

2012 9 2  
浸透性農薬フォーラム

「**脳の発達障害(ADHD、自閉症など)**  
**の原因としての浸透性農薬:**  
**ネオニコチノイド**」

Systemic Pesticides as a Causal Factor of  
Developmental Brain Disorders (ADHD, autism, etc.)

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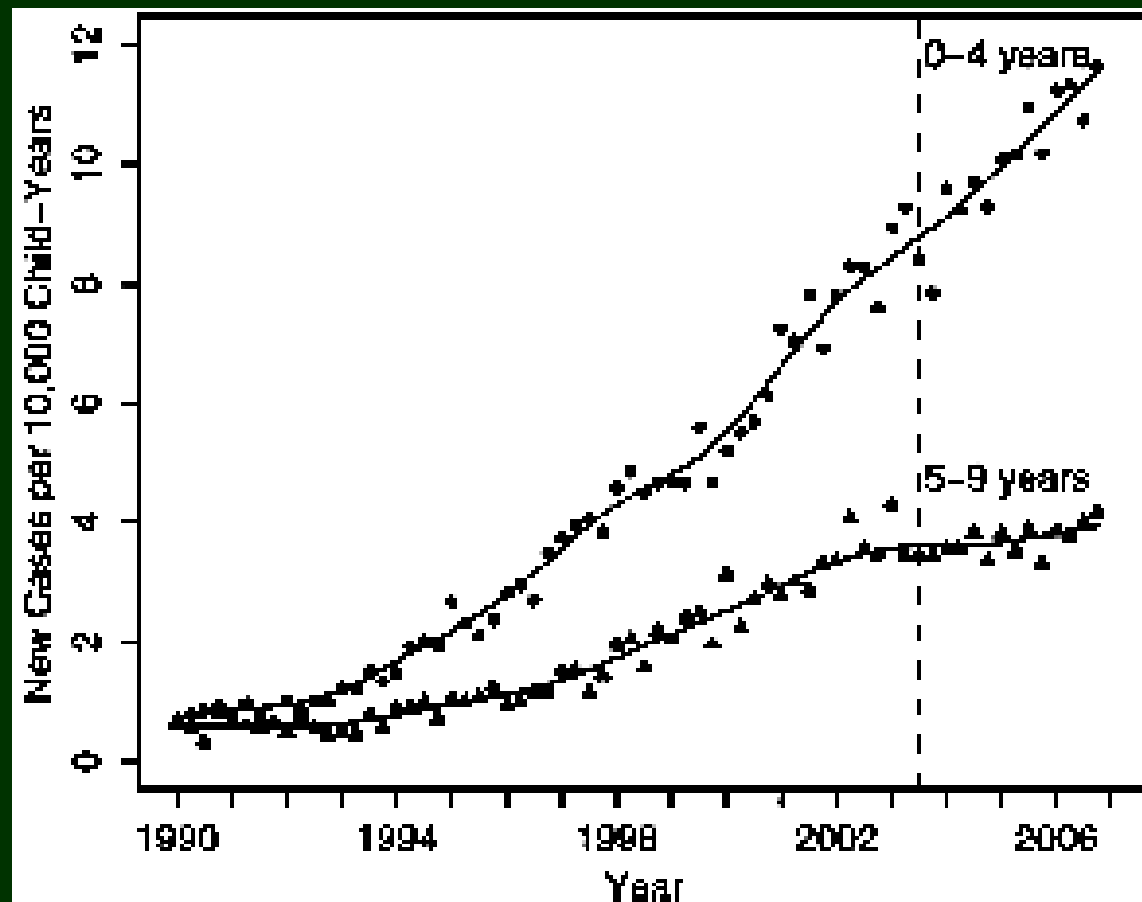
## Increase of Children with developmental disorders(ADHD, autism etc) in US and Japan

In Japan, Ministry of Education published a report that 6.3% of schoolchildren are supposed to have symptoms of developmental disorders (Learning Disorders, ADHD: Attention-Deficit Hyperactivity Disorders and Autism)

In US, autistic children registered in California State increased in the last several decades.

Real increased numbers of autistic children showed the cause is not genetic but environmental.

# Increase of autism children in California, USA



## Increase of autism is caused by environmental toxicants such as pesticides?

The decades when children with developmental disorders increased were following ones when environmental chemical pollutions including pesticides did spread in US and Japan.

