

รายวิชา 3804662

วิชา จิตสรีรวิทยาพัฒนาการ (Psychophysiological Development)

จำนวน 3 หน่วยกิต ประจำปีภาคการศึกษาปลาย ปีการศึกษา 2553

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วันที่เรียน- เวลา: วันพุธ เวลา 18.00 - 21.00 น.

นายพินิจ คชภักดี Naiphinich Kotchabhakdi Ph.D.

Research Center for Neuroscience, Institute of Molecular Biosciences, and Salaya Stem Cell Research and Development Project ,

Brain Development Research Project, National Institute for Child and Family Development,

Mahidol University, Salaya, Nakornpathom 73170 Thailand.

Email: [scnkc@mahidol.ac.th](mailto:scnkc@mahidol.ac.th); [naiphinich@gmail.com](mailto:naiphinich@gmail.com)

Web: <http://www.neuroscience.mahidol.ac.th>

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วิชา จิตสรีรวิทยาพัฒนาการ (Psychophysiological Development)

Lecture 15

Psychophysiological Development:  
Abnormal Development and Disease (II)

อาจารย์นายแพทย์ วรสิทธิ์ สิริพรพานิช

**Vorasith Siripornpanich, M.D.**

Research Center for Neuroscience, Institute of Molecular Biosciences, and Salaya Stem Cell Research and Development Project ,

Brain Development Research Project, National Institute for Child and Family Development, Mahidol University, Salaya, Nakornpathom 73170 Thailand.

Email: [scnkc@mahidol.ac.th](mailto:scnkc@mahidol.ac.th); [naiphinich@gmail.com](mailto:naiphinich@gmail.com)

Web: <http://www.neuroscience.mahidol.ac.th>

## Abnormal Development and Diseases (II)

Vorasith Siripornpanich, M.D.  
Research Center for Neuroscience  
Mahidol University

**MR**  
(mental retardation)

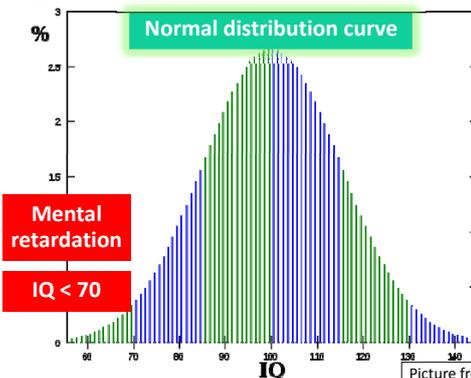
### What is “Mental retardation (MR)”?

- **Diagnosis of mental retardation**

- (1) Low intelligence quotient (IQ)  
and
- (2) Difficulties in at least two areas of adaptive functioning: communication, self care, home living, social skills, community use, self-direction, health and safety, functional academics, leisure, and work

$$\text{Intelligence quotient (IQ)} = \frac{\text{mental age}}{\text{chronological age}} \times 100$$

### IQ curve



## Degree of mental retardation

	IQ
• Normal	90-110
• Borderline intellectual functioning	70-80
<b>Mental retardation</b>	
• Mild mental retardation	50-69
• Moderate mental retardation	35-49
• Severe mental retardation	20-34
• Profound mental retardation	< 20

## Impact of mental retardation

Degree of MR	Family & Social support
• Mild MR (IQ 50-69)	intermittent support
• Moderate MR (IQ 35-49)	limited support
• Severe MR (IQ 20-34)	extensive support
• Profound MR (IQ < 20)	pervasive support

## Causes of mental retardation

- **Prenatal causes** (60-80%)
  - Genetic disorders: Down syndrome, Fragile X syndrome
- **Perinatal causes** (8-12%)
  - Asphyxia, birth trauma
- **Postnatal causes** (10%)
  - CNS infection, trauma, malnutrition

Some individuals may have more than one etiologic cause of their developmental disability

## Down syndrome

- Neurological manifestations
  - Mental retardation (mean IQ = 43)
  - Hypotonia
  - Seizures: infantile spasms
  - Risk for Alzheimer disease (in cases with apolipoprotein E4 allele)



