consumption ceased. Indeed, 1, 2 ½, 4 ½, 7 ½, 10, 12 ½, 15, 28 hours after weaning, the ants' linear speed, increased by theophylline, decreased from 22.5 to 23.3, 21.3, 17.2, 17.8, 16.7, 15.6, and 14.4 mm/sec, respectively.

When fed with a diet containing atropine, ants never developed dependence on this alkaloid [5]. When presented with sugar water + atropine and sugar water, only 5 ants drank the former liquid, whereas 63 ants drank the latter. The effect of atropine decreased very slowly after withdrawal. The ants' orientation, affected by atropine, equaled 67.7, 60.4, 59.4, 55.7, 45.4, 43.1 and 41.1 angular degrees 0, 1, 2 1/2, 4 1/2, 7 1/2, 10 and 24 hours after atropine was removed, respectively.

Cocaine

This alkaloid is a rather strong drug [6]. Ants that consumed cocaine developed a strong dependence on this alkaloid [5]. When presented with sugar water + cocaine and sugar water, 52 ants chose the former liquid and only 11 chose the latter liquid. The effect of cocaine rapidly decreased over 5 hours after withdrawal. The ants' linear speed equaled 8.8, 9.4, 12.0 and 13.0 mm/sec 0, 1, 2 ½ and 4 ½ hours after having no longer had access to cocaine, respectively.

Nicotine

This product is one of the most frequently used compounds by humans [7] and it has harmful effects [8]. Its effects on ants were very interesting [9]. First, conditioning was not possible until the reward was nicotine itself! Nicotine thus represents some kind of reward or pleasant element. Second, strong dependence was observed when ants required food (Figure 1), and no dependence occurred when ants had previously received food. More precisely, when presented with sugar water + nicotine and unadulterated sugar water, 73.6% of hungry ants chose the former liquid, whereas after having received food, only 33.3% of them preferred the liquid with nicotine. In the same way, only 50% of well fed ants chose the liquid with nicotine, but after starvation, 100% of them preferred the sugar water + nicotine solution. Dependence on nicotine occurred thus when the ants were food-deprived, or perceived a lack of food. Regarding the loss of effect after nicotine consumption was stopped, a rapid decrease was observed between 8 and approximately 12 hours after withdrawal. More precisely, 1, 3, 5, 8, 11, 15, 25, and 29 hours after weaning, the ants' orientation equaled 69.0, 60.2, 59.5, 61.3, 49.5, 43.4, 35.6, and 35.8 angular degrees, respectively. The rapid decrease from 61.3 to 49.5 angular degrees occurred between 8 and 11 hours, thus within only 3 hours.

Quinine

This substance is used throughout the world as a treatment for malaria. When presented with sugar water + quinine and sugar water, the ants rapidly went onto the sugar water and avoided the liquid containing quinine (Figure 1). Only 12 ants were recorded on the sugar + quinine solution, whereas 120 ants were observed consuming the sugar water. Thus, no dependence, but rather avoidance, was observed for quinine [10]. The effect of that alkaloid slowly and regularly decreased after its consumption ceased. Indeed, the ants' linear speed successively decreased from 22.1 to 21.4, 19.5, 18.2, 17.5, 14.9, 11.8, and