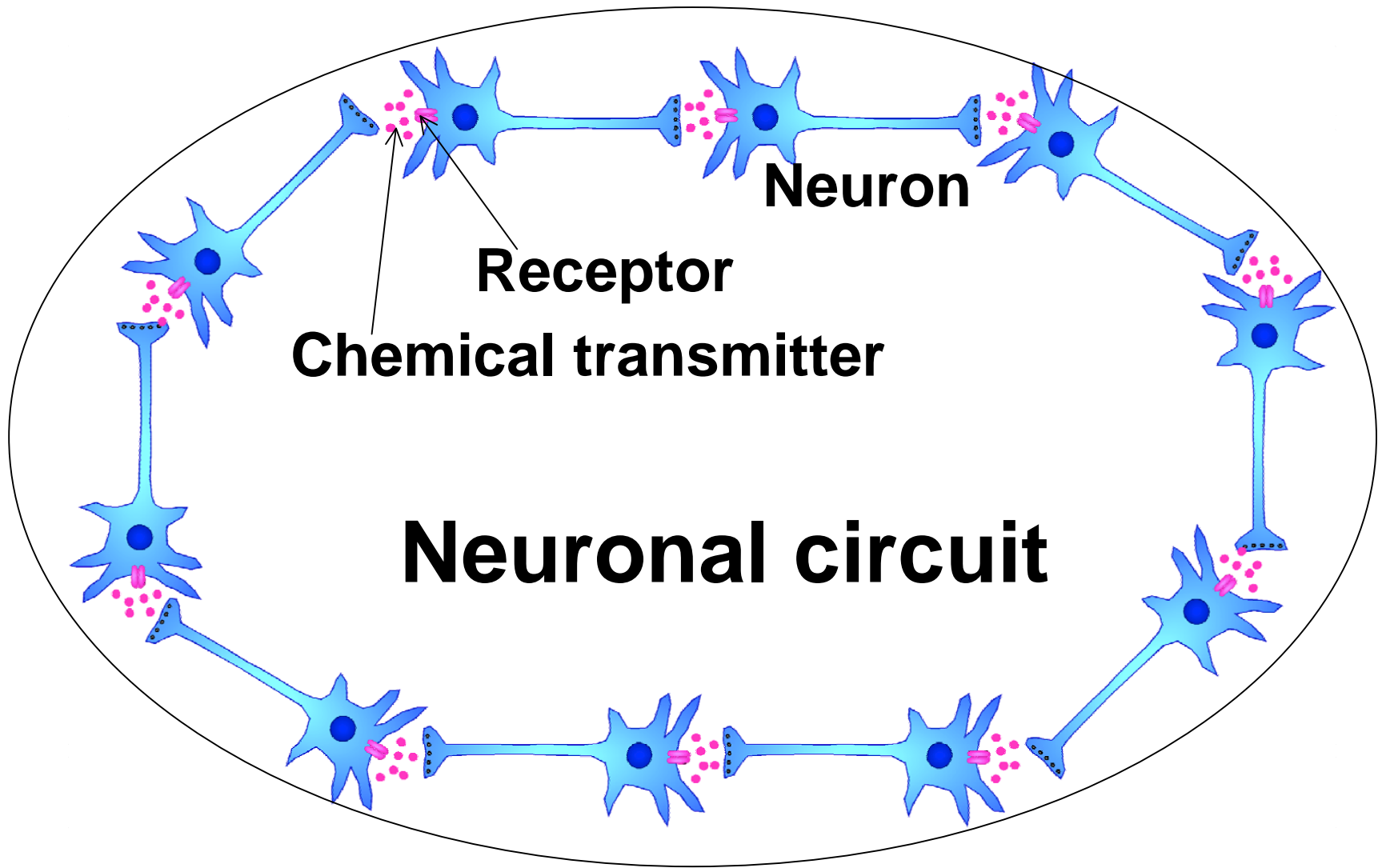
Researchers started to think that neurotoxic chemicals such as insecticides contaminated into fetal or newborn brain cause the developmental disorders.

