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Late effect of developmental exposure to glycidol on hippocampal neurogenesis in mice: Loss of parvalbumin-expressing interneurons

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A B S T R A C T

Developmental exposure to glycidol of rats causes axonal injury targeting axon terminals in dams and transient disruption of late-stage differentiation of hippocampal neurogenesis, accompanying sustained increase in the number of reelin-producing or calretinin-expressing interneurons in offspring. The molecular mechanism of disruptive neurogenesis probably targets the newly generating nerve terminals. We previously found differences between mice and rats in the effects on hippocampal neurogenesis after developmental exposure to the same neurotoxic substances. In the present study, we examined the effects and underlying mechanisms of developmental exposure to glycidol on hippocampal neurogenesis in mice. Glycidol (800 or 1600 ppm) was administered in drinking water to mated female mice from gestational day 6 to postnatal day 21. Compared to mice drinking water without glycidol (control), the exposed dams showed axon terminal injury at both concentrations of glycidol. The offspring of the dams that had received 1600 ppm glycidol had fewer parvalbumin (PVALB)$^+$ γ-aminobutyric acid (GABA)-ergic interneurons and neuron-specific nuclear protein$^+$ postmitotic neurons in the hilus of the hippocampal dentate gyrus. Thus, exposure of glycidol to adult mice induced axonal degeneration equivalent to that seen in the rat; however, the target mechanism for the disruption of hippocampal neurogenesis by developmental exposure was different from that in rats, with the hilar neuronal population not affected until adulthood. Considering the role of PVALB$^+$ GABAergic interneurons in the brain, developmental glycidol exposure in mice may cause a decline in cognitive function in later life, and involve a different mechanism from that targeting axon terminals in rats.

1. Introduction

Glycidol is a viscous liquid which is soluble in water and organic solvents. It is used as a stabilizer in the manufacture of vinyl polymers, as a chemical intermediate in the pharmaceutical industry, and as an additive for oil. It causes necrosis of the cerebellum and demyelination in the medulla of rodent brains (NTP, 1990). In a previous oral toxicity study in rats, we administered glycidol daily for 28 days and observed progressive gait abnormalities accompanied by the presence of spheroids in the cerebellar granule cell layer and dorsal funiculus of the medulla oblongata; in addition, there was central chromatolysis in the trigeminal nerve ganglion cells and axonal degeneration in the sciatic nerves (Akane et al., 2014).

The hippocampus is located on the inner side of the temporal lobe and plays an important role in learning and memory. In the dentate gyrus, one structure—the subgranular zone (SGZ)—has the capacity to generate new neurons throughout adult life (Kempermann et al., 2004; McDonald and Wojtowicz, 2005). Adult neurogenesis involves self-renewal of stem cells to produce progenitor cells; proliferation and differentiation of progenitor cells; and maturation involving neuritogenesis and synaptogenesis of granule cell lineages (Hodge et al., 2008; Kempermann et al., 2004; Knoth et al., 2010). Adult neurogenesis is a highly regulated process that begins with type-1 neural stem cells, which produce proliferative progenitor cells (type-2a, type-2b, and type-3). Type-3 progenitor cells differentiate into postmitotic immature granule cells and finally into mature granule cells that populate the granule cell layer (GCL; Hodge et al., 2008; McDonald and Wojtowicz, 2005). In the hilus of the dentate gyrus, there is a subpopulation of γ-

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aminobutyric acid (GABA)-ergic interneurons, such as those expressing calcium-binding protein, i.e., calbindin (CALB1), calretinin (CALB2), or parvalbumin (PVALB), that regulates neurogenesis in the SGZ (Masiulis et al., 2011). Reelin, an extracellular protein produced by a subpopulation of GABAergic interneurons, is essential for neuronal migration (Gong et al., 2007). In addition to inputs from GABAergic interneurons, there are various synaptic connections between neurons in the dentate gyrus and those outside the SGZ. For example, cholinergic neurons originating from the septal nucleus and the nucleus of the diagonal band of Broca innervate neurons in the dentate hilus; and glutamatergic neurons in the entorhinal cortex provide axonal inputs to the dentate gyrus (Fonnum et al., 1979). Cholinergic and glutamatergic neuronal inputs to the SGZ are important for maintaining proper proliferation and differentiation of granule cell lineages (Cameron et al., 1995; Freund and Buzsáki, 1996).

We previously reported that a number of chemicals and agents affected proliferation and differentiation of progenitor cells in the SGZ (Shibutani, 2015). In addition to changes in granule cell lineage subpopulations, we also reported aberrant numbers of GABAergic interneuron subpopulations, as well as cholinergic or glutamatergic inputs, as part of the regulatory system of neurogenesis (Shibutani, 2015). Therefore, monitoring granule cell lineage in the SGZ, and GABAergic interneurons in the dentate hilus, as well as cholinergic or glutamatergic inputs, is important for the detection of target cell populations in the study of developmental neurotoxicity in adult neurogenesis.