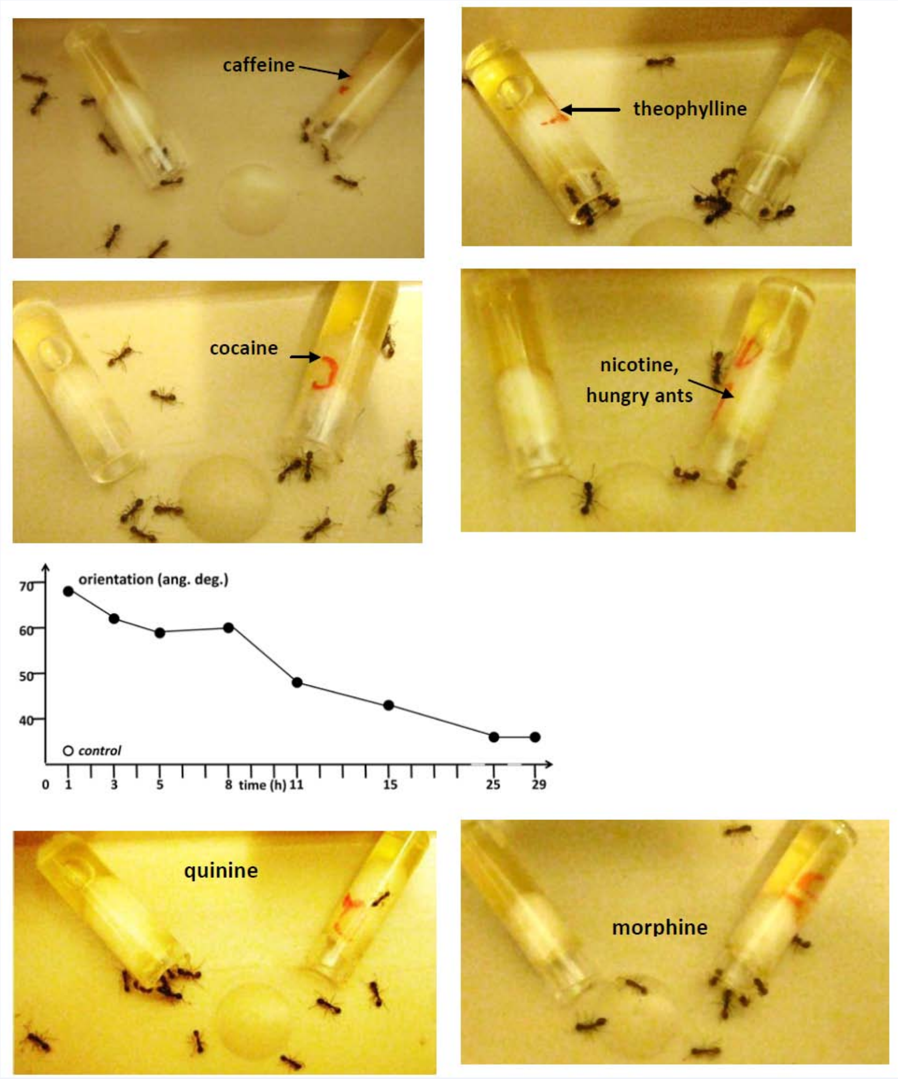

Figure 1 Experiments revealing the potential dependence of ants on six alkaloids and the decrease of the effect of nicotine after withdrawal (with a rapid decrease from 8 to 11 hrs). Dependence occurred for cocaine, nicotine in some circumstances, and morphine. Reproduced from [5,9,10].

14.9 mm/sec 0, 1, 3, 5, 7, 10, 14 and 24 hours after consumption ceased, respectively.

Morphine

This substance is used in medicine, but it is also used as a strong drug by dependent persons [11]. In the presence of sugar water + morphine and sugar water, 93 ants selected the former liquid, whereas only 17 chose the latter. This finding indicated a strong physical dependence of ants on morphine [10] (Figure 1). The effects of this drug immediately and rapidly decreased after its consumption ceased. Indeed, 0, 1, 2, 4, 7, and 10 hours after drug withdrawal, the ants' orientation equaled 77.7, 56.6, 48.8, 42.6, 37.9, and 33.4 angular degrees, respectively.

Antidepressants (anafranil, efexor, fluoxetine, and paroxetine)

Anafranil was the first antidepressant to be prescribed, whereas paroxetine is the most recent and nowadays the most frequently prescribed.

Ants did not exhibit a dependence on the TCA antidepressant anafranil (the active ingredient is clomipramine hydrochloride) [2] (Figure 2). When presented with sugar water + anafranil and sugar water, only 3 ants preferred the former liquid, whereas 221 ants preferred the latter. The effects of this antidepressant slowly and regularly decreased over time after withdrawal. Efexor, a SNaRI antidepressant (the active ingredient is venlafaxine), did not produce dependence in ants [2] (Figure 2). During our choice experiment, 4 ants chose the sugar + efexor solution, whereas 67 ants chose the sugar solution. The effects of this antidepressant slowly and regularly decreased over time after withdrawal, reaching baseline levels within 28-36 hours.

Fluoxetine is the active component of the most consumed SSRI antidepressant a few years ago. This substance did not lead to dependence [1] (Figure 2). Indeed, 32 ants chose the sugar + fluoxetine solution, and 51 ants chose the sugar water. The effects of this antidepressant slowly and regularly decreased over time after withdrawal.