## Fragile X syndrome

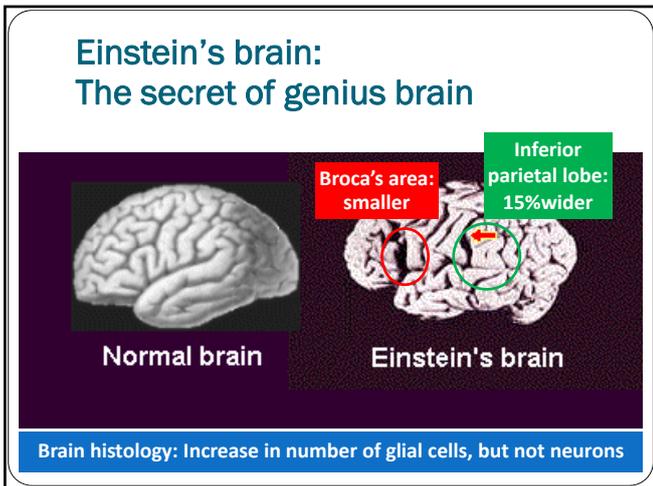
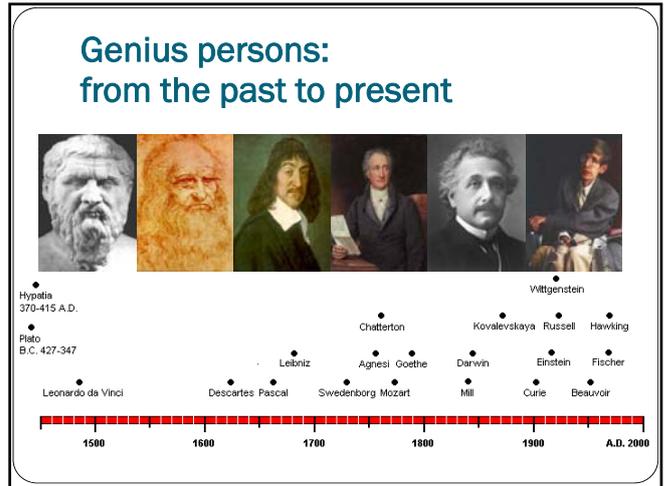
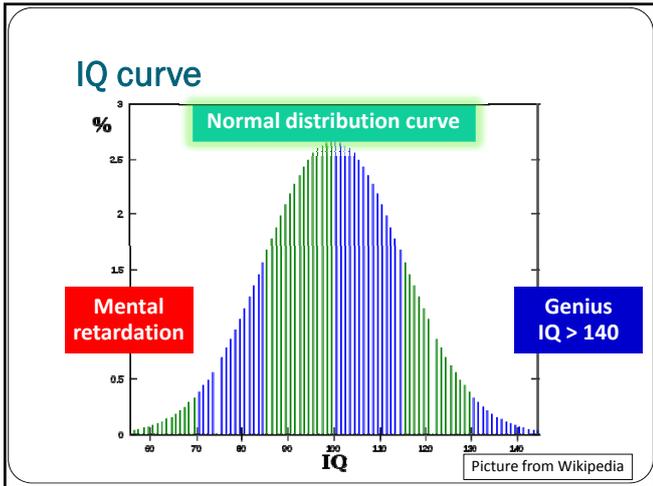
- Trinucleotide (CGG) repeated disorder
- Clinical characteristics
  - Dysmorphic features: long face, prominent brow, large & floppy ears, macroorchidism
  - Mental retardation
  - Autistic symptoms
  - Seizures