Many Epidemiological Data  
have been published: Children  
intoxicated with  
organophosphate tend to become  
ADHD

- Pediatrics(2010) Harvard group
- Environmental Health Perspectives(2010-11)
- 1 for ADHD, 3 for low IQ, memory deficit

# Children with Developmental Disorders have abnormal neuronal circuits in the brain

- Each behavior acquired by establishing specific neuronal circuits for it.
- When a child failed to develop the neuronal circuit corresponding to social communications, he will become autism.



**Neuron**

**Receptor**

**Chemical transmitter**

**Neuronal circuit**

To develop neuronal circuit, a huge numbers of gene expressions controlled by chemical information are necessary.

- Physiologic chemicals are
  - Hormones: thyroid hormone, etc
  - Neurotransmitters: **acetylcholine**, glutamate, GABA, etc



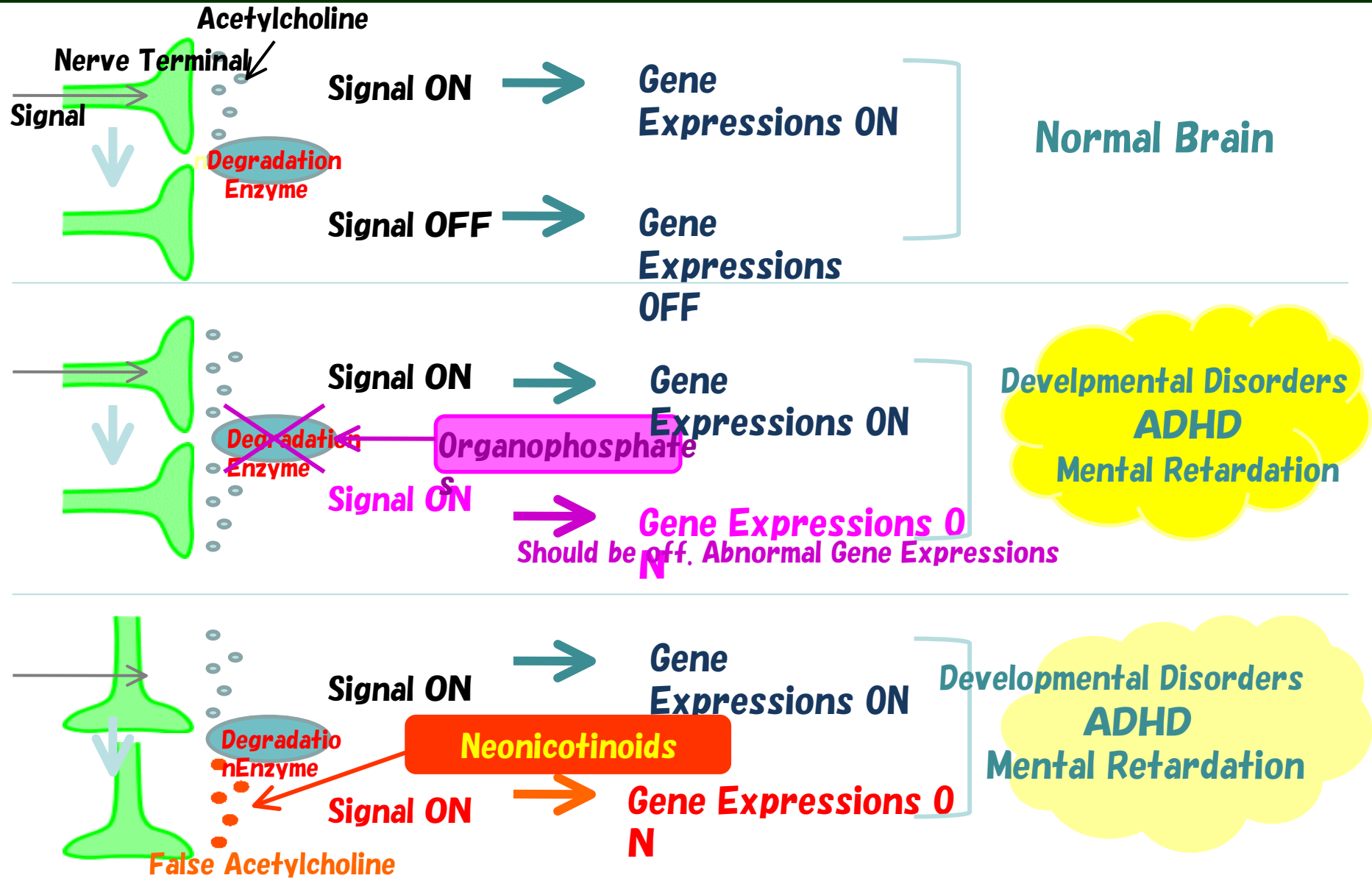
**Acetylcholine** is known as a critical information chemical to control gene expressions for neuronal circuits of higher functions such as attention and memory

- Neonicotinoids can disrupt highly developed memory system of worker bees and/or its development during larval stages.