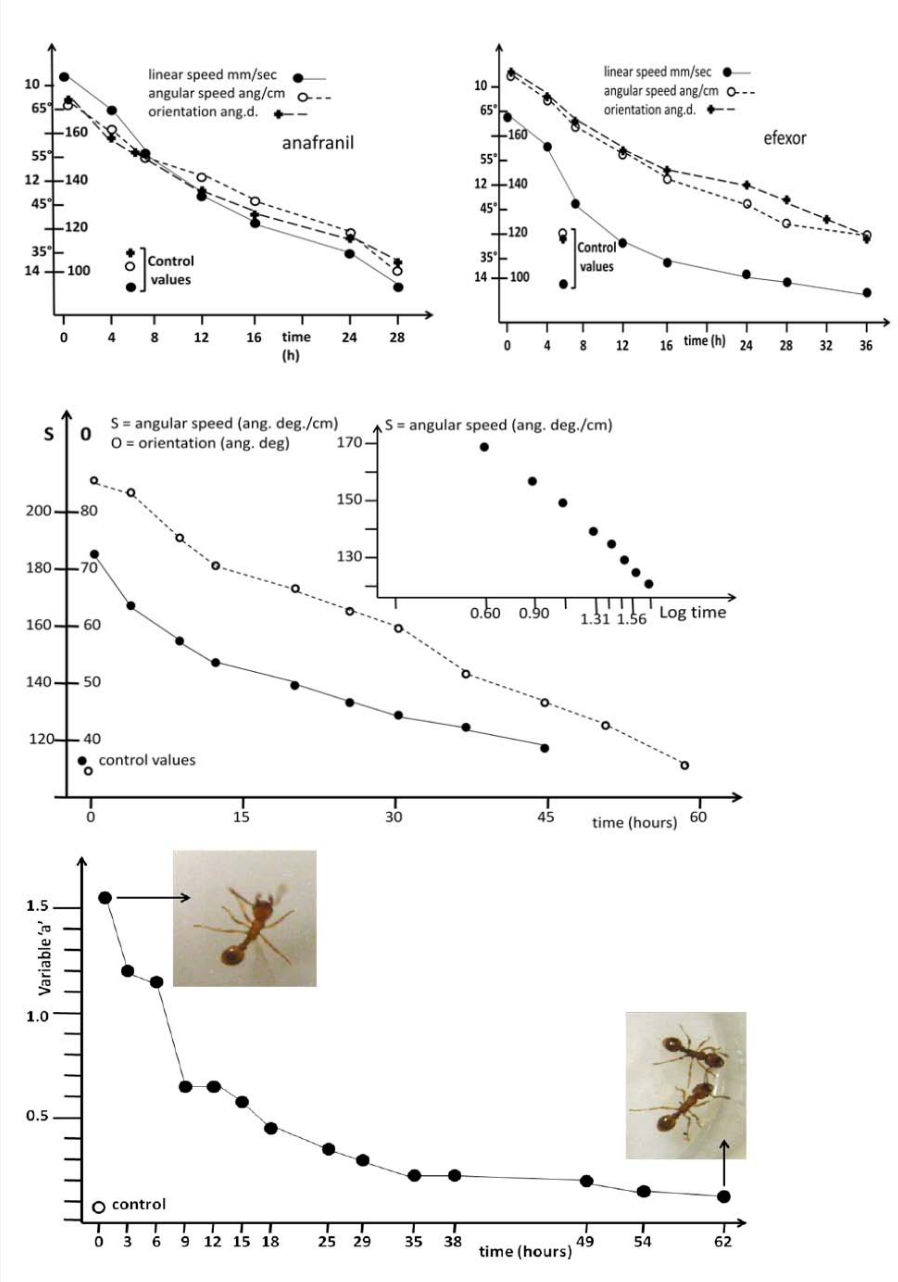

Figure 2 Decrease of the effect of 4 kinds of antidepressant. The effect of the last and nowadays most used one, paroxetine, rapidly decreases, and this antidepressant leads to dependence, contrary to the three older generations of antidepressants. Reproduced from [1,2,12].

The active substance of the newest and currently most consumed SSRI antidepressants is paroxetine. This substance induced dependence in ants [12] (Figure 2). When ants had the opportunity to choose between sugar + paroxetine and sugar, 30 ants that had consumed paroxetine chose the former solution, whereas 20 chose the latter solution. Ants that had never been exposed to paroxetine behaved differently: only 5 chose the former solution, whereas 18 chose the latter solution. Thus, ants that had consumed paroxetine developed some dependence on that antidepressant. The effects of paroxetine rapidly decreased during the first eight hours after withdrawal, and required a further 54 hours to reach baseline levels.

The newer antidepressants are less toxic than the previous ones. However, they lead to dependence, causing problems upon withdrawal.

Buprenorphine and methadone

These substances are used as analgesics in animals and as treatments for dependency (fr.wikipedia.org/wiki/Buprénorphine, fr.wikipedia.org/wiki/Méthadone). Little dependence on buprenorphine was observed [13] (Figure 3). Indeed, 71 ants were observed on the liquid containing the drug, and 53 ants on the liquid lacking buprenorphine. This observation did not differ from the expected population sizes if

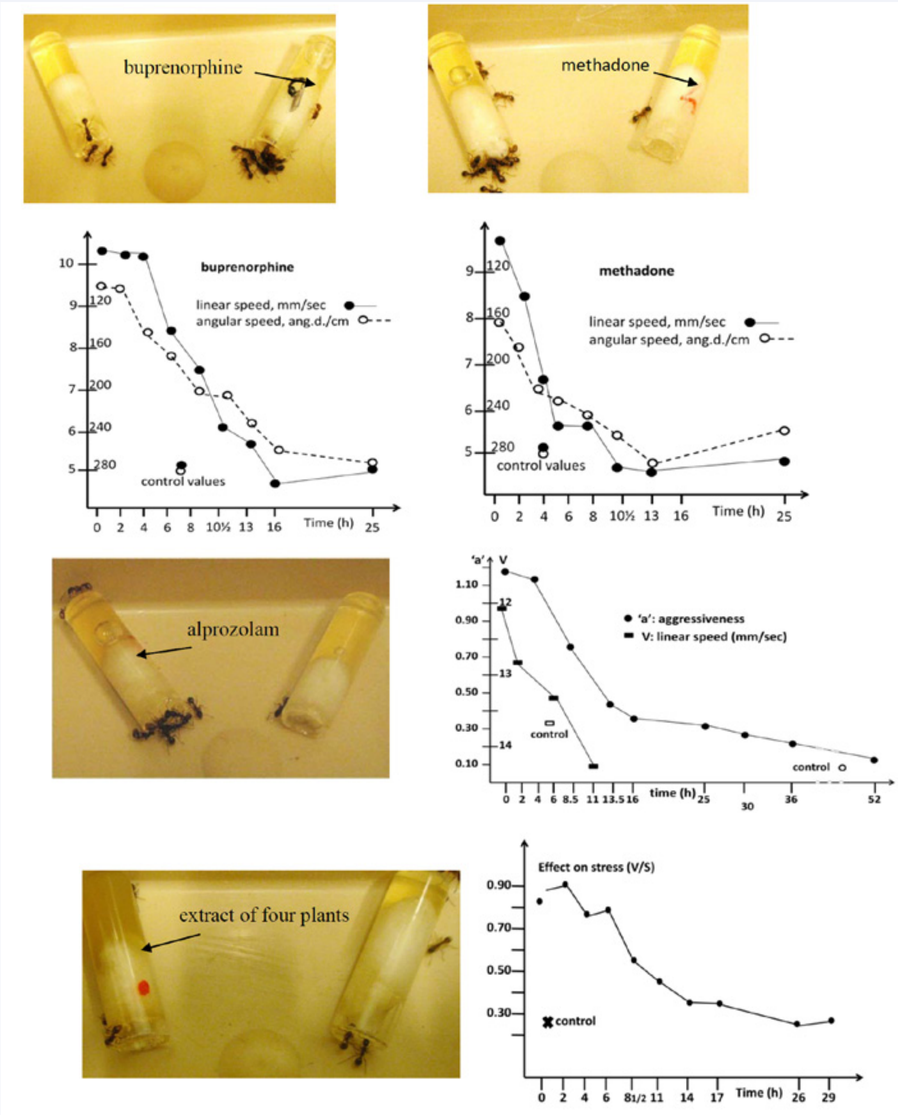

Figure 3 Appearance of dependence on drugs (photos), and decrease of the effect of these drugs after withdrawal. Alprozolam rapidly lose its effect and leaded to dependence. Reproduced from [13-15].