Picture from cas.bellarmine.edu

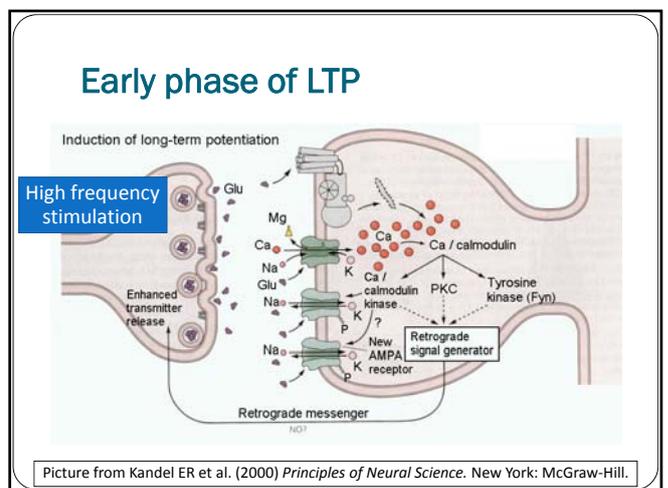
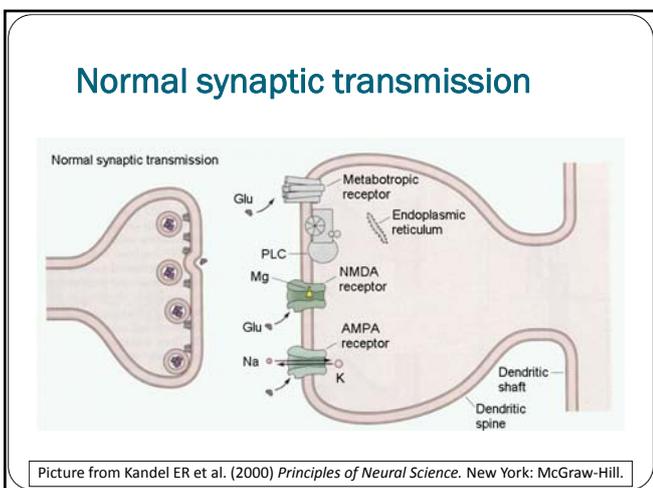
## Management of mental retardation

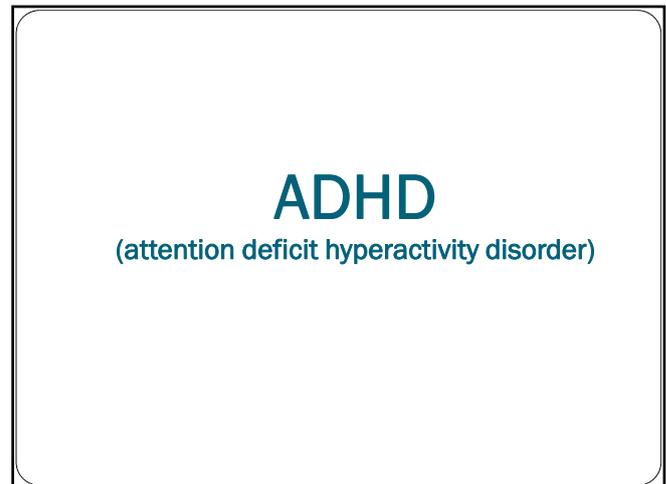
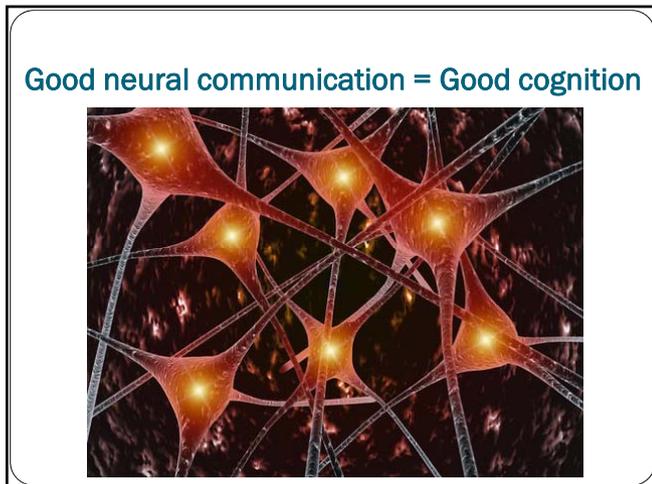
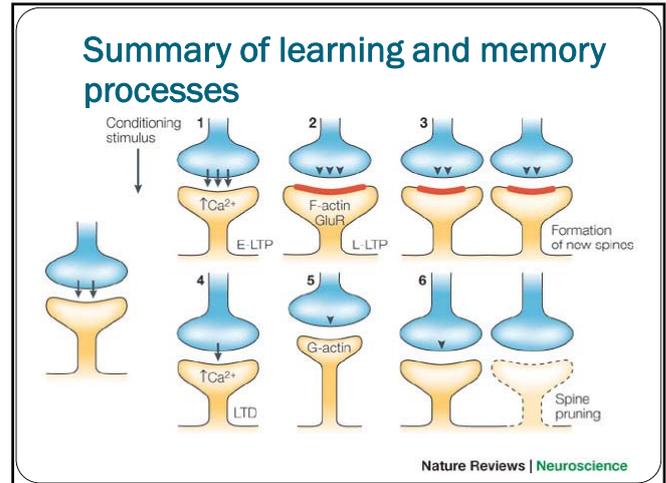
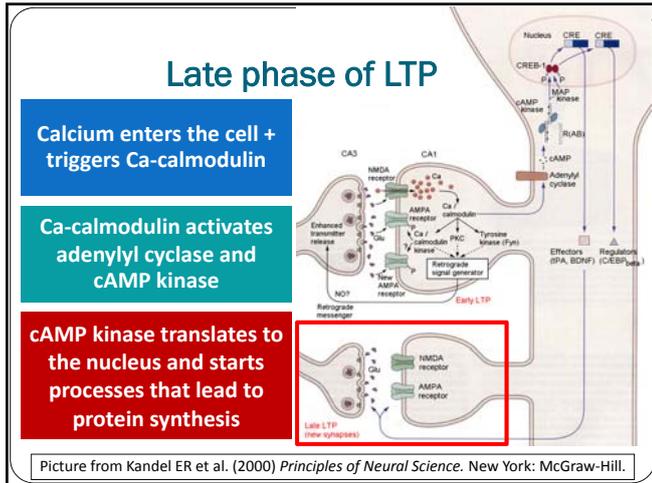
- **No specific drug for this condition**
- The management of children with MR focuses on finding the appropriate educational setting for children with mild MR, vocational training for those with moderate MR, and determining home or institutional placement for those with severe and profound MR