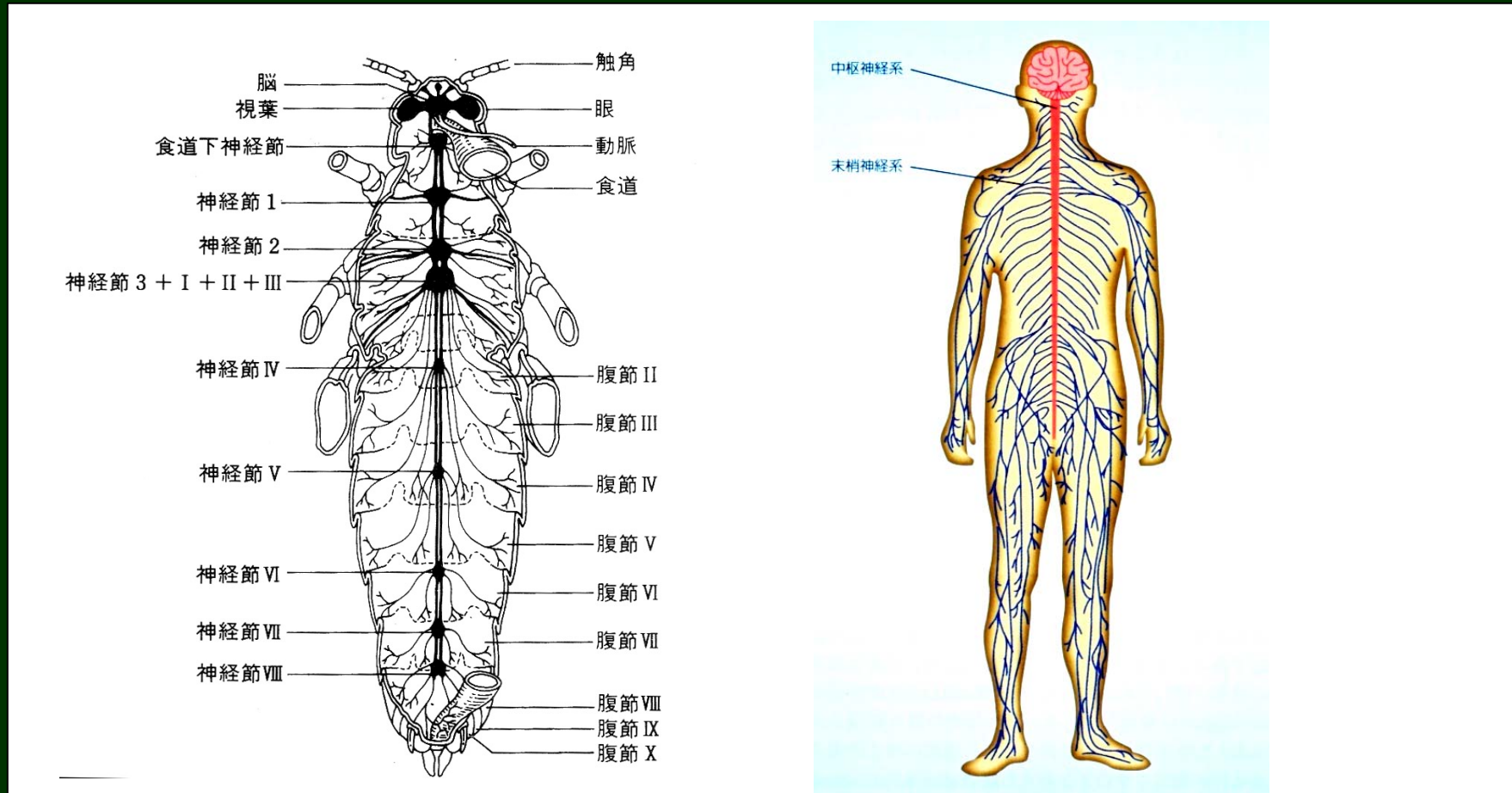
Organophosphates and  
Neonicotinoids **disrupt**  
**acetylcholine** information to  
control gene expressions for the  
neuronal circuits