ants randomly drank each liquid (62 *vs* 62). The decrease of the effects of the drug after weaning was examined by monitoring the ants' locomotion on a rough substrate. During the first four hours, the ants continued to walk as if they did not perceived the rough character of the substrate. Thus, a substantial delay was observed before the drug lost its effect. Subsequently, the ants' linear speed on a rough surface decreased and their angular speed increased, according to sigmoid curves. For the linear speed: $y = 10.52 – 0.14x – 0.034x^2 – 0.0012x^3$, and for the angular speed: $y = 108.35 + 11.42x – 0.19x^2$ (with x in hours, and y in mm/sec or ang.deg./cm, respectively). Sixteen hours after weaning, the linear and angular speed values were similar to the control values. Thus, the effect of buprenorphine disappeared slowly in approximately 15 hours with an initial latency period prior to the decrease.

Methadone dependence was not observed [13] (Figure 3). Indeed, 19 ants selected the liquid containing the drug and 68 selected the liquid lacking methadone. Ants thus exhibited some aversion to methadone. After withdrawal, the ants' locomotion on a rough substrate (initially rapid) changed; then, from 3½ to 7½ hours, it presented little change (a level thus existed), and thereafter, it again changed, such that it was similar to the control one 10 - 13 hours after withdrawal. The decrease displayed a sigmoid curve: for the linear speed: $y = 9.36 – 0.72x + 0.02x^2$, for the angular speed: $y = 161.99 + 16.75x -0.50x^2$ (with x representing by in hours, and y representing by in mm/sec or ang.deg./cm, respectively). Thus, the effect of methadone disappeared in a three step mechanism: a short decrease, no decrease during about five hours, and a final rather slow decrease during about six hours.

Alprazolam, and an extract from four plants (sedinal plus)

These two substances are anxiolytics; the former is a synthesized compound, the latter is a natural food supplement (http://www.vulgaris-medical.com) [14,15] (Figure 3).When presented with sugar water and sugar water containing alprazolam, the ants strongly preferred the latter solution. Eighty-two ants were observed drinking the alprazolam solution and 11 consuming the drug-free solution. The ants developed thus a physiological dependence on alprazolam. After weaning, the ants' linear speed approached the control value within 2 h, and equaled that control value after a total of 11 hours. These findings revealed a rapid decrease of the effect of alprazolam on the ants' speed, and this was confirmed by the quick vanishing of the ants' aggressive behavior between 4 and 13½ hours after weaning. Thus, alprazolam becames rapidly inactive after withdrawal.

Regarding the extract of four plants (VHPB = *Valeriana officinalis* L., *Humulus lupulus* L., *Passiflora incarnata* L., and *Ballota nigra* L.), when ants that consumed that extract were presented with pure water and water containing the extract, 22 ants selected the VHPB solution, and 44 ones the water free of the mixture (Figure 3). This result did not statistically differ from the expected result if ants randomly chose each of two solutions. Thus, the VHPB mixture did not lead to dependence. After withdrawal, the effect on ants' stress slowly disappeared over 29 hours. Specifically, stress remained unchanged for two hours. Then, the calming effect was somewhat decreased during the next 2 hours. After that, the effect of the VHPB mixture on stress was again unchanged for the next two hours. Then, from 6 to 14 hours after withdrawal, its effect notably but not excessively decreased. The effect then unchanged for at least 3 hours. Thereafter, from 17 to 26 hours after withdrawal, a slight last decrease was observed. Finally, the values obtained after 29 hours were similar to the control ones. The disappearance of the effect of the VHPB mixture was thus a slow process, with two distinct plateaus.

Sucralose

Sucralose is a synthesized sweetener that has a very strong and nice sugary taste [16] (Figure 4). When presented with a sugar/sucralose solution and a solution of pure sugar, 49 ants that had consumed this sweetener (60.5%) selected the sugar/sucralose solution and 32 (39.5%) selected the sugar solution. The ants thus displayed a slight dependence on sucralose. While consuming sugar/sucralose, the ants exhibited aggressive behavior towards their nestmates. This trait rapidly changed from 2 to approximately 8 hours after weaning. Thereafter, the decrease in agonistic behavior slowed. After 29 hours, the ants were no longer aggressive toward their nestmates; the value was similar to the control one. The impact of sucralose on behavior decreased thus quickly from 2 to 8 ½ hours, and then slowly from 8 ½ to 29 hours after weaning.