### What is the mechanism in learning and memory processes?

- **Long-term potentiation (LTP)**
  - The mechanisms that increase synaptic strength
  - The cellular and molecular bases for memory in the brain





### DSM-IV diagnostic criteria for ADHD

I. Either A or B:

(A.) Six or more of the following signs of inattention have been present for at least 6 months to a point that is disruptive and inappropriate for developmental level:

9 items of inattention\*

(B.) Six or more of the following signs of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for developmental level:

6 items of hyperactivity and 3 items of impulsivity\*\*

### Inattention category

- Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- Often has trouble keeping attention on tasks or play activities
- Often does not seem to listen when spoken to directly
- Often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
- Often has trouble organizing activities
- Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time (such as schoolwork or homework)
- Often loses things needed for tasks and activities (such as toys, school assignments, pencils, books, or tools)
- Is often easily distracted
- Often forgetful in daily activities

## Hyperactivity-impulsivity categories

### Hyperactivity

- Often fidgets with hands or feet or squirms in seat
- Often gets up from seat when remaining in seat is expected
- Often runs about or climbs when and where it is not appropriate (adolescents or adults may feel very restless)
- Often has trouble playing or enjoying leisure activities quietly
- Is often "on the go" or often acts as if "driven by a motor"
- Often talks excessively

### Impulsivity

- Often blurts out answers before questions have been finished
- Often has trouble waiting one's turn
- Often interrupts or intrudes on others (example: butts into conversations or games)

## DSM-IV diagnostic criteria for ADHD

- II. Some signs that cause impairment were **present before age 7 years**
- III. Some impairment from the signs is **present in two or more settings** (such as at school/work and at home)
- IV. There must be clear evidence of **significant impairment in social, school, or work functioning**
- V. The signs do not happen only during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder. The signs are not better accounted for by another mental disorder (such as Mood Disorder, Anxiety Disorder, Dissociative Identity Disorder, or a Personality Disorder)

## ADHD subtypes

- Predominantly hyperactive-impulsive (5%)
- Predominantly inattentive (15%)
- Combined hyperactive-impulsive and inattentive (80%)

