Necessity knows no law in a snail

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Abstract
In the present review, we outline the relationship between starvation and taste-aversive learning (conditioned taste aversion: CTA) in the pond snail

*Lymnaea stagnalis and introduce the “necessity knows no law” concept. When snails were food-deprived for a short period, the snails learned and formed memory of CTA well, whereas when snails were food-deprived for a prolonged period, the snails appeared not to learn CTA or form long-term memory (LTM) of it. However, in severely food-deprived snails (i.e. snails that were food-deprived for a prolonged period), memory was found to indeed form but was overpowered by the effect of severe food deprivation. That is, snails are partially restricted in the “necessity knows no law” concept. Moreover, this CTA-LTM was context dependent and was observed only when the snails were in a context similar to that in which the training occurred. In addition, when insulin was injected into the severely food-deprived snails, they started to exhibit learning and memory. That is, insulin rescued the snails’ “hidden” ability of memory retrieval. In addition to these topics in snails, we survey the literature on starvation and learning obtained in other animals for general discussion. We hope that this review will stimulate further detailed studies of motivation in invertebrates.

Keywords: Context dependency, insulin, learning, mollusc, starvation

Introduction
W. G. Quinn described that “an ideal subject for studying the cellular and molecular bases of learning should, probably, have ten large nerve cells, ten genes, a generation time of 1 week, and the ability to play a cello and recite Shakespeare” (quoted in Dudai 1989, p. 49). Although it is hard to find animals that can play a cello and recite Shakespeare, molluscan gastropods, such as Aplysia, Hermisenda, Limax, Lymnaea and so forth, have been widely recognized as useful animals with which to study the molecular and cellular mechanisms underlying learning and memory (Kandel & Tauc 1965; Gelperin 1975; Alkon 1976; Kemenes & Benjamin 1989; Ito et al. 1994, 2013; Lukowiak et al. 1996; Kobayashi et al. 1998; Kojima et al. 1998; Fujie et al. 2005; Martens et al. 2007). For example, after the central pattern generator of feeding behavior was discovered in the pond snail

*Lymnaea stagnalis in 1979 (Benjamin & Rose 1979; Rose & Benjamin 1979), many attempts to clarify the cellular and molecular mechanisms underlying taste-appetitive and -aversive learnings have been carried out (Benjamin et al. 2000).

Our research group has particularly studied one kind of taste-aversive learning, called conditioned taste aversion (CTA), in *Lymnaea* (Yamanaka et al. 1999; Wagatsuma et al. 2004; Kita et al. 2011; Otsuka et al. 2013; Sunada et al. 2017a). Innately, sweet food attracts various kinds of animals, as it is one of the sources that can be converted into energy in the body. Likewise in snails, a sucrose solution evokes the feeding response (i.e. the number of bites in response to sucrose), and thus a sucrose solution can be used as a conditioned stimulus (CS) in our conditioning paradigm (Sadamoto et al. 2000; Sugai et al. 2006). On the other hand, an aversive stimulus (e.g. a potassium chloride [KCl] solution or an electric shock) induces a withdrawal response in snails. A withdrawal response is a very important behavior for snails, and so when the snail body withdraws into the shell, the feeding response is also stopped. Thus, an aversive stimulus inducing a withdrawal response can be used as an unconditioned stimulus (US) in our paradigm.
In the CTA paradigm, the CS is paired with the US. After repeated temporally contingent presentations of the CS and US, the CS no longer elicits a feeding response (i.e. an unconditioned response), and this aversive conditioning persists for at least a month as long-term memory (LTM) (Kojima et al. 2001; Ito et al. 2012). Further, whether or not CTA and its consolidated LTM will form depends on the snail’s internal state (i.e. starvation or satiety), and indeed the members of the Ito laboratory have uncovered some important phenomena regarding this issue (Mita et al. 2014a; Yamagishi et al. 2015).

In the present review, we discuss the relationship between starvation and CTA performance in snails. We outline the following points: (1) One-day food-deprived snails can learn CTA and form its LTM well. (2) However, the 5-day food-deprived snails indeed form CTA-LTM but do not exhibit its memory phenotype. Here we introduce the “necessity knows no law” concept for such extremely hungry snails, because they cannot restrain themselves from eating the food they must not eat. (3) The CTA-LTM in snails is controlled by insulin working in the central nervous system (CNS). For example, the poor scores for CTA in the 5-day food-deprived snails are improved by an injection of insulin. We also introduce the changes in dopamine and octopamine contents in the CNS during food deprivation. (4) Finally, we survey the literature on the relationship between starvation and learning in vertebrates and invertebrates for general discussion.