- Organophosphates: Block degradation enzymes cause **flood of acetylcholine**
- Neonicotinoids: Bind to Nicotinic acetylcholine receptor work **false-acetylcholine**

# A Possible Mechanism of Abnormal Brain Development by Organophosphates and Neonicotinoids



# Basic structure of human nervous system is similar to insect one

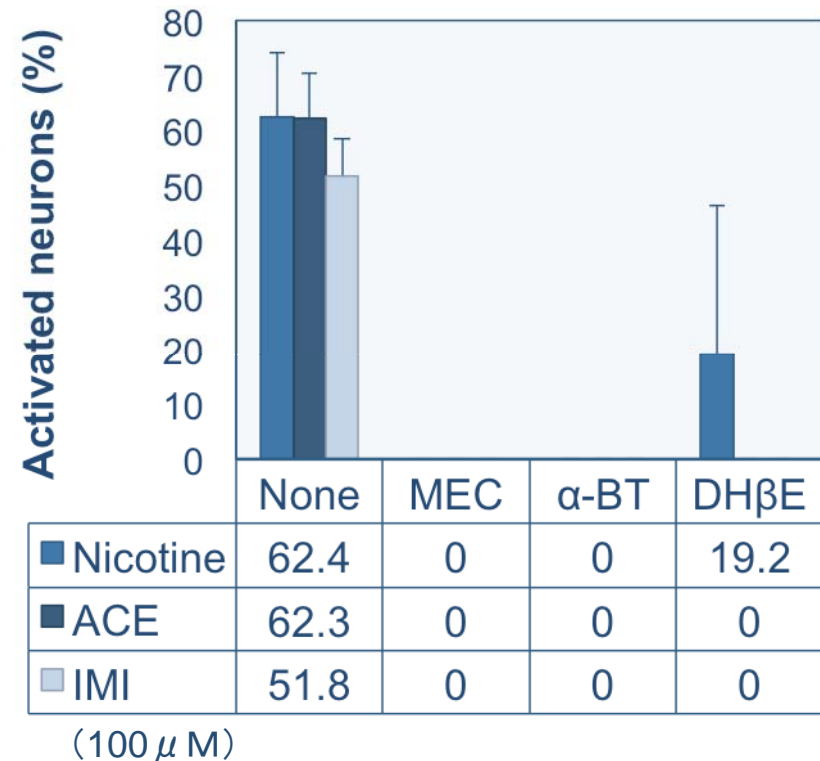
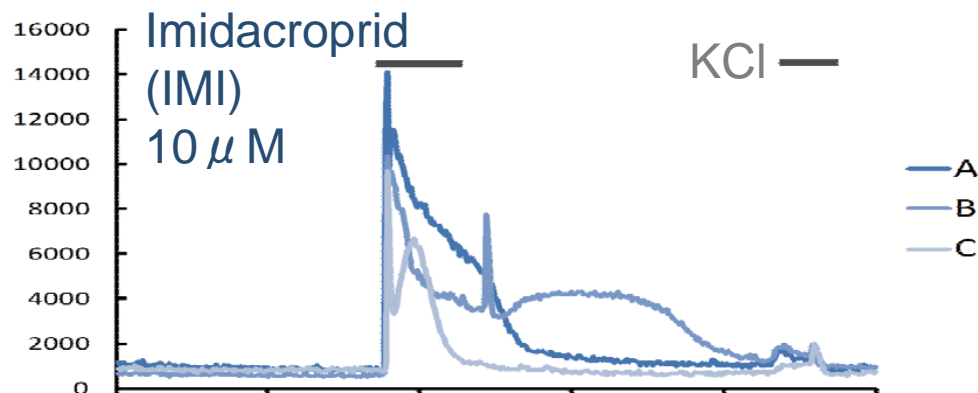
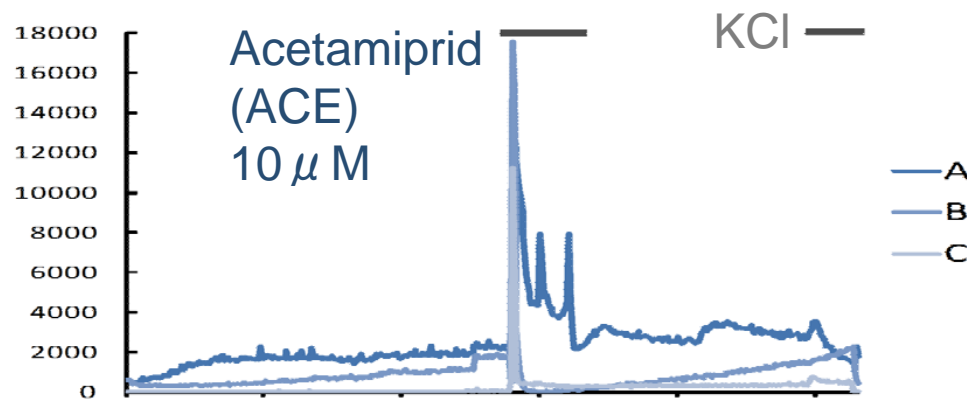
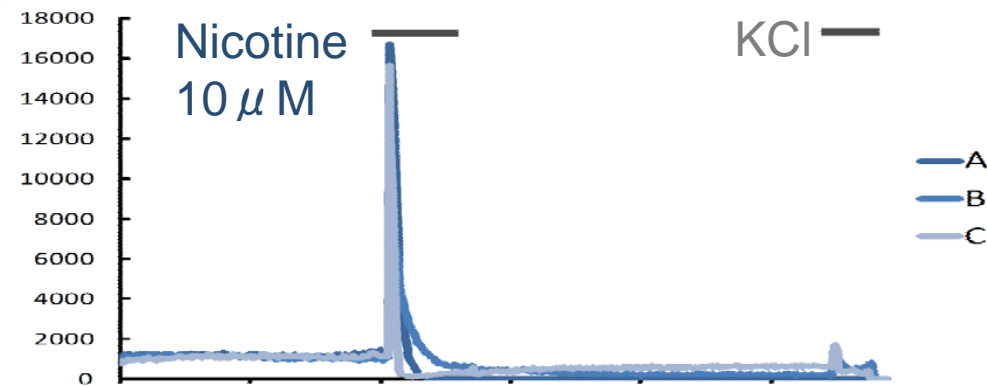


