The Neural Basis of Addic2on in Honeybees (*Apis mellifera*)

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Introduc2on

Drug addicLon is a chronic disease that alters the brain and changes the individual's behaviour. It causes 12% of deaths worldwide [1] and contributes an annual cost of £15.5 billion in the UK alone [2].

Mammalian models such as rodents have previously been used in an aDempt to mirror human addicLon, and have aided in understanding the basis of the neural pathways involved, however, the pathways and process of addicLon remains incomplete. In recent years aDenLon has turned to the possibility of using insects as models to study addicLon, due to their considerably simpler nervous system [3,4]; and the fact that dopamine, the primary neurotransmiDer involved in reward processing, is conserved across phyla.

Bees display a rich array of behaviours, given that addicLon is clinically diagnosed by the idenLficaLon of aberrant behaviour, indicates that bees may be a suitable insect with which to study the components of addicLon.

Aim

To idenLfy if honeybees display a preference for nicoLne in sucrose, over sucrose alone; self--administraLon of drugs in the face of an alternaLve of equal value supports the reinforcing properLes of the drug on the insect.

Methods

- 20 honeybees were placed in plasLc cages (Figure 1), and were housed within an incubator that mimics the hives temperature and humidity.

Figure 1. Cages used in the feeding assays showing cohorts of 20 bees, and a single bee feeding from a feeding tube.

- Feeding tubes were filled with either 1 M sucrose alone (control), or 1 M sucrose containing either 25 or 100 µm nicoLne.
- The bees were given one of 3 feeding schedules:
  1)72 h of conLnuous nicoLne
  2)Brief intermiDent: 48 h conLnuous nicoLne, followed by 24 h conLnuous sucrose
  3)ConLnual intermiDent: 12 h conLnuous nicoLne, followed by 12 h conLnuous sucrose for a total period of 72 h
  Immediately following the feeding schedule, bees were offered a two–way choice between either 1 M sucrose alone, or 1 M sucrose containing the concentraLon of nicoLne the bees had previously been administered. Control bees received sucrose throughout.
- In order to assess total consumpLon of either soluLon, tubes were weighed before and aeer the two–way choice. EvaporaLon was controlled for by subtracLng the values from feeding tubes that were housed in empty cages.

Results

Bees display no preference for 25 or 100 µM nicoLne in a 24 h two–way choice, following 72 h conLnuous access to the drug (figure 2). Following the brief intermiDent feeding schedule, bees displayed a significant preference for 25, but not 100 µM nicoLne (Figure 3). Whereas, following the conLnual intermiDent schedule, bees displayed a preference for both 25 and 100 µM nicoLne (Figure 4).

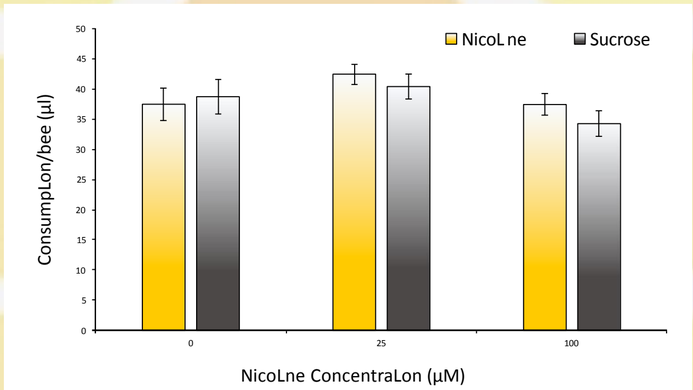

Figure 2. Bees display no preference for 25 or 100 µM nico2ne following 3 days con2nual consump2on. GLM with soluLon type and treatment set as main effects, p = 0.602. n = 0 µM (29), 25 µM (35), 100 µM (35).

