Effects of glyphosate and glyphosate-based herbicides like Roundup™ on the mammalian nervous system: A review ☆

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Highlights

- Glyphosate and glyphosate-based herbicides are known to increase risk of some cancers and cause reproductive abnormalities.
- There is increasing evidence that these chemicals also affect the nervous system.
- We review the evidence for harm from glyphosate and mixtures with glyphosate adversely alter brain function and behavior.

Abstract

Glyphosate is the active ingredient in glyphosate-based herbicides (GBHs), such as Roundup™, the most widely used herbicides in the world. Glyphosate targets an essential enzyme in plants that is not found in animals. However, both glyphosate and GBHs are rated as Group 2A, probable human carcinogens, and also have documented effects on reproduction, acting as endocrine disruptive chemicals. We have reviewed reports of the effects of glyphosate and GBHs on mammalian nervous system function. As with several other herbicides, GBHs exposure has been associated with an increased risk of Parkinson's Disease and death of neurons in the substantia nigra. There is also some evidence implicating Roundup™ in elevated risk of autism. Other studies have shown the effects of GBHs on synaptic transmission in animal and cellular studies. The major mechanism of action appears to be oxidative stress, accompanied by mitochondrial dysfunction. In addition, some gut bacteria utilize the enzyme used by plants, and glyphosate and GBHs use has been shown to alter the gut microbiome. There is a large and growing body of evidence that the gut microbiome alters susceptibility to great number of human diseases, including nervous system function. The weight of the evidence indicates that in addition to cancer and reproductive effects, glyphosate and GBHs have significant adverse effects on the brain and behavior and increase the risk of at least some serious neurological diseases.

Introduction

Roundup™ and other glyphosate-based herbicides (GBHs) are the most widely used herbicides in the world. The active ingredient in Roundup™ is glyphosate, which inhibits enolpyruvyl-shikimate-phosphate synthase, an enzyme responsible for the synthesis of aromatic amino acids in plants but an enzyme that is not found in animals. The development of "Roundup™-ready" genetically engineered crops has greatly increased the use of Roundup™ to kill weeds and save corn, soybeans and grains from damage. Roundup™ contains many "inert" ingredients, which are assumed to be inactive, but at least some of the toxic actions that have been reported due to Roundup™ exposure appear to be due to these other ingredients (Defarge et al., 2017; Hao et al., 2020; Mesnage et al., 2022).

In spite of the known mechanism of action specific to plants, the International Agency for Research on Cancer (IARC) has classified glyphosate and GBHs as probably carcinogenic to humans (Group 2A) (IARC, 2015). The meta-analysis of human epidemiological studies suggests that exposure to GBHs is associated with an increased risk of non-Hodgkin lymphoma (NHL) (Zhang et al., 2019), multiple myeloma (De Roos et al., 2005), and several other cancers (Portier, 2020).

Glyphosate has also been found to cause reproductive damage in animals. These adverse effects include disruption of key regulatory enzymes in androgen synthesis, alteration of estrogen and testosterone levels in the blood, damage to reproductive tissues, and impairment of gametogenesis (Jarrell et al., 2020).

There have been scattered reports of adverse effects of glyphosate on the nervous system of mammals from *in vitro* and *in vivo* studies and increasing concern of the potential harm to the nervous system of humans. Our goal is to review the degree of evidence of the effects of glyphosate and the commercial products containing glyphosate on the mammalian nervous system.

Section snippets

Methods

A search was conducted on PubMed to identify published articles linking glyphosate exposure to nervous system dysfunction. The following keywords were used "glyphosate", "glyphosate-based herbicides" or "Roundup™" and "nervous system", "synaptic transmission", "neurodegeneration", "neurobehavior", "neurodevelopmental disorders" or "neurological diseases." We also performed a manual search of the references of the selected articles to identify potentially missing papers that may be worthy of

Parkinson's disease, dopamine-containing neurons, and glyphosate

The human neurological disease for which there is the greatest concern over exposure to glyphosate and GBHs is Parkinson's Disease. Parkinson's Disease is a result of the death of dopamine-containing neurons in the substantia nigra and is the fastest growing neurological disorder in the world (Dorsey et al., 2018). The dopaminergic neurons contain neuromelanin, hence the name "nigra", and also contain higher concentrations of iron and other metals than do most neurons, making them particularly

Can exposure to glyphosate increase the risk of autism?

There is some evidence that exposure to agricultural pesticides, especially organophosphate pesticides, may increase the risk of autism (Biosca-Brull et al., 2021; Brown et al., 2018; Shelton et al., 2014). Glyphosate is an organophosphate pesticide. von

Ehrenstein et al. (2019) examined children's pre- and post-natal exposure to ambient pesticides and autism spectrum disorder (ASD) using the California Pesticide Use Reporting System, which provides information on pesticide applications on

Effects of glyphosate on synaptic transmission and transmitter systems

Neurotransmitters such as glutamate and glycine are released at neuronal synapses and are involved in learning and memory. Glyphosate has structural similarities to both glutamate and glycine (Fig. 1). Glutamate is the major excitatory neurotransmitter in the brain, glycine is a major inhibitory neurotransmitter but also a transmitter that helps regulate activity at the N-methyl-D-aspartate (NMDA) type of glutamate receptor (Li et al., 2009). There is a specific binding site for glycine on the

Effects of glyphosate on animal behavior, learning, memory and cognitive function

Ait Bali et al. (2017) exposed one-month-old mice to Roundup™ (250 or 500 mg/kg/day). There were no obvious effects of acute exposure. They report that the animals exposed sub-chronically (6 weeks) or chronically (12 weeks) showed a reduction in locomotor activity in an open field test and an increase in anxiety- and depression-like behavior on the basis of an Elevated-Plus-Maze test. There was an increase in immobility and a decrease in grooming time. After behavioral tests, they performed

Effects of glyphosate on gut microbiota

The shikimate pathway is essential to the metabolism of some species in the human gut microbiome, and glyphosate inhibits it (Mesnage et al., 2021). As gut homeostasis declines, pathogenic strains increase, with a variety of immune system, cardiovascular, and neurological complications (Bonaz, 2013; Foster, 2022). Studies with germ-free mice show clearly that gut microbiota are essential for normal development of the blood-brain barrier, myelination, and glial development. There is strong

Mechanisms of glyphosate action

Fig. 2 shows our understanding of how glyphosate and Roundup™ cause biological effects in humans and other mammals. The primary sites of action are damage to mitochondria and the generation of oxidative stress, effects that are tightly coupled. These primary sites of action also explain the basis of the cause of cancer and most of the effects on reproductive health, not only effects on the nervous system. The effects mediated by the action on steroid hormone receptors and change in gut

Are concentrations causing these effects on the nervous system relevant to human exposures?

Most of the studies on nervous systems effects described above use concentrations of GBHs or glyphosate that are much higher than ones to which most humans are likely to be exposed. However, developmental failure and altered metabolic functions have been linked to chronic exposure to GBHs and glyphosate at levels regulated for drinking water via direct effects on the host and indirect effects on gut microbes (Suppa et al., 2020). Several studies have concluded that glyphosate is toxic at levels

Conclusion and future directions

While there is a significant body of evidence that glyphosate and BHs are likely human carcinogens (IARC, 2015) and have adverse reproductive effects (Milesi et al., 2021), whether current concentrations in foods and drinks pose a hazard to the mammalian nervous system is less clear. Both have been found to have reproducible effects on nervous system function, but most cellular and animal studies were done at concentrations unlikely to be found in humans. However, as information grows, it

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Carpenter has served as an expert witness in Roundup cases with all reimbursement going to support students and staff.

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