### Starvation and learning performance: Yerkes–Dodson/Hebb law

Empirically, we have so far noticed that modestly food-deprived snails are better capable of taste-aversion learning (i.e. CTA) and forming LTM than satiated snails, whereas severely food-deprived snails cannot form CTA-LTM (Sugai et al. 2007). Thus, snails are usually trained with a conditioning paradigm after 1-day (i.e. modest) food deprivation.

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**Figure 1.** Training paradigm for conditioned taste aversion (CTA) and learning performance. (a) Three types of trainings. Forward: a conditioned stimulus (CS, a sucrose solution) is paired with an unconditioned stimulus (US), a KCl solution or an electric shock. After the application of the US, an intermission is needed. This forward training is CTA training. Backward: the US is paired with the CS, and after the application of the CS, the same intermission as for forward training is needed. That is, the backward conditioning is a control procedure. Naïve: both the CS and the US are replaced by the application of distilled water (DW). This is also a control procedure. (b) Schematic presentations of the changes in the number of feeding responses (bites/min) in response to the sucrose CS before and after training. At the pretest, there are no significant differences in the feeding responses among the three cohorts (i.e. forward, backward and naïve snails). After the training, the feeding response to sucrose in forward snails is suppressed, and this suppression remains for at least 1 month. The scale of the y-axis is arbitrary (the expression of the y-axis is similar in the other figures).
Hatakeyama et al. (2006) (Figure 2(a)). These 1-day food-deprived snails are called “Day 1 snails”. These learning and memory-forming abilities can be explained by an inverted-U law in which there is an optimal level of arousal for learning (Yerkes & Dodson 1908; Hebb 1955; Ito et al. 2015b). Stress alters learning and memory formation. Yerkes and Dodson (1908) stated that “an easily acquired habit may be readily formed under strong stimulation, whereas a difficult habit may be acquired only under relatively weak stimulation” (Yerkes & Dodson 1908). Hebb (1955) discussed stress and memory using the words of inverted-U law (Hebb 1955). That is, 1-day food deprivation (hereafter Day 1) is an optimal level of stress that results in the best memory, whereas 5-day food deprivation (hereafter Day 5) is a stress that results in poorer memory formation and/or its recall.

Necessity knows no law concept in severely food-deprived snails

The memory phenotype in severely food-deprived snails was carefully studied. We considered that severely food-deprived snails might in fact learn CTA and form LTM, but that the severe deprivation would block their performance that acts on their memory and thus snails would be expected to exhibit “necessity knows no law” behavior (Ito et al. 2015a). The concept of “necessity knows no laws” has been considered an English proverb since the 1550s (see the Oxford English Dictionary). It basically means that “during a famine a very honest person may break the law to feed their children”, or “if one is desperate one may have to do illegal things”. Thus, if snails are fed until 1 day before CTA training (i.e. 1-day food deprivation) as usual, they will adhere to the rule and not eat (i.e. CTA). However, if snails are 5-day food-deprived (i.e. being desperate), they will break the rule and eat (Ito et al. 2015a). In other words, Day 5 snails were expected to learn CTA but not to exhibit its memory phenotype.