Statins and arterin

These two substances are used as treatments for hypercholesterolemia [17,18] (Figure 4). Statins (e.g., simvastatin) are synthesized, whereas arterin is a natural product containing lovastatin; it is red yeast living on rice. When presented with a sugar solution lacking statin and a sugar solution containing the drug, 21 ants chose the former solution and 24 ants chose the latter. These numbers did not differ from those expected if ants randomly drank each solution. Thus ants did not develop dependence on statin. The effect of simvastatin decreased slowly, regularly, and nearly linearly over time. The effect at time t after weaning (E_t) could be estimated using the linear function: $E_t = E_i - 3.75t$, where E_i is the initial effect. Twelve hours after weaning, the effect of simvastatin on ants' boldness was still significant, differing from the control value and being similar to its initial value. After 24 hours, this trait was still different from the control one, and was this time slightly different from its initial one. Later, 33 ½ hours after weaning, the ants' boldness no longer statistically differed from the control one, and 38 hours after weaning, it was identical to that control value. Thus, the effects of simvastatin lasted approximately 1 ½ days and decreased slowly, regularly during that time period.

When presented with sugar water + arterin and sugar water, 28 ants drank the former liquid and 36 drank the latter liquid. These numbers did not differ from those expected if ants randomly consumed each liquid (32 and 32). The ants presented thus no dependence on arterin. The variable used to examine the loss of the effect of this food supplement after withdrawal was the ants' angular speed on rough paper. During the first four hours, this sinuosity did not change. Then, a slow decrease occurred. However, after 7 ½ hours, the ants' angular speed still differed from the control one, and was similar to that before weaning. After 10 ½ hours, the angular speed still differed from the control one but differed from the value under arterin diet. Seventeen hours after weaning, the ants' angular speed was nearly identical to the control value, and after 25 hours, it was the same as that value. The decrease of the effect of arterin displayed a logarithmic curve the function of which was: $e_t = e_i - k \text{ Log } t$ (where e = effect, t = time, and k = a constant). The decrease gradually slowed over time.

Carbamazepine

This substance is used as a treatment for epilepsy and neuralgias (http://fr.wikipedia.org/wiki/; Carbamazépine) [19] (Figure 5). When presented with sugar water free of carbamazepine and sugar water containing the drug, 46.35% of ants chose the former liquid, whereas 53.95 of ants preferred the latter liquid. Thus, ants did not develop dependence on carbamazepine. After carbamazepine withdrawal, its effects disappeared slowly in 20, 26 or 32 hours, according to the examined traits, i.e., the ants' linear speed, sinuosity or orientation. The linear speed became identical to the control value 20 hours after withdrawal, the decrease being a linear function of the running time (V = 8.666 + 0.2498 T (r = 977, P = 0.0002)). The sinuosity was identical to the control value 32 hours after weaning, the decrease being a linear function of time (S = 188.37 – 3.112 T (r = - 0.979, P = 0.00002)). The orientation towards an alarm signal was the same as the control value 36 hours after weaning, this decrease occurring according to a linear function of (O = 65.05 – 0.95 T (r = - 0.962, P = 0.00004)). Consequently, the loss of the effects of carbamazepine was very slow.

Paracetamol, ibuprofen, curcumin

Paracetamol was the most consumed analgesic until these last two years; it is the active substance in Dafalgan®, Efferalgan®, Doliprane®, and Perdolan® [20,21] (Figure 5). When presented with pure sugar water and sugar water containing paracetamol,

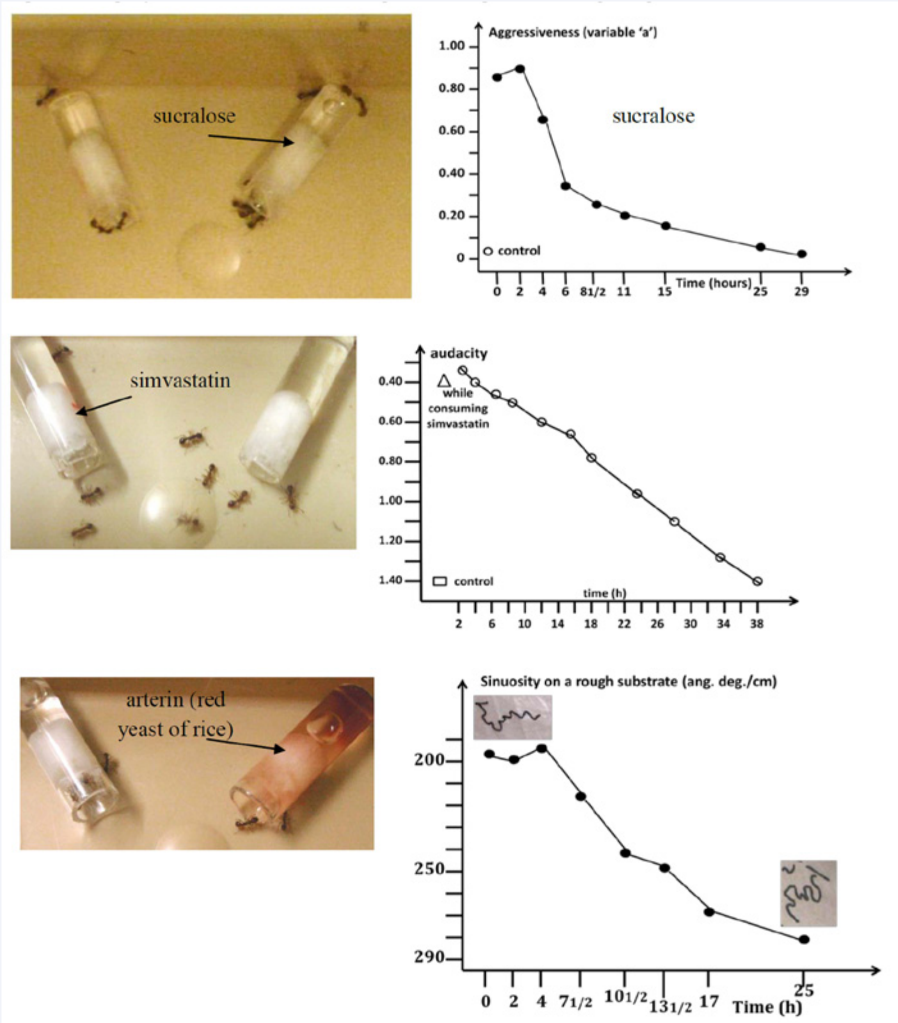

Figure 4 Dependence on substances, and decrease of the effect of these substances after withdrawal. Sucralose produced dependence, and its effect rapidly decreased after weaning. Reproduced from [16-18].

