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Review

Cellular and molecular neuropathology of the cuprizone mouse model: Clinical relevance for multiple sclerosis

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ABSTRACT

The cuprizone mouse model allows the investigation of the complex molecular mechanisms behind nonautoimmune-mediated demyelination and spontaneous remyelination. While it is generally accepted that oligodendrocytes are specifically vulnerable to cuprizone intoxication due to their high metabolic demands, a comprehensive overview of the etiology of cuprizone-induced pathology is still missing to date. In this review we extensively describe the physico-chemical mode of action of cuprizone and discuss the molecular and enzymatic mechanisms by which cuprizone induces metabolic stress, oligodendrocyte apoptosis, myelin degeneration and eventually axonal and neuronal pathology. In addition, we describe the dual effector function of the immune system which tightly controls demyelination by effective induction of oligodendrocyte apoptosis, but in contrast also paves the way for fast and efficient remyelination by the secretion of neurotrophic factors and the clearance of cellular and myelinic debris. Finally, we discuss the many clinical symptoms that can be observed following cuprizone treatment, and how these strengthened the cuprizone model as a useful tool to study human multiple sclerosis, schizophrenia and epilepsy.

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1. Introduction & historical perspectives

Multiple sclerosis (MS) is generally accepted to be an autoimmune demyelinating disease of the central nervous system (CNS). While the first real medical descriptions of MS date back to the early 18th century, only little progress in understanding MS pathology was made during the 18th and 19th century as research was limited to post-mortem examination of brain tissue from MS patients. During the 20th century however, several immune-mediated animal models for MS were developed like the experimental autoimmune encephalomyelitis (EAE) model and the Theiler murine encephalomyelitis virus model. Besides these, toxin-induced demyelinating models like the cuprizone (bis-cyclohexanone-oxalyldihydrazone, CPZ) model, the lysophosphatidyl choline injection model and the ethidium bromide injection model are often used to investigate the molecular factors contributing to de- and remyelination. The first description of CPZ by Gustav Nilsson dates back to 1950 following his observation that CPZ, which is the condensation product of oxalylhydrazide and cyclohexanone, induced a sensitive blue color reaction upon chelation with copper (Cu) salts (Nilsson, 1950). The first biomedical application however, dates back to 1966 when Carlton observed reproducible low serum Cu levels and demyelination in mice following administration of CPZ (Carlton, 1966). During the following 3 decades, CPZ was mainly used to induce demyelination in Swiss mice, but other mice strains (Albino, BALB/c, BSVS, CD1, ICI & SJL) or animal species (Albino and Wistar rats, guinea pigs and Syrian and Chinese hamsters) were also known to display a variable degree of demyelination upon CPZ intoxication (Adamo et al., 2006; Basoglu et al., 2013; Elsworth and Howell, 1973; Franco et al., 2008; Kanno et al., 2012; Ludwin, 1978; Skripuletz et al., 2011a; Wakabayashi et al., 1977).

Hiremath et al. (1998) published a key study in which the variability of CPZ-induced pathology was reduced to a minimum. In this study, it was determined that feeding 8 week old C57BL/6 mice with a 0.2% CPZ-supplemented diet for 6 weeks consistently induced demyelination with minimal clinical toxicity, making this experimental setup quickly the most used variant of the CPZ mouse model. Following these experiments, 2 experimental setups are now often used on the C57BL/6 background: (i) feeding C57BL/6 mice with a 0.2% CPZ-supplemented diet for 4–6 weeks followed by recovery on a normal diet, resulting in the induction of acute demyelinating lesions followed by spontaneous remyelination and (ii), feeding C57BL/6 mice with a 0.2% CPZ supplemented diet continuously for 12 weeks, resulting in the induction of chronically demyelinated lesions with limited remyelination capacity (Matsushima and Morell, 2001). Acute/chronic demyelination and remyelination, as well as micro- and astrogliosis, following CPZ treatment are represented in Fig. 1.

While the CPZ mouse model has been applied on different animal species and mouse strains during the past 4 decades, currently this model is mainly used on mouse C57BL/6 background as reproducible de- and remyelination is accompanied by microgliosis and astrogliosis. In addition, the availability of many transgenic mouse strains on C57BL/6 background (Table 1), combined with the high reproducibility of the CPZ model on this background, makes CPZ intoxication a favorable model to study both acute and chronic demyelination, as well as remyelination.

2. CPZ-induced metabolic stress predisposes oligodendrocytes to apoptosis

While it is generally accepted that CPZ induced toxicity originates from a perturbation of the very active metabolism in OLGs, no real consensus exists yet concerning the actual modus operandi of CPZ. Within the following chapter, we unify all current knowledge concerning the biochemical and molecular events triggered by CPZ administration, and how these eventually lead to OLG apoptosis and demyelination.

2.1. Physico-chemical behavior of CPZ

Cu, as a cofactor for various cuproenzymes, plays a very important role in many cellular processes and therefore has its concentration tightly regulated within the cell. A disturbed Cu homeostasis can result in neurodegeneration, as for example observed in Wilson's and Menkes disease. Therefore, it is tempting to assume that CPZ-induced pathology originates either from Cu buildup due to entrapment within the cell or from Cu deficiency due to chelation (Rossi et al., 2004). To date, two hypotheses regarding the physico-chemical behavior of CPZ have been investigated.

The first hypothesis suggests that CPZ-induced pathology originates from Cu deficiency. The authors of this hypothesis proposed that CPZ induces a functional Cu deficit as: (i) they could not detect CPZ in brain and liver extracts or serum samples from CPZ-treated mice, and (ii) the chelation of Cu^{2+} by CPZ resulted in precipitating CPZ-Cu^{2+} oligomers in the gastrointestinal tract (Benetti et al., 2010; Taylor et al., 2010b; Venturini, 1973). However, the second hypothesis states that Cu is chelated by CPZ as Cu^{3+} and requires 2 CPZ molecules for each Cu atom bound. Zatta et al. (2005) proposed that CPZ had to be present in the brain as: (i) they could detect CPZ in blood plasma, (ii) a 5-fold increase in brain Cu concentrations after 9 months of a very mild CPZ treatment was observed due to CPZ-Cu oligomer precipitation, and (iii) the hydrazone group of CPZ will be partially hydralized upon binding of Cu, giving rise to the corresponding hydrazide, and CPZ has to be present within the brain for hydrazide-dependent enzyme inhibition to occur (Messori et al., 2007).

Summarizing, the pathological effects of CPZ treatment are due to: (i) in situ disturbance of Cu homeostasis, and (ii) a neurotoxic effect due to enzyme inhibition. However, given the existence of two contradictory hypotheses, further research will be required to fully elucidate the physico-chemical behavior CPZ.

2.2. Megamitochondria and oxidative stress

Suzuki (1969) was the first to report that CPZ induces the formation of megamitochondria in liver tissue of mice (Petronilli