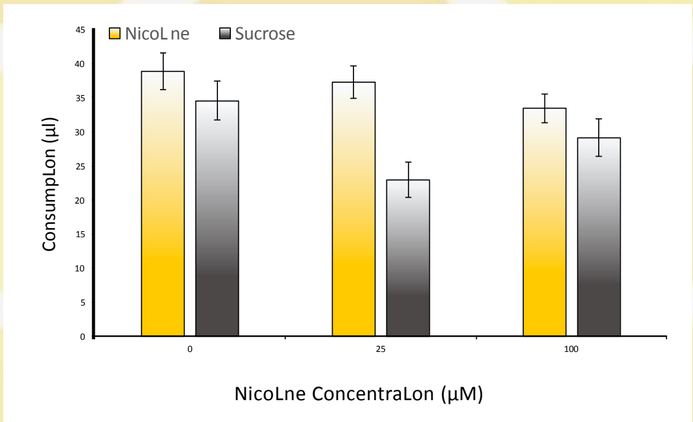

Figure 3. Bees display a significant preference for 25, but not 100 µM nico2ne following 48 h access to nico2ne followed by 24 h abs2nence. GLM with soluLon type and treatment set as main effects, p = 0.003, $\chi_3^2 = 0.75$, $F_{2,114} = 9.043$. Post hoc LSD: 25 µM (p = 0.004). n = 20.

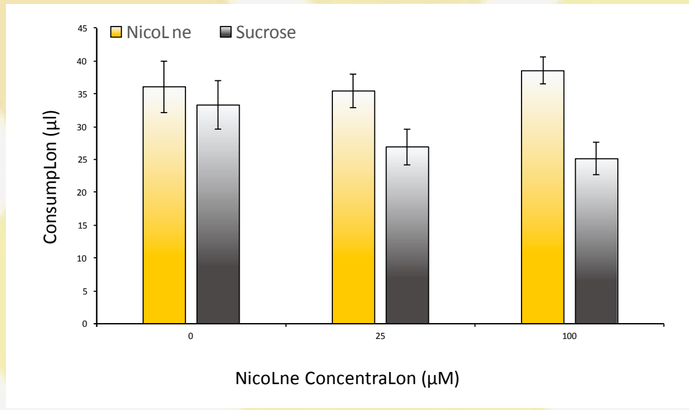

Figure 4. Bees display a significant preference for 25 and 100 µM nico2ne following a 12 h intermiPent access/abs2nence schedule of feeding. GLM with soluLon type and treatment set as main effects, p = <0.001, $\chi_3^2 = 0.94$, $F_{2,108} = 11.465$. Post hoc LSD: 25 µM (p = 0.047), 100 µM (p = 0.016). n = 20.

Discussion

The fact that intermiDent access is sufficient to generate a preference for nicoLne in bees, suggests that nicoLne is having a reinforcing effect on these insects. Furthermore, the clear indicaLon that intermiDent, but not conLnual access, is required in order to generate a preference for nicoLne, suggests that similar to mammalian models of addicLon, honeybees require periods of drug absLnence in order to develop a preference for the drug. It is hypothesised that this intermiDent drug access more closely mirrors that of human nicoLne addicLon, whereby smokers do not conLnually receive nicoLne, but rather have brief periods of smoking, followed by extended (typically 1 to 3 hours) periods of absLnence from the drug. These intermiDent schedules are believed to follow the 'cycle of addicLon', whereby both posiLve (pleasurable), and negaLve reinforcement (unpleasant, i.e. withdrawal) periods are both required in order to generate an addicLve state (Figure 5).

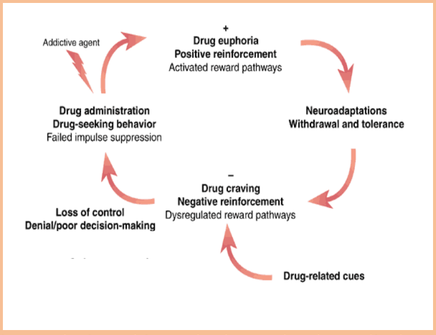

Figure 5. The cycle of addic2on. Posi2ve reinforcement i.e. the 'high' of nico2ne, ins2ls the repeated seeking of the drug in the ini2al stages. Following repeated use of the drug, neuroadap2ons occur, making the user sensi2ve to symptoms of withdrawal. These symptoms then lead to a period of nega2ve reinforcement, in an aPempt to avoid the aversive symptoms encountered during drug-abs2nence.

In conclusion, this study shows that bees display a preference for the drug, however future studies are required to fully idenLfy the full range of behavioural and physiological traits present in addicLon.

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