## Epidemiologic data of ADHD

- Prevalence of ADHD = 2-20% (6-7%)
  - The male to female ratio = 2-3 : 1
- In Thailand, prevalence of ADHD = 2.4-6.5%
- It now appears that ADHD persists in 70% of adults (with history of childhood ADHD) and caused significant social-emotional difficulties

## Etiology of ADHD

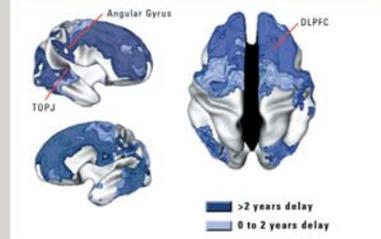
- **No known specific cause**
- **Genetic factors**
  - Dopamine transporter and dopamine receptor genes, etc.
- **Environmental factors**
  - Alcohol and tobacco smoke exposure in utero?
  - Lead exposure?
  - Perinatal complications and premature birth?
  - Early-life infection?

## The neuropathology of ADHD

- **Structural abnormalities:** smaller size of prefrontal cortex, basal ganglia, and cerebellum
- **Functional abnormalities:** abnormal in dopamine and noradrenaline neurotransmission

## Delayed cortical maturation in ADHD

ADHD is Characterized By a Delay in Cortical Maturation



Role of  
DLPFC =  
executive  
functions

DLPFC=dorsolateral prefrontal cortex; TOPJ=temporal-occipital-parietal junction.

Shaw P, Eckstrand K, Sharp W, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci U S A*. 2007;104(49):19649-19654. Reprinted with permission from *Proceedings of the National Academy of Sciences*, (Copyright 2007). All rights reserved.

Spencer, 2008

## Management of ADHD

- Behavioral modification
- Pharmacotherapy
  - Psychostimulants: methylphenidate
  - Alpha agonists: clonidine
  - Antidepressants: SSRIs, TCAs
  - Antimanics
  - Mood stabilizers
  - Beta blockers
  - Anxiolytics
  - Neuroleptics

## Management of ADHD

- Behavioral modification
- Pharmacotherapy
  - **Psychostimulants: methylphenidate (drug of choice)**
  - Alpha agonists: clonidine
  - Antidepressants: SSRIs, TCAs
  - Antimanics
  - Mood stabilizers
  - Beta blockers
  - Anxiolytics
  - Neuroleptics

## Characteristics of methylphenidate preparations

Methylphenidate preparations				
Short-acting				
Focalin	2.5, 5, 10 mg cap	2.5 mg bid	20 mg	60 mg
Methylin*	5, 10, 20 mg tab	5 mg bid	60 mg	>50 kg: 100 mg
Ritalin*	5, 10, 20 mg	5 mg bid	60 mg	>50 kg: 100 mg
Intermediate-acting				
Metadate ER	10, 20 mg cap	10 mg qam	60 mg	>50 kg: 100 mg
Methylin ER	10, 20 mg cap	10 mg qam	60 mg	>50 kg: 100 mg
Ritalin SR*	20 mg	10 mg qam	60 mg	>50 kg: 100 mg
Metadate CD	10, 20, 30, 40, 50, 60 mg	20 mg qam	60 mg	>50 kg: 100 mg
Ritalin LA	10, 20, 30, 40 mg	20 mg qam	60 mg	>50 kg: 100 mg
Long-acting				
Concerta	18, 27, 36, 54 mg cap	18 mg qam	72 mg	108 mg
Daytrana patch	10, 15, 20, 30 mg patches	Begin with 10-mg patch qd, then titrate up by patch strength	30 mg	Not yet known
Focalin XR	5, 10, 15, 20 mg cap	5 mg qam	30 mg	50 mg

bid indicates twice a day; FDA, US Food and Drug Administration; qam, every morning; qd, every day; tid, 3 times a day.  
\*Short-acting formulations of methylphenidate may be dosed up to 20 mg 2 or 3 times a day in adults.  
Adapted from Pliszka S, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.

