Ferment in the family: alcohol hormesis in workers of the honeybee *Apis mellifera*

Hormesis is a non-linear relationship between the dose and response – a relationship characterized by certain doses affecting the organism positively, but lower and higher doses affecting it negatively. In alcohol hormesis, low levels of alcohol consumption affect the organism positively, but abstinence and alcohol abuse act negatively. Naturally, alcohol abuse is also addictive, which is why the negative effects of high doses are magnified. Hormesis occurs due to evolutionary adaptations to certain typical doses. As alcohol occurs in nature only in low doses, so alcohol hormesis occurs in organisms adapted for the consumption of food spiked with low levels of alcohol. Such food may include, for example, ripe fruits or slightly fermenting floral nectar. The evolutionary hangover hypothesis (EHH) connects the emergence of alcoholism in the modern human with alcohol hormesis. The EHH poses that natural selection acted on human ancestors by creating their preferences for the identification and adaptations for the consumption of low levels of alcohol present in their main and desirable food source, namely ripe fruits. Today, these preferences and adaptations lead humans to doom because of the widespread availability of alcohol.

An analogous scenario as the one proposed for humans by the EHH might be imagined for other organisms. The main objective of the project here is to investigate whether alcohol hormesis occurs in the honeybee (*Apis mellifera* L.). There are multiple premises for thinking so. The honeybee ancestors likely encountered low levels of alcohol in the environment, in the collected floral nectar and juices of overripe fruits, and adapted for such an encounter. Today, the honeybee likely encounters such food as well, possesses metabolic adaptations for the consumption of alcohol and shows preferences for food spiked with low levels of alcohol. Moreover, in a recent study, we have demonstrated that honeybees get addicted to alcohol when they consume it repeatedly. As such, the honeybee seems an excellent candidate for testing the occurrence of alcohol hormesis and being a model for studying the effects of alcoholism.

In our project, we will feed honeybees with various types of diets, either without alcohol at all, with sporadic low-level alcohol encounter or constant exposure to low levels of alcohol. We will investigate the effects of these different diets on the physical condition of the body expressed in terms of mortality, body parameters and flight abilities as well as on the cognitive behaviour expressed in terms of learning abilities. In every case, we will confirm whether the diet with constant exposure to low levels of alcohol leads to addiction and alcoholism. Therefore, in the project, we will obtain a complex picture of alcohol hormesis in the honeybee and the effects of alcoholism on various aspects of functioning. We predict that the diet with only sporadic low-level alcohol encounter will be beneficial for honeybees in comparison to the diet with no alcohol at all. Furthermore, we predict that the diet with constant exposure to low levels of alcohol will act negatively and in an addictive way.

The significance of the project focuses on the problem of hormesis. Hormesis is worth investigating in many different organisms and various contexts in order to recognize its universality. Other than that, the project significance concerns alcoholism, which is one of the most serious public health issues among humans. Discovering and developing appropriate animal models for the study of alcoholism is of paramount importance for a better understanding of that disease. A not less important aspect of the significance of the project lies in studying the evolutionary genesis of alcoholism. The EHH, like all hypotheses concerned with the evolutionary past, is difficult to study. This, however, does not mean that obtaining additional premises verifying the EHH and revising our understanding of how evolution has shaped the processes of health and disease among today's organisms is not possible. The project offers to provide such premises and revision.