43 ants went drinking the latter liquid and 27 ants the former one (Figure 5). These values did not differ from those that would have been obtained if ants had randomly consumed each liquid. However, when presented with the same two sugar solutions, ants that had never consumed paracetamol made a different choice: 15 chose the solution lacking the drug, and 3 chose the solution containing it. The values (43 *vs* 27) obtained from ants that had consumed paracetamol differed from the values (3 *vs* 15) obtained from ants on a normal diet. Based on the results of this last comparison, ants that had consumed paracetamol presented some dependence on the drug. After weaning, the effect of paracetamol decreased immediately and very rapidly over a few hours, and had nearly disappeared within 4-4 ½ hours (Figure 5). As early as after 3 hours, paracetamol displayed a weak effect. The ants' linear speed on a rough substrate already largely differed from the value observed before weaning. However, the drug was still somewhat active since the ants' angular speed on a rough substrate differed from the control value. Thereafter, 4 ½ hours after weaning, the ants' linear speed on a rough surface was identical to the control value, but the ants' sinuosity still slightly differed from the control value. Seven hours after weaning, that sinuosity was similar to the control value. The effect of paracetamol decreased thus rapidly, and vanished in about 4 ½ hours.

Ibuprofen is the nowadays most used analgesic [22]. Confronted to sugar water and to sugar water containing ibuprofen, 23 ants were seen on the latter solution and 24 ants on the former one. Thus, ibuprofen did not lead to dependence. As for the decrease of the effect of this drug after weaning (the trait examined being the ants' sinuosity), after 4 to 6 hours, the sinuosity was still similar to that observed under ibuprofen consumption. Eight hours after weaning, it was lower than that before weaning, but still somewhat different from the control one. Ibuprofen had thus still some slight effect. Ten hours after weaning, the sinuosity was statistically not different from the control one, though being slightly higher, and 12 hours after weaning, it was similar to the control one. Consequently, the effects of ibuprofen slowly vanished in a total of about 10 hours, following the quadratic function: $E = -0.396\ t^2 - 1.553\ t + 191{,}976$ ($R^2 = 0.99$).

