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Oliver, Shune

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The effect of environmental and metabolic stress on the expression of insecticide resistance phenotype and longevity in the Southern African malaria vectors *Anopheles arabiensis* and *Anopheles funestus*

Shüné Oliver

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Abstract

Anopheles arabiensis and *Anopheles funestus* are the two dominant malaria vector species of Southern Africa. Insecticide resistance in these two species plays a major role in complicating malaria control efforts in the region. This study aimed to determine the role of environmental and metabolic stress on the insecticide resistance phenotype, development and longevity of malaria vectors. Furthermore, it aimed to whether the insecticide resistance phenotype affected the vector's capacity to cope with environmental stress, as well as examining the biochemical mechanisms that underpin these responses. Two laboratory *An. arabiensis* strains from Sudan were used: SENN, an unselected strain displaying baseline insecticide resistance and SENN DDT, a strain selected for DDT resistance from SENN. The unselected and permethrin-selected *An. funestus* strains FUMOZ and FUMOZ-R were used, with the fully insecticide susceptible FANG strain used as a baseline control. The insecticide resistance phenotype, as well as a synergist and enzyme activity profile of all the strains were determined. Three environmental and metabolic stresses were examined: larval nutritional stress, oxidative stress and multiple bloodmeals. SENN DDT was found to be resistant to multiple classes of insecticide, with the phenotype mediated by both the L1014F *kdr* mutation as well as elevated detoxification enzyme activity. Pyrethroid and bendiocarb resistance in the FUMOZ-R strain was confirmed to be metabolically mediated. Larval nutrient deprivation in *An. arabiensis* resulted in an increased developmental time and smaller adults with an increased susceptibility to DDT. In the SENN strain increased DDT susceptibility was found to be due to reduced vigour tolerance, while in the SENN DDT strain, the effect was due to significantly reduced metabolic enzyme activity. Insecticide resistant *An. arabiensis* and *An. funestus* strains were found to have a higher tolerance for oxidative stress, with this effect being mediated by significantly higher catalase and glutathione peroxidase enzyme activities in these strains. As all classes of insecticides were found to induce oxidative stress, it was hypothesised that this increased capacity to cope with oxidative stress was due to the requirement of coping with xenobiotic-derived reactive oxygen species. Synergism of oxidative stress enzymes had an effect of the pyrethroid resistance phenotype, with synergism of the enzyme catalase strongly negating the phenotype of SENN DDT and returning the FUMOZ-R strain full pyrethoid susceptibility. Multiple blood feeding sustained the DDT and pyrethroid resistance phenotype

of SENN DDT for up to 21 days. Multiple bloodmeals also had a greater effect of the longevity of the SENN DDT strain. These effects appeared to be mediated by the sustenance of the activity of Glutathione S-transferases with peroxidises in the SENN DDT strain. The blood component insulin significantly reduced the longevity of the SENN, but not the SENN DDT strain. Insulin supplementation also augmented the DDT resistance phenotype of SENN DDT in young females. This study therefore determined that that environmental stress affected both the life history and insecticide resistance phenotype of two major malaria vectors. Furthermore, resistant individuals appeared to cope better with the stresses, with the only marked fitness cost was reduced longevity in the SENN DDT strain. The study highlighted the importance of common environmental stressors on life history characteristics of importance for vector control, as well as the complicating role of insecticide resistance in the biology of vector species.