Dopheide, 2009

## Methylphenidate – adverse reactions

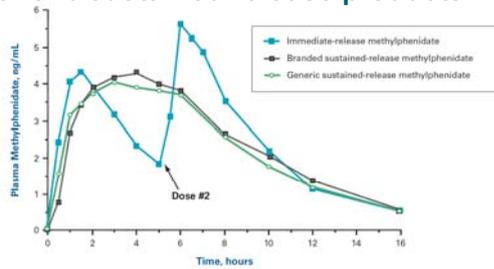
Pharmacologic Treatment	Safety Considerations/ Potential Adverse Events	Management Strategies
<b>Methylphenidate</b> Immediate release (short-acting; ie, dextro, levo-MPH, d-MPH)	Risk for tachycardia, arrhythmia, sudden death Risk for growth suppression Risk for tics Potential for abuse and diversion Risk for hallucinations Risk for GI adverse events (abdominal pain, vomiting, decreased appetite)	Heart rate/BP monitoring; ECG and/or echocardiogram in high-risk cases; baseline ECG not recommended Baseline height/weight with periodic monitoring; dietary consultation and/or nutritional supplementation Decrease anxiety; monitor for appearance/exacerbation of tics; adjust dose; change medication Counsel; nonstimulants; extended-release formulations of stimulants Inquire about vision symptoms; discontinue use if hallucinations occur Inquire about GI symptoms; decrease dose if these occur
Extended release (intermediate- and long-acting; ie, MPH-LA, MPH-CD, OROS MPH, d-MPH XR)	Presumed same risk for cardiovascular adverse events as IR, but not studied Risk for growth suppression and tics similar to or lower than IR formulations Possible lower potential for abuse and diversion, but not well studied	See recommendations for IR formulations

Dopheide, 2009

## Methylphenidate (Ritalin®)

- **A psychostimulant drug**
- **Preparations:** 5, 10, 20 mg/tablet
  - Sustained-release form: 20 mg/tablet
- **Time to peak rate** (in children) = 1.9 hr (0.3-4.4 hr)
  - Sustained-release form = 4.7 hr (1.3-8.2 hr)
- **Current indications:** ADHD, narcolepsy
- **Contraindication:**
  - Marked anxiety, tension, agitation, hypersensitivity to this drug, glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome
  - Beware when using with monoamine oxidase inhibitors

## Pharmacokinetic profile of immediate-release methylphenidate (twice/day) compared with that of the branded and generic sustained-release products

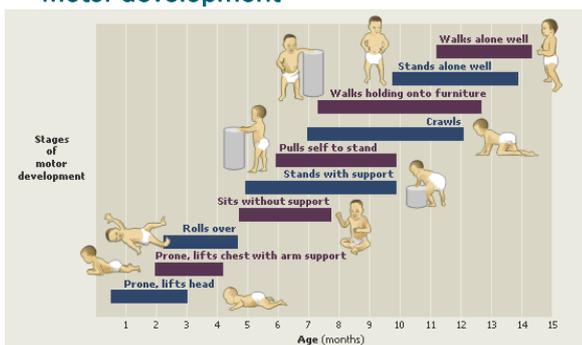


Source: Patrick KS, et al. *Biopharm Drug Dispos.* 1995;10:165-171.

Dopheide, 2009

## CP (cerebral palsy)

## Developmental milestones: Motor development



Picture from distud.blogspot.com

## What is “Cerebral palsy (CP)”?

- **Definition of cerebral palsy (CP)**  
“A **static** encephalopathy of prenatal or perinatal origin that affected **motor** tone and function, resulting in spasticity, hypotonia, ataxia, and dyskinesias”
- The diagnosis requires a history of delayed motor milestones and a static motor disturbance

**Cerebral palsy ≠ Mental retardation**

## Types of cerebral palsy

- Spastic cerebral palsy
  - The most common form of cerebral palsy (50-80%)
  - Further classified into **spastic quadriplegia** (affect both arms and legs), **spastic diplegia** (affect both legs > arms), and **spastic hemiplegia** (affect one side of body)
- Ataxic (cerebellar) cerebral palsy
- Athetoid/dyskinetic (extrapyramidal) cerebral palsy
- Hypotonic (atonic) cerebral palsy