To examine this hypothesis, Day 5 snails were trained under various conditions. One condition included the idea that food deprivation produces a very specific behavioral state, which was considered to be the context (Palmer & Kristan 2011; D’yakonova 2014). In this case, the context was the state associated with food deprivation (Ito et al. 2015a). (Figure 2. The “necessity knows no law” concept in food-deprived snails. (a) Definition of food-deprived snails. The day on which the snails start food deprivation is Day 0. Day −1 snails have access to food ad libitum. Day 1 snails are the modestly food-deprived snails, which were food-deprived for only 1 day. Day 5 snails are the severely food-deprived snails. To test the hypothesis that Day 5 snails would indeed learn conditioned taste aversion (CTA) and form its long-term memory (LTM), the snails were given access to food ad libitum for 7 days following the 5-day food deprivation and CTA training, and then they were food-deprived for 1 day. Finally, they were tested by an application of the sucrose CS (i.e. Day 13 snails), resulting in the exhibition of CTA-LTM. (b) Schematic presentations of the differences in the number of feeding responses (bites/min) in response to the sucrose CS between Day 5 snails and Day 13 snails. As mentioned above, Day 13 snails recall their “hidden” memory by a context of “starvation” (i.e. the final 1-day food deprivation). That is, the feeding response to sucrose in Day 13 snails is suppressed. This figure shows that the memory phenotype is established on Day 12, and thus a suppression of bites occurs just before the first post-test.)
To be specific, Day 5 snails were trained with the CTA training paradigm (i.e. pairings of 10 mM sucrose CS and 3-s electric shock US). After 20 pairings of the CS and US in a single day, the snails were given access to food for 7 days right after the training. When these snails were tested at this point, they did not exhibit CTA memory. However, this 7-day period was followed with a 1-day food deprivation period, and then the snails were tested again (i.e. an application of the CS; Figure 2(a)). The snails exhibited CTA memory, which was the suppression of the feeding response to the CS (Figure 2(b)). It was concluded that the memory was indeed formed but that the severe food deprivation rendered the snails unable to act on that memory. That is, the memory retrieval and the memory performance are differentiated even in snails. The severely food-deprived snails have the ability of memory retrieval, but they do not exhibit the memory performance (i.e. the suppression of feeding response to the sucrose CS) without a motive (i.e. a modest starvation).

Moreover, this CTA-LTM was judged to be context dependent and was observed only when the snails were in a context similar to that in which the training occurred. That is, when the memory test was conducted right after the 7 days of food access and without depriving the snails for 1 day before the test, the snails did not exhibit CTA memory. Therefore, the phenomenon is considered to be “a consequence of conflict resolution”, and so the snails are indeed subject to the “necessity knows no law” concept (Ito et al. 2015a).

Here the possible biological functions of the “necessity knows no law” concept in snails are discussed. Generally, animals avoid poisonous substances to keep their own safety. That is, food preference is a kind of self-defense mechanism. CTA allows snails to learn that sucrose signals the delivery of shock, and to withdraw from it even despite the fact that it is a substance that they innately like and consume. Snails that are severely food-deprived (i.e. Day 5) must eat something to survive, even if that something has become a reliable predictor of an aversive event such as an electric shock. The fact that the memory phenotype was not exhibited in Day 5 snails has a biological meaning that has to do with the “necessity knows no law” concept (Ito et al. 2015a).

Rescue of poor learning in severely food-deprived snails by insulin

A snail’s behavior is partially restricted in the “necessity knows no law” concept. On the other hand, our research group found that insulin plays an important role in the consolidation of LTM (Azami et al. 2006; Hatakeyama et al. 2013; Murakami et al. 2013a; Kojima et al. 2015). The experiments were designed to inject 100 nM insulin into severely food-deprived snails (i.e. Day 5 snails), which were poor learners for CTA (Mita et al. 2014b). Then these snails were trained with the CTA paradigm using a sucrose solution and electric shock. As expected, CTA-LTM was formed (Figure 3), whereas the control experiments (i.e. vehicle injection) failed to form CTA-LTM. That is, insulin rescued the ability of “hidden” learning and memory. On the other hand, when an insulin receptor antibody was injected into modestly food-deprived snails (i.e. Day 1 snails), which readily learned CTA, they did not form a memory (Murakami et al. 2013b). It was concluded that, in snails, insulin plays a key role in learning and memory in starved states. Further, we would like to point out that intranasal insulin is used for the prevention or the symptomatic treatment of Alzheimer’s disease in humans (Ribe & Lovestone 2016).

However, this effect of insulin on learning and memory varies in other animals. For example, in Drosophila, flies show aversive taste learning in a food-deprivation state induced for 9–16 hours before the conditioning, corresponding very well to the state of our Day 1 snails. This was thought to be due to the downregulation of the insulin signaling pathway and the upregulation of the signaling pathway of cAMP-regulated transcriptional coactivator (CRTC) (Altarejos & Montminy 2011; Hirano et al. 2013). Hirano and Saitoe (2013) explained this mechanism as follows (Hirano & Saitoe 2013). Blocking the activity of cyclic-AMP response element binding protein (CREB) in the memory center, mushroom bodies, impairs this fasting-LTM. CREB is well known to be required for LTM, and CREB requires co-activators, one of which is CRTC to activate transcription. The fasting-LTM in flies is dependent on CRTC. On the other hand, CRTC is regulated by insulin signaling. During fasting, insulin signaling is suppressed, which in turn activates CRTC. Hirano and Saitoe concluded that reduced insulin signaling is essential for CRTC-dependent fasting-LTM formation (Hirano & Saitoe 2013). On the other hand, when facing severe food deprivation, flies abolish the formation of aversive LTM (Plaçais & Preat 2013). The correspondence between our Day 5 snails and very severely food-deprived flies is still unsolved.