Curcumin is extracted from the rhizome of *curcuma longa*

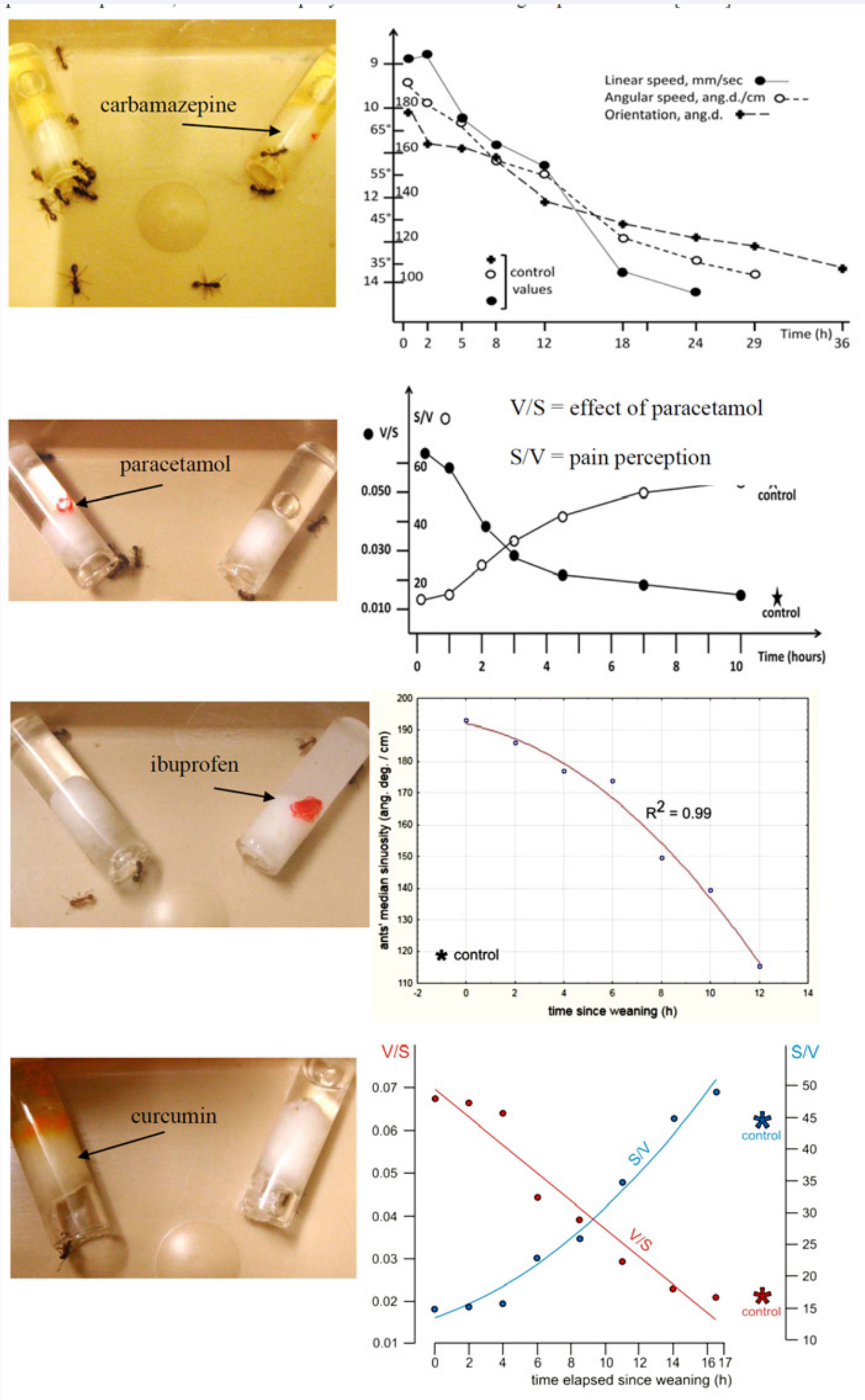

Figure 5 Photos of tests revealing probable dependence on four drugs and decrease of the effects of these drugs after weaning. Paracetamol leads to addiction, and its effect decreased very rapidly over time. Reproduced from [19, 21-23].

and is known for having analgesic properties [23]. In front of a sugar solution free of curcumin and a similar solution containing this product, 40 ants preferred the former solution and 32 ants the latter one. These numbers did not differ from those expected (36 and 36) if ants went randomly drinking each kind of sugar water. Consequently, the ants developed no dependence on that product. The decrease of the analgesic effect of curcumin was studied examining the ants' linear and angular speeds on a rough substrate. Six hours after weaning, these traits went on differing from the control ones, and were statistically similar to those before weaning. Eight and an half hours after weaning, the analgesic effect of *curcuma* became less efficient. At that time, the ants' locomotion on a rough substrate was at the limit of differing from the control one, though being still not different from that

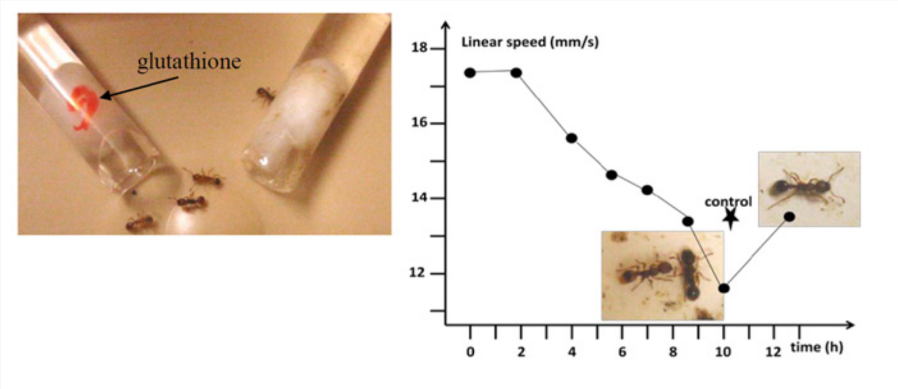

Figure 6 Dependence on glutathione (the photo) and quick decrease of the effect of this compound after weaning (the graph). Reproduced from [24].

before weaning. Eleven hours after weaning, the ants' linear and angular speeds became statistically similar to the control ones and different from those before weaning. After that, they still somewhat better approached the control ones. Thus, after weaning, the analgesic effect of curcumin stayed intact for 6 hours and then vanished in a total of about 9-11 hours.

Glutathione

Glutathione is a natural compound present in every cell, and essentially acting as an antioxidant. It is nowadays produced by humans as a food complement recommended for staying in good health [24]. When ants that have consumed this product were presented with sugar water containing it, and sugar water free of it, 38 ants went on the former liquid and 13 ones on the latter. These numbers statistically differed from those expected if ants went randomly drinking each provided liquid. Consequently, ants developed some dependence on glutathione consumption. However, glutathione might have a pleasant taste for the ants. Therefore, as a precaution, a similar experiment was performed on ants having never consumed glutathione. During this experiment, 23 ants were counted on the liquid containing glutathione and 38 ones on that free of it. These results (23, 38) did not statistically differ from those expected if ants randomly went drinking each kind of liquid (30.5, 30.5). Consequently, ants having never consumed glutathione did not prefer the liquid containing that food complement, on the contrary (23 vs 38). This confirmed that ants having 'known' glutathione acquired some dependence on that product (which we showed acting as a doping substance [24]). The decrease of the effect of glutathione was examined looking to the ants' linear speed. Four hours after weaning, this trait was still similar to that before weaning. Five and an half hours after weaning, the ants' linear speed no longer differed from the control one, and 7 hours after weaning, the ants walked nearly as usually. Their linear speed became similar to the control one 8½ hours after weaning. Unexpectedly, 10 hours after weaning, the ants walked more slowly than usually. They recovered until 12½ hours after weaning, and walked at that time at their usual speed. Such a recovering time period was in agreement with the doping effect of glutathione.

GENERAL, OTHER AUTHORS' AND PERSONAL COMMENTS ON DEPENDENCE AND ADDICTION

The present paper examines the phenomenon of dependence from a new and original perspective, using ants as model. We thus considered only true physiological dependence, and not psychological one. The difference between dependence and addiction is subtle. Addiction encompasses both a mental and physical reliance on a given substance, so, in the present study, we investigated on physiological dependence.