## Spastic cerebral palsy

### Spastic diplegia



### Spastic quadriplegia



Pictures from hubpages.com (left) and kianh.org.uk (right)

## Management of CP

- **No curative treatment!!!**
- The main goals of treatment are to improve the child's motor function and to modify the environment to improve mobility

## Management of CP

- Medication: GABA agonists (benzodiazepine, baclofen), botulinum toxin type A
- Orthopedic interventions: braces, surgery
- Speech therapy
- Physical therapy
- Occupational therapy

Aim of treatment = improve quality of life

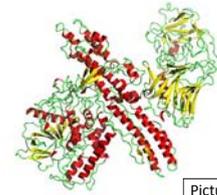
## Baclofen (Lioresal®)

- **An antispastic agent**
- **Preparations:** 10 and 20 mg/tablet; intrathecal form
- **Indications:** used for the treatment of spastic movement, especially in instances of spinal cord injury, spastic CP, multiple sclerosis, etc.
- **Adverse reactions:** drowsiness, weakness, dizziness, headache, seizures, nausea, vomiting, low blood pressure, constipation, confusion, respiratory depression, etc.

\*\*Abrupt discontinuation of oral baclofen may cause seizures and hallucinations\*\*

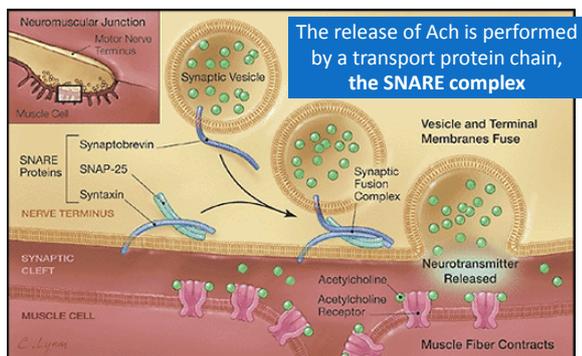
## Botulinum toxin

- Botulinum toxin is a neurotoxic protein produced by the bacterium *Clostridium botulinum*
- It consists of a heavy chain and a light chain linked together by a single disulfide bond
- It exists in 7 different serotypes named A, B, C, D, E, F, and G



Picture from www.3dchem.com

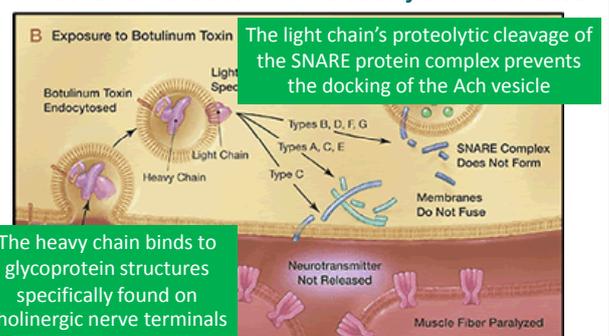
## Normal neurotransmitter release



Picture from <http://ntiasipacific.org>

## Botulinum toxin:

Mechanism of action = inhibit acetylcholine release



JAMA. 2001;285:1059-1070. © American Medical Association

# Autism

## What is autism?

- **Autism** is the most common neurodevelopmental disorder
- **Triad of signs & symptoms**
  - Deficits in all aspects of social reciprocity
  - Pragmatic communication deficits and language delays
  - An assortment of behavioral problems such as restricted interests, sensory sensitivities and repetitive behaviors

APA, DSM IV 1994

## Pervasive Developmental Disorder (PDD)

- Pervasive Developmental Disorder (PDD) or Autistic Spectrum Disorder (ASD)
  - **Autism or autistic disorder**
  - Rett's syndrome
  - Asperger syndrome
  - Childhood disintegrative disorder
  - Pervasive developmental disorder not otherwise specified (PDD-NOS)

## Incidence rate of PDD in Thailand

Year	Incidence rate
• 2002	6.94 cases / 10,000 children
• 1998	1.43 cases / 10,000 children

Plubrukarn R et al., 2005

## Etiology of PDD

### Genetic factors

#### Genes

- Reelin
- 5-HTT
- Homeobox
- BDNF

#### Chromosome

- Chromosome 2
- Chromosome 7
- Chromosome 15
- Chromosome 17
- X chromosome

### Environmental factors

#### Prenatal

- Infection?
- Teratogens?
- Pesticides?
- Stress?