Effects of starvation on general learning and memory in mammals – two important regions in the mammalian brain: the hippocampus and the amygdala

There is a limited number of studies that explore the relationship between starvation and CTA in rats, for example the studies about anorexia nervosa (Liang...
et al. 2011). Liang et al. (2011) showed that experience with anorexia nervosa-like behaviors results in an acquired aversion to a preferred food sooner and a longer retention of the negative food associations. This study remained at the behavioral level. Thus, we should expand our discussion to the relationship between starvation and general learning and memory in mammals. In studies using mammals, two specific brain regions, the hippocampus and the amygdala, are noted.

In mammals, several brain regions are well known to play important roles in learning and memory (Izquierdo et al. 2016; Schwabe 2017), and interestingly some functions of those brain regions are regulated by starvation. For example, the hippocampus is known to be affected by hunger signals, and thus it is thought to regulate food intake (Davidson & Jarrard 1993). Further, food-restricted rats showed higher long-term potentiation at hippocampal CA1 excitatory synapses compared with rats fed ad libitum, and these food-restricted rats showed a reinforcement of long-term spatial memory (Talani et al. 2016). These effects of food restriction on learning and memory may involve changes in the expression of cannabinoid type-1 receptors in the hippocampus. The hippocampal cannabinoid system is thought to control cognition, behavior and some diseases like epilepsy (Lupica et al. 2017). Indeed, the involvement of cannabinoid receptors in learning and memory has also been shown to be important in snails (Sunada et al. 2017b).

The relationship between a kind of associative learning, fear conditioning and starvation has also been examined in mammals. The main brain region controlling fear conditioning is the amygdala in mammals. Recent studies revealed that short-term food deprivation before fear conditioning impaired long-term fear memory, whereas food deprivation before fear extinction facilitated extinction learning (Verma et al. 2016). Another research group clarified that food deprivation enhanced fear extinction and elucidated the relationship between deprivation and extinction (Huang et al. 2016). Using pharmacological techniques, Huang’s group further explored the features of fear extinction and long-term depression at the lateral amygdala synapses.

These two main regions in the mammalian brain, the hippocampus and the amygdala, change their functions as a result of starvation. In invertebrates like *Lymnaea*, used in the present study, as well as in vertebrates, the mechanisms underlying learning and memory are affected by starvation, telling us that the internal state of experimental animals is an important factor for brain function.

**Effects of monoamine level on CTA-LTM in snails**

In both vertebrates and invertebrates, dopamine functions as a reward system in the brain (Mizunami et al. 2015; Bourgeois et al. 2016). Some psychological studies paid attention to the difference in the dopamine system between food-satiated and food-deprived states (Nader et al. 1997). Recently, the effects of dopamine/octopamine level on CTA-LTM were examined at various starvation states in *Lymnaea* (Aonuma et al. 2016, 2017). Modestly food-deprived (Day 1) snails were the best learners and had significantly lower dopamine/octopamine levels compared to snails under the other conditions. In contrast, severely
food-deprived (Day 5) snails showed poor performance and had higher dopamine/octopamine levels. That is, severe starvation increased the dopamine/octopamine levels in the Lymnaea CNS. In particular, dopamine functions as a reward transmitter as described above, and thus CTA in the severely deprived snails was thought to be mitigated by a high dopamine level.

**Conclusion**

Starvation causes a change in learning performance in CTA of snails. As a result, snails eat what they should not eat, even though they know they should not eat it. The reason that they “know” it is easily understandable by the fact that the “hidden” memory was recalled in a context-dependent manner. On the other hand, insulin is a de novo target molecule for studies of learning and memory. Insulin plays an important role in improvement of deficits of learning and memory-forming abilities in snails.

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