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Neonatal programming of pesticide-induced neurodegeneration

Permethrin (PERM) is a pesticide of the pyrethroid class widely used in agriculture to protect crops and in general its main application is as insect repellent. It is also a component of many creams against skin diseases (i.e. scabies) or human parasites. Many studies demonstrated the presence of PERM in fruit and vegetables with the consequence that, through food chain, also humans and animals are unconsciously exposed to this pesticide. The exposure of population to PERM is in fact confirmed by the presence of the main pyrethroid metabolite, 3-phenoxybenzoic acid (3-PBA) in people's urine. Despite PERM toxicity for mammals has been considered low, meta-analysis underlines the correlation between the exposure to pesticides and the onset of Parkinson's disease (PD).

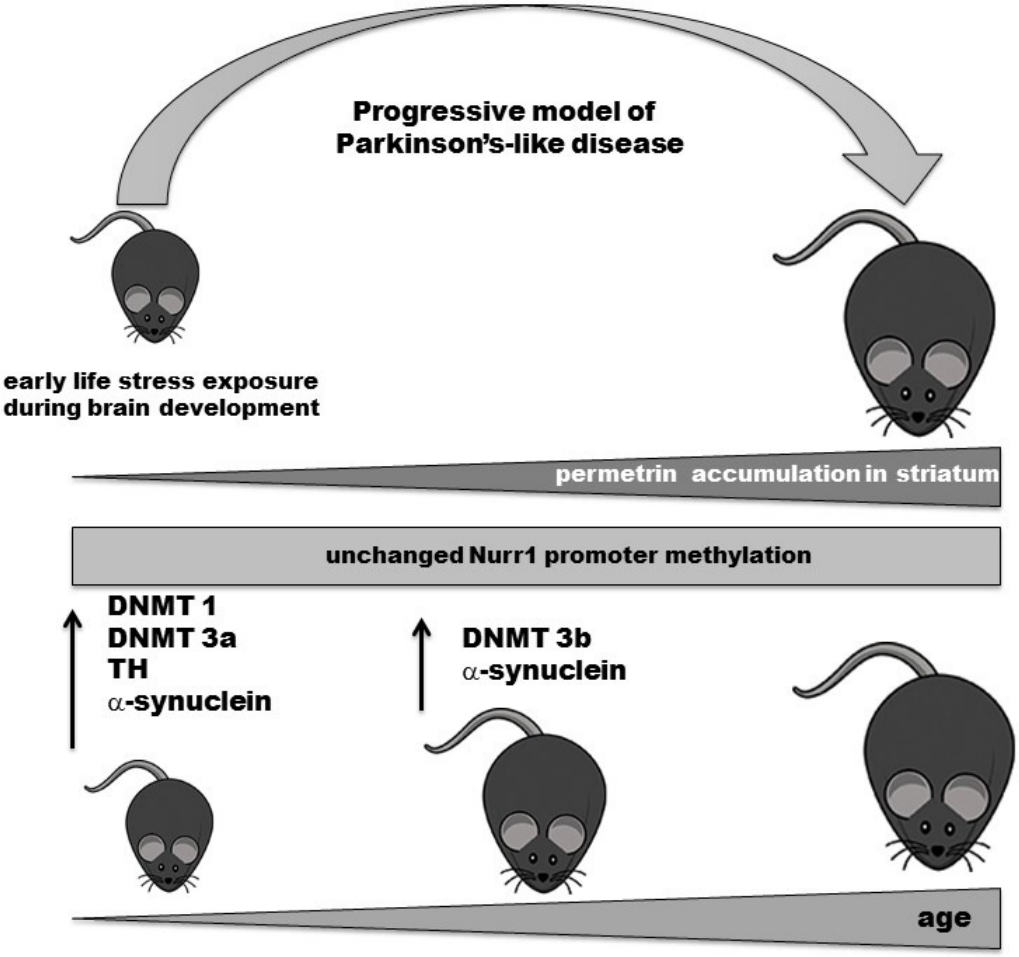

Fig. 1. Long term effects of neonatal exposure to permethrin pesticide.

Rats exposed to PERM during neonatal period develop a progressive Parkinson's-like disease. Impair in the dopaminergic system, increase of oxidative stress and pro-inflammatory production have been demonstrated.

Last but not least, recent studies demonstrate that the neonatal exposure to PERM has an intergenerational effect.