#### Perinatal

- Birth injury?

#### Postnatal

- Leaky gut?
- Virus?
- Metals?
- MMR?
- Rearing?
- Oxidative stress?

## Comorbidity in PDD

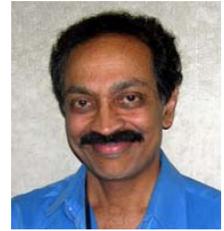
- **Neurological disorders**
  - Mental retardation 50-70%
  - Epilepsy 4-32%
  - Hearing deficits 10-20%
- **Psychiatric disorders**
  - ADHD 40-60%
  - Tic / Tourette's disorders 8%
  - Mood disorders 44%
  - Anxiety or fears 17-74%
  - Obsessive compulsive behaviors 37-86%
  - Sleep disorders 11-30%

## The neuropathology of autism

- Many information in autistic researches demonstrate abnormalities in...
  - Head circumference
  - Brain volume
  - Fusiform face area (FFA)
  - Cerebral white matter and corpus callosum
  - Neurotransmitters such as serotonin, GABA, acetylcholine, etc.
  - Neuroendocrine system such as oxytocin hormone
  - Mirror neuron system

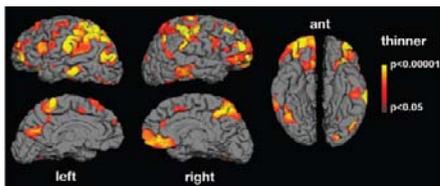
## Mirror neuron system

**“A loss of mirror neurons is the key deficit in autism”**



V. S. Ramachandran, M.D., Ph.D.

## Mirror neuron system



- Cortical thinning was observed in autism group
- Significant thinning was found belonging to the mirror neuron system and areas involving in facial expression production and recognition, imitation and social cognition

Hadjikhani N et al., 2006

## Investigations in autism

- **Chromosome analysis and genetic consultation**
  - **Indications:** specific dysmorphic feature, history of mental retardation in family
- **MECP2 gene analysis** for diagnose Rett syndrome
- **Metabolic screening test**
  - Screening for inborn error of metabolism such as Phenylketonuria (PKU) – depend on clinical findings
  - Lead level, if suspected lead poisoning

## Investigations in autism

- **EEG, neuroimaging studies and neurological consultation**
  - **Indications:** seizure, developmental regression, abnormal neurological examination
- **Hearing test and communication assessment**
  - **Indications:** speech and language delay
  - **Test:** Brainstem auditory evoked response
- **IQ test and adaptive behavior assessment**

## Management of autism

- **No curative treatment!!!**
- The primary goals of treatment are to minimize the core features and associated deficits, maximize functional independence and quality of life, and alleviate family distress

## Management of autism

- Educational interventions
  - \*\*Early intensive intervention: better outcome\*\*
  - Speech and language therapy
  - Social skills instruction
  - Occupational therapy
  - Sensory integration therapy
- Behavioral modification
- Psychopharmacotherapy

## Psychopharmacotherapy in autism

- Pharmacologic interventions may be **considered for maladaptive behaviors** (aggression, self-injurious behavior, repetitive behaviors, sleep disturbance, mood lability, irritability, anxiety, hyperactivity, inattention, destructive behavior, or other disruptive behaviors) **that cause significant impairment in functioning and are suboptimally responsive to behavioral interventions**

## Conclusion:

### Drugs for manage some of abnormal behaviors in autism

- **SSRIs**                    **repetitive behaviors, aggression, anxiety, depressive phenotype**
- **Atypical antipsychotics**    **repetitive behaviors, hyperactivity, aggression, bipolar phenotype**
- **Psychostimulants**    **hyperactivity**
- **Anticonvulsants**    **repetitive behaviors (sodium valproate), aggression, bipolar phenotype**
- **Alpha2-agonist**    **hyperactivity, aggression, sleep dysfunction**

**THANK YOU  
FOR  
YOUR ATTENTION**