Acrylamide is a well-known neurotoxicant that causes degeneration of distal axons in the central and peripheral nervous systems (LoPachin, 2004). We previously revealed in rats that developmental exposure to acrylamide affects late-stage neurogenesis by targeting immature granule cells that have developing neurites (Ribak et al., 2004) in the SGZ of the dentate gyrus (Ogawa et al., 2012). In that study, we hypothesized that the effects of acrylamide on neurogenesis might involve a common mechanism targeting mature axon terminals causing distal axonopathy in adult animals. We also previously found disruptive hippocampal neurogenesis targeting late-stage differentiation in a developmental exposure study and a 28-day oral toxicity study of glycidol in rats (Akane et al., 2013b, 2014). We speculated that glycidol affects hippocampal neurogenesis with a similar mechanism to that of acrylamide.

However, there are differences between mice and rats in the effects of developmental exposure to some chemicals on hippocampal neurogenesis (Itahashi et al., 2015a; Kato et al., 2016; Ohishi et al., 2012, 2013; Wang et al., 2012, 2013a). These differences may reflect different processes or regulatory systems of neurogenesis in the two species. For example, adult-born hippocampal neurons are more numerous and faster-maturing in rats than in mice (Snyder et al., 2009). CALB2 is produced in GABAergic interneurons in rats (Freund and Buzsáki, 1996), but is expressed in excitatory mossy cells in mice (Fujise et al., 1998). Moreover, the cellular distribution pattern of guanosine 3′,5′-cyclic monophosphate-immunoreactive neurons and astrocytes in the hippocampus, including in the dentate gyrus, differs between rats and mice (Staveren et al., 2004).

The present study was conducted to examine the effects of developmental exposure to glycidol on hippocampal neurogenesis in mice. We administered glycidol to pregnant mice during periods of gestation and lactation, and examined the dose–effect relationship in the distribution, proliferation, and apoptosis of granule cell lineages in the SGZ, and on the distribution of interneuron subpopulations in the dentate hilus of the offspring, upon weaning and at the adult stage. We also examined cholinergic and glutamatergic neuronal inputs in the dentate gyrus at both stages.

2. Materials and methods

2.1. Chemicals and animals

Glycidol (2,3-epoxy-1-propanol; CAS No. 556-52-5) was purchased from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan). Mated female Slc:ICR mice were purchased from Japan SLC, Inc. (Hamamatsu, Japan) at gestational day (GD) 1 (appearance of vaginal plug was designated as GD 0), and were individually housed in polycarbonate cages with paper bedding until day 21 after delivery on postnatal day (PND) 21 (where PND 0 is the day of delivery). Dams and offspring were maintained in an air-conditioned animal room (temperature: 23 ± 2 °C, relative humidity: 55 ± 15%) with a 12-h light/dark cycle. Dams were provided *ad libitum* with a pelleted basal diet (MF; Oriental Yeast Co., Ltd., Tokyo, Japan) throughout the experimental period and with distilled water until the start of exposure to glycidol. From PND 21 onwards, offspring were reared with three or four animals per cage and provided with the pelleted MF basal diet and distilled water *ad libitum*.

2.2. Experimental design

Mated female mice were randomly assigned to three groups of 13 animals and treated with 0, 800, or 1600 ppm glycidol in drinking water from GD 6 to PND 21. Based on a previous 13-week repeated-dose toxicity study in mice (NTP, 1990), the preliminary experiments initially had four groups consisting of glycidol concentrations of 0, 800, 1000, and 1200 ppm in the drinking water. In the preliminary dose finding study, all dams maintained pregnancy, delivered and nursed offspring normally. Dams showed very slight histopathological changes suggestive of distal axonal degeneration as well as transient gait abnormalities only at 1200 ppm. In this study, therefore, the high-dose level was set at 1600 ppm, which was the dose that can be expected to show a slight but apparent maternal toxicity. Body weights and food and water consumption of dams were measured throughout the experimental period. After delivery, the litters were culled randomly on PND 4 to preserve 6–8 male and 0–2 female pups per litter. The offspring were weighed at 3- or 4-day intervals until weaning. To assess neurological abnormalities, dams and offspring after weaning were scored on the appearance of gait abnormalities into the following four categories: grade 0, normal gait; grade 1, slightly abnormal gait with slight degrees of shuffling; grade 2, moderately abnormal gait with moderate degrees of shuffling; and grade 3, severely affected gait including inability to support the body weight and spreading of all extremities.

On PND 21, 10 male offspring per group (one or two offspring per dam) were subjected to perfusion fixation for immunohistochemistry through the left cardiac ventricle with ice-cold 4% (w/v) paraformaldehyde (PFA) in 0.1 M phosphate buffer (pH7.4) at a flow rate of 10 mL/min after deep anesthetization with CO_2/O_2. For mRNA expression analysis, 31–35 male offspring per group (three or four male pups per dam) were euthanized by exsanguination from the abdominal aorta under CO_2/O_2 anesthesia and subjected to necropsy. Dams and all female offspring per group (zero to two female pups per dam) were euthanized by exsanguination from the abdominal aorta on PND 21, respectively.

Male offspring remaining were maintained without administration of glycidol until PND 77, and body weight was measured once a week. On PND 77, 10 male offspring per group (one or two male offspring per dam) were subjected to perfusion fixation with 4% PFA buffer solution for immunohistochemistry at a flow rate of 10 mL/min.

All animal experiments were conducted in accordance with the "Guidelines for Proper Conduct of Animal Experiments" (Science Council of Japan, June 1, 2006), and the protocols were approved by the Animal Care and Use Committee of the Tokyo University of Agriculture and Technology. All efforts were made to minimize animal

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