To characterize the molecular mechanisms associated to the long term effect of neonatal exposure to PERM, Nurr1, a transcription factor belonging to the orphan nuclear receptor family required for the regulation of genes involved in dopamine neurotransmission, was studied *in vivo* and *in silico*. For *in vivo* studies, we treated rats with PERM at a dose close to NOAEL for 14 days, during neonatal period of life, and striatum from animals at different age was collected. We observed that PERM accumulates in striatum of treated rats while the metabolite 3-PBA was present only during 24h. This different behavior due to the more lipophilicity of PERM respect to 3-PBA demonstrates that PERM can cross the blood brain barrier and accumulates in the brain. PERM accumulation in the brain and the long term effect of the pesticide on Nurr1 expression might be correlated with epigenetic mechanisms. Our results didn't show any change in Nurr1 promoter methylation in adolescent, adult and old rats confirming that there is not a direct correlation between Nurr1 promoter methylation and Nurr1 gene expression in striatum of our animal model and suggesting that other genetic and epigenetic mechanisms are responsible for dopamine decrease already measured. However, we detected an increase in DNMT1, DNMT3a, Tyrosine hydroxylase, monomeric and aggregated a-synuclein protein levels in striatum of adolescent treated rats suggesting that relevant changes occur in the first phase of the life and that PERM activates DNMTs expression and increases the TH expression, probably to counterbalance the increase of Nurr1 protein induced by PERM (Fig. 1).

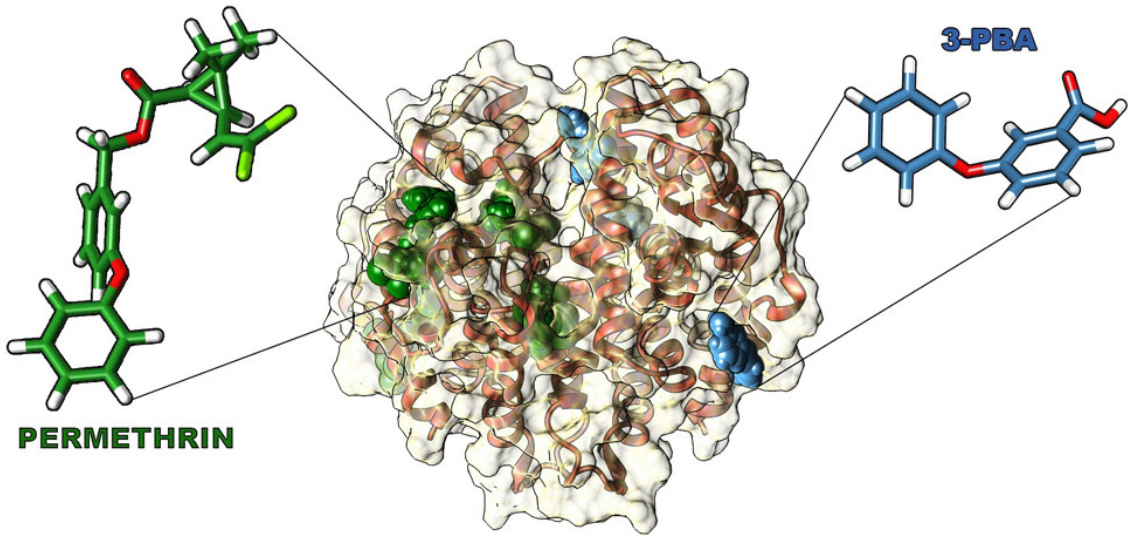

Fig. 2. Overview of in silico outcomes: affinity binding sites for PERM and its metabolite 3-PBA, suggesting a strong binding with Nurr1.

In silico studies have confirmed the direct binding of PERM with Nurr1. Through computational analysis we observed different binding sites for PERM on Nurr1 protein and these bounds are more stable than what observed with 3-PBA. These analyses confirm the additional interference of PERM with dopaminergic

neuron pathway during the accumulation of pesticide in the brain and its role as risk factor in the PD development (Fig. 2).

Rosita Gabbianelli
Unit of Molecular Biology, School of Pharmacy, University of Camerino, Italy

Publication

In vivo and in silico studies to identify mechanisms associated with Nurr1 modulation following early life exposure to permethrin in rats.
Fedeli D, Montani M, Bordoni L, Galeazzi R, Nasuti C, Correia-Sá L, Domingues VF, Jayant M, Brahmachari V, Massaccesi L, Laudadio E, Gabbianelli R
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