- Major information chemicals (for example **acetylcholine**, glutamate) are same in human and in insect.
- Organophosphates and neonicotinoids obviously effect both on human and on insect.

# Neonicotinoids are enough toxic to human brain and nervous system

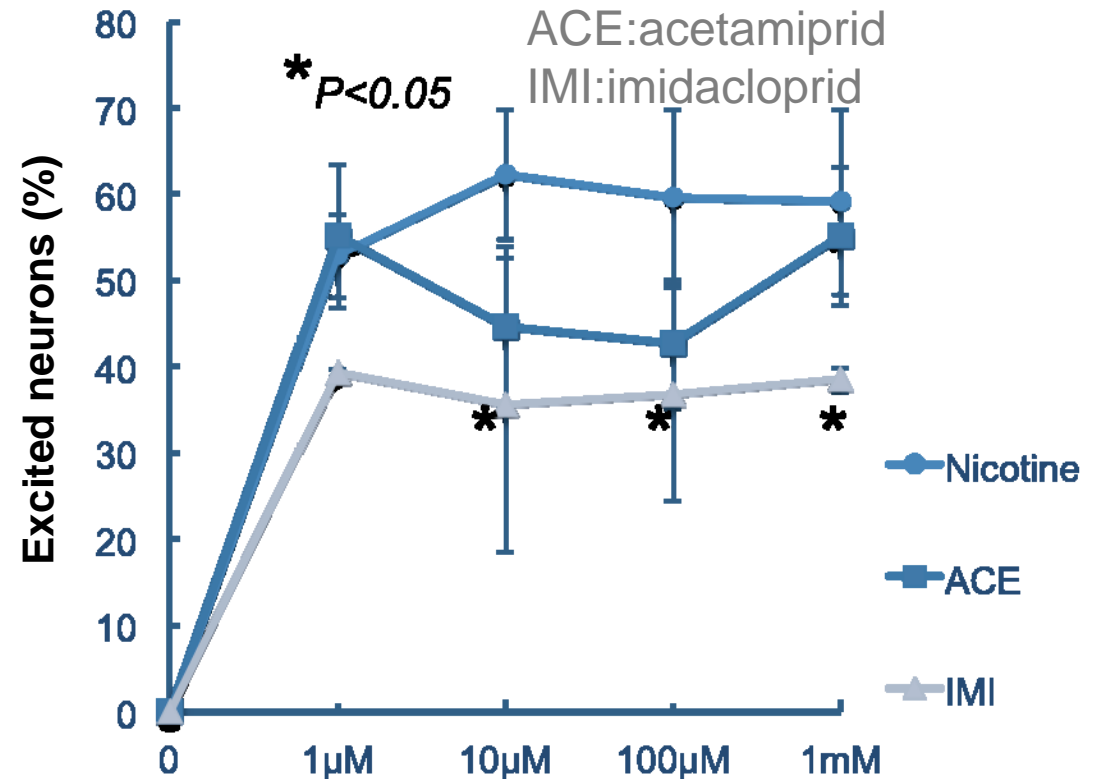
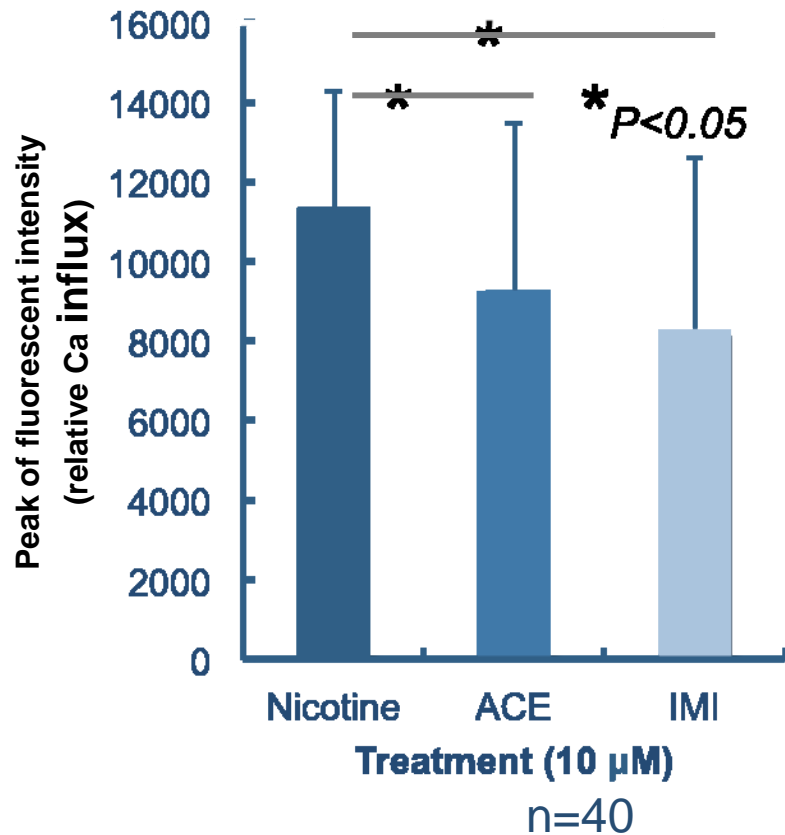
- Pesticide company defends that neonicotinoids are not so toxic to human
- But no safety tests have been carried out on the developmental behavioral toxicities in mammals.
- Clear evidence of human toxicities are acute symptoms, even death cases.

