

Development-progressive neurotoxicity regulated neuroinflammation with prenatal chemical exposure on the rat.

・ 炎症が制御する発達依存的な神経毒性発現

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Background

Autism (AD),
Attention deficit hyperactivity disorder (ADHD),
Learning disorder (LD),
Pervasive Developmental Disorder (PDD)
Mental disorders are increased in modern societies.

How do these risk factors induce neuronal disorders?

Autism-inducing risk factors from cohort study

- Smoking
- Organophosphate
- Organochlorine
- Antibiotics
- Age of fathers
- Assisted reproduction
- Caesarean birth

4 times up as smoking in first pregnancy
2.25 times up to mother expose
1.71 times up to children expose
6.1 times up to children expose
Some risk material risk
1.13 times up
Interrelated

T.FUJIWARA, I. TAKAMATSU
J.Natl.Inst.Public Health,59(4):2010

Administrating schedules

Case studies: Valproate (VPA)
Lipopolysaccharide (LPS)
Glyphosate (GLY)
Chlorpyrifos (CPF) and donepezil (DPZ)

behavior

Drug administration to pregnant rat

Lipopolysaccharide (LPS)

Experimental inducer of autism or schizophrenia.

Well-known **endotoxins** found in the outer membrane of Gram-negative bacteria. It binds the CD14/TLR4/MD2 receptor complex in many cell types, but especially in monocytes, dendritic cells, macrophages and B cells, which promotes the secretion of pro-inflammatory cytokines.

Valproate (VPA)

A HDAC inhibitor and autism-inducer for human.

Medications primarily used to treat epilepsy and bipolar disorder and prevent migraine headaches.

Glyphosate (GLY)

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Aminomethyl-phosphonic acid (AMPA)

Glyphosate is readily degraded by soil microbes to aminomethylphosphonic acid (AMPA).

a broad-spectrum systemic herbicide and an organophosphorus compound, interfering with the shikimate pathway.
It would influence microbiota of administrated animals.

Lipopolysaccharide (LPS)

PC number / PL length (100 μm)

P14

Control LPS10 μg/kg LPS50 μg/kg LPS100 μg/kg

PC

Glyphosate (GLY)

Cont AGLY 25 AGLY 100 AGLY 250 AAMPA 250 CGLY 250

Number of Purkinje cells

Dunnett, *:p<0.05,**:p<0.01(v.s. Cont.)

Valproate (VPA)

(a) P14 Control (b) P14 VPA

P16 control P16 VPA

Number of Purkinje cells/500μm
PL length / depth (ratio to VPA)
Average dendrite length

Control E16-VPA

Chlorpyrifos (CPF)

Length of ML [μm]

PC number in 100 μm

Control CPF DPZ

PC formation stained with CalbindinD-28k antibodies

Conclusions

	LPS	VPA	GLY	CPF
Inflammatory cytokines	high	low	transient	N.D.
Microglia	±	—	+	+
PC number	Delayed decrease	±	decrease	increase
Dendrite length of PC	elongate	elongate	shorten	shorten
Excess folding	+	++	±	+
GFAP/GLAST expression	N.D.	+	—	N.D.

・ Chemical-induced inflammation would induce neuronal dead-or-alive, however, it is not definitive. delayed.
・ Microglia is one of the important key factors for neuronal development.
・ [glutamate]_{out} control would decide neuronal death or excess survival.