The existence of dependent persons (to drugs or behaviors) leads to social, economic, behavioral, security and professional problems [25]. Caring of and weaning dependent persons is a long and painful process, which also requires extensive social and financial costs. During withdrawal, dependent persons are often physically ill and 'lost' to the community (santeweb.ch/santeweb/Maladies/khb.php?Addiction_et...khb_lng_id=2...). Numerous studies are continuously being reported on the subject; approximately 50 studies are published each month, many of which are available at the following website: Recent Drug and Alcohol Dependence Articles; https://www.journals.elsevier.com/drug...dependence/recent-article...

What are optimal methods for preventing addiction and caring of addicted persons as soon as possible?

Based on our studies, we ultimately concluded that dependence and a rapid loss of an effect are correlated, and that lack of dependence is associated with a slow decrease of the effect of the substance. The main cause of physical dependence on a substance is thus a rapid decrease of its effect after withdrawal. The potentially dependent person must be managed, treated, and cared of at the time at which the previously consumed drug is known to rapidly lose a rather large fraction of its effect, this in order to prevent dependence. During this critical time period, alternative solutions must be given to the person so that he (she) does not consume the drug. Alternatives include good food or drink, pleasant music, pleasant smells, or films; as well as activities such as playing, resting, relaxing, having fun, or any activity that allows the individual to forget that the drug is no longer available for a time. The care of dependent persons during a given critical time period should probably be repeated several times before complete withdrawal is achieved. However, if the strategy is used correctly, it will succeed.

Ants appear to be excellent models for revealing the appearance of some form of physiological dependence on a substance, as well as for defining the critical 'time period' after withdrawal during which the effect of the substance rapidly decreases. Results obtained on ants should be checked by experiments on mammals and humans, and then used to care of dependent persons during their 'critical time period', with the aim of helping them suppressing their dependence.

Insects, including bees and ants, are currently being used as models in an increasing number of studies. ['The elaborate organization of the arthropod brain suggests circuits and functions that typify the brain of vertebrates' (Strasfeld)]. Several studies have been published on different topics useful for humans, including the effects of drugs, the dependence phenomenon, and the biochemical activities of substances. Let us cite studies [26] on morphine addiction in ants (the authors revealed that ants developed a dependence on morphine and described the subsequent neurochemical changes), [27] on ethanol consumption in *Drosophila* models, [28] on *Drosophila melanogaster* as a model for studying drug addiction, and [29] on the use of invertebrates for studying addiction. However, none of these reports describe the link between dependence and the rapid loss of the effects of the substances described in the present study.

We have examined dependence on substances humans can and sometimes must consume (drugs available in drugstores, antidepressants, anxiolytics, sweeteners, etc.). This finding may be extended to other substances humans should normally not consume, such as alcohol, cannabis, and some kinds of food or drink. Dependence on gambling, driving at high speed, playing video games, smart phone use has also been reported. The same method as that here proposed can be used to treat these dependencies. The dependent person will miss his/her 'drug' at a time, will begin to suffer from this lack after a given time, and should then receive care and support, including appropriate alternatives during this critical time period until the craving has passed.

The observation that dependence occurs when the effect of the 'drug' rapidly decreases during a given time is valid for the weaning procedure. In other words, any weaning procedure will succeed only if the process is a slow, step-wise procedure that follows a specific regimen, and is combined with the use of palliative elements. A quick weaning process performed in one step without any palliative elements has a poor probability of succeeding without relapse.

Another cause of dependence and of weaning failure has been discovered by B.K. Alexander [references here below], but this finding was firstly refuted. Rats housed alone in skinner boxes became addicted to cocaine. Subsequently, B.K. Alexander revealed that rats housed all together in boxes did not develop dependence [30-33]. Thus, persons become dependent on drugs or behaviors when (and nearly only when) these persons suffer from some social, psychological, moral difficulties. Treating these persons must include not only help during the critical period following weaning (see above) but also help for solving their social problems. These ideas were also reported by Sotto [25]. This was well illustrated by our experiments on ants consuming nicotine: when ants were not hungry, they did not display dependence; when they were hungry (had a social problem), they showed a strong dependence on nicotine.

In our studies, ants developed dependence on a substance because they were experimentally provided with only a sugar solution containing the substance. They lived under a drug diet; they could not choose between the 'drug' solution and a drug-free solution. After a few weeks under drug diet, they were tested in front of a 'drug' solution and a drug-free one, and this allowed revealing a potential dependence. Future experiments will examine if ants maintained under normal diet and optimum conditions instinctively avoid solutions containing harmful products, as well as those leading to dependence.

CONCLUSION

In conclusion, dependence is a personal and social problem [34-36]. Prevention and early intervention are the best methods to treat dependence. Dependence occurs when some social or similar problem occurs, and when a substance is consumed that displays a rapid decrease of its effect during a given 'critical' time period. Consequently, social or personal problems encountered by the dependent person must be at least partially solved, and the dependent person must receive care during the 'critical' time period following withdrawal to prevent, treat, or resolve dependence. In addition, the weaning process must be slow and include several steps, with particular attention during each successive 'critical time period', and palliative elements must be provided to the initially dependent persons during each critical time period. The 'critical' time period of drugs must be defined (to know when assisting dependent persons) thanks to experiments (made on ants, mice, rats, monkeys and humans). In the present work, we define the 'critical' time period of eight products: cocaine, nicotine, morphine, paroxetine, alprazolam, sucralose, paracetamol, and glutathione.

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