# Neonicotinoids bind to rat acetylcholine receptors and excite neurons



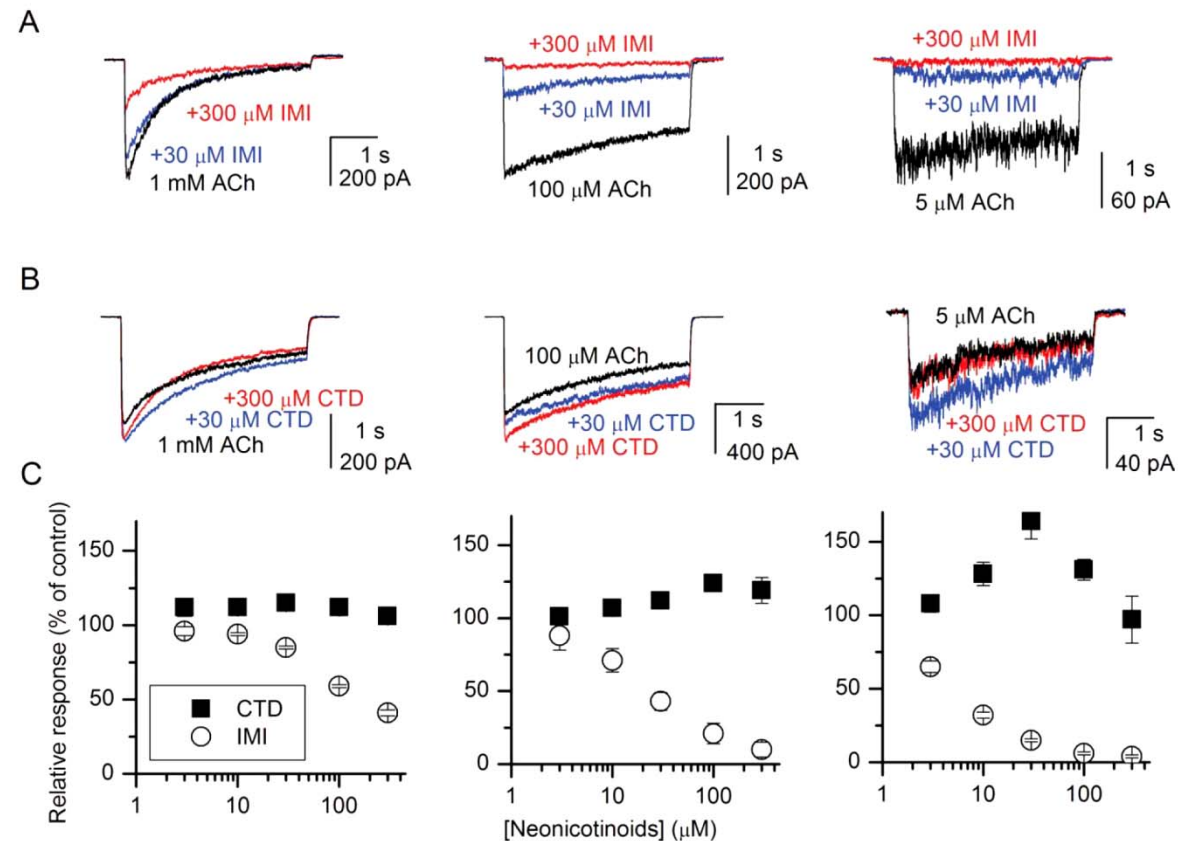
The nAChR specific antagonists Inhibit Ca influx Induced by neonicotinoids and nicotine.  
 MEC: mecamylamine 100  $\mu$  M  
 $\alpha$ -BT:  $\alpha$ -bungarotoxin ( $\alpha$ 7specific) 1  $\mu$  M  
 DH $\beta$ E: dihydro- $\beta$ -erythroidine 1  $\mu$  M  
 ( $\alpha$ 4 $\beta$ 2specific)

# Neonicotinoids excite rat neurons like nicotine



The firing patterns, proportion of excited neurons, and peak excitatory  $\text{Ca}^{2+}$  influxes induced by ACE and IMI showed differences from those induced by nicotine. However, ACE and IMI had greater effects on mammalian neurons than those previously reported in binding assay studies.

# Neonicotinoids disrupt human acetylcholine receptor functions



IMI: imidacloprid  
CTD: clothianidin

•IMI and clothianidin modify the amplitude of responses to acetylcholine (ACh) by human nAChR  $\alpha 4 \beta 2$  subtype receptors even at a low concentration (3  $\mu$ M) that did not activate these receptors when administered alone. It is possible that the binding of ACh to nAChRs modifies the structure of the nAChRs, which may allow neonicotinoids to affect mammalian nAChRs.



# Hazards of Neonicotinoids can be more serious and nicotine-like wider spectrum

- They bind directly to nicotinic acetylcholine receptors and behave like nicotine.
- Nicotinic acetylcholine receptors distribute many parts of human body.
- Nicotine acts on fetus, resulting ADHD, premature birth and sudden infant death syndrome.