

제9회 특별강좌 의학

2017. 10. 15

제4강.

치매의 단백질 경로

[Intro]

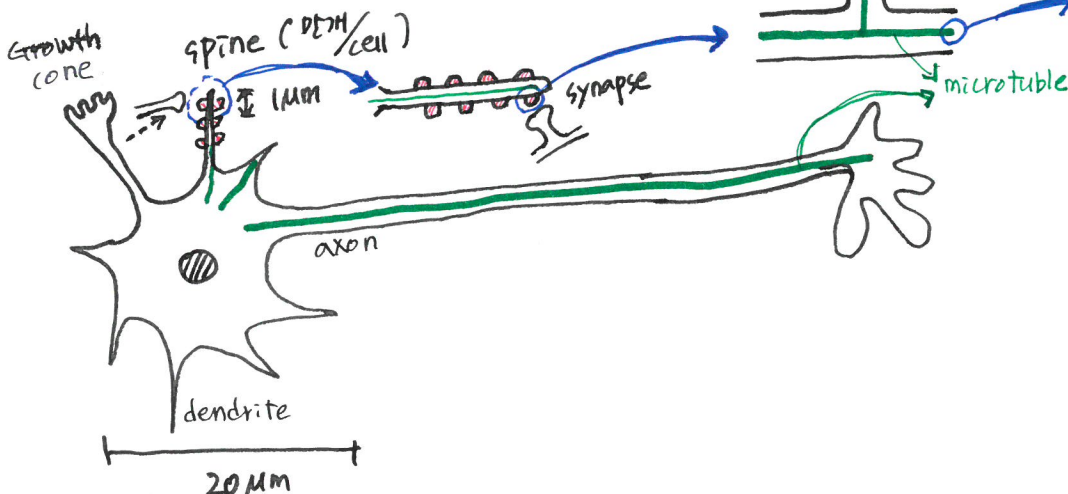
- '치매'의 핵심 단백질 경로를 살펴본다.

↳ $A\beta$, Tau

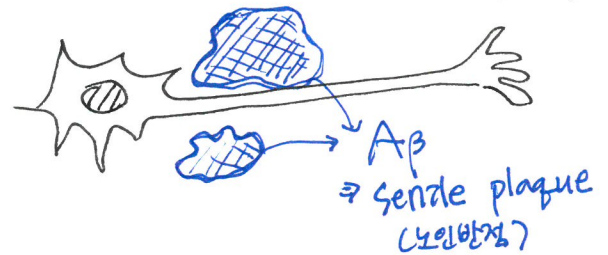
이렇게 정상인의 '뇌'세포를 공격하여, 위축시키는가?

100억개의 세포가 최소 10여년에 걸쳐 서서히 쪼그라드는 현상이 바로 "치매"이다.

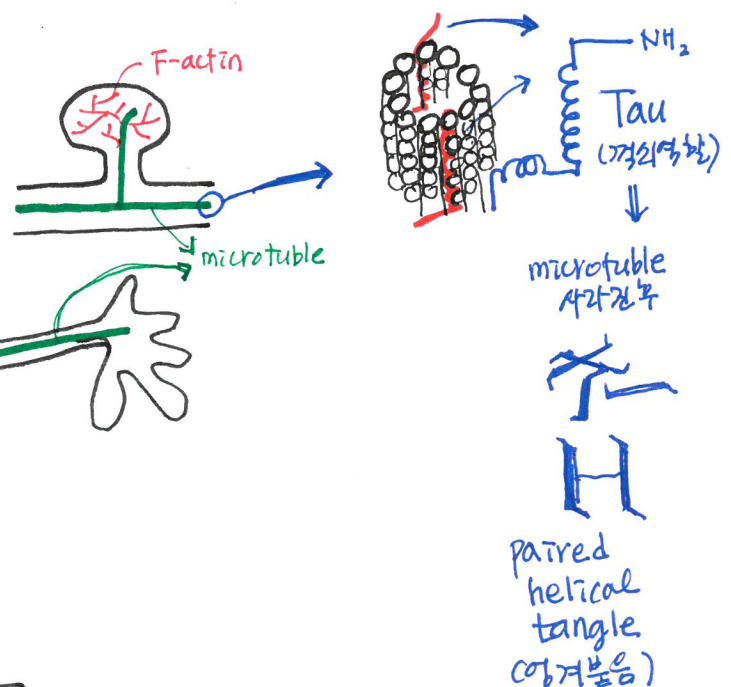
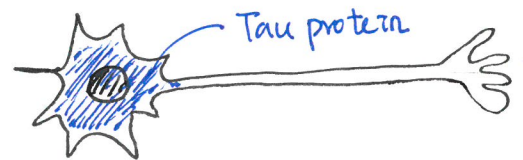
- 원핵세포의 크기는 진핵세포의 약 $1/10$ 만
spine 돌기와 synapse는 세포 전체 크기의 약 $1/100$ 수준
⇒ 이렇게 미세한 공간에서 일어난 uncontrol 현상이 1억배나 큰 세포 전체에 영향을 미친다
= 세포 말단의 불균형이 세포 위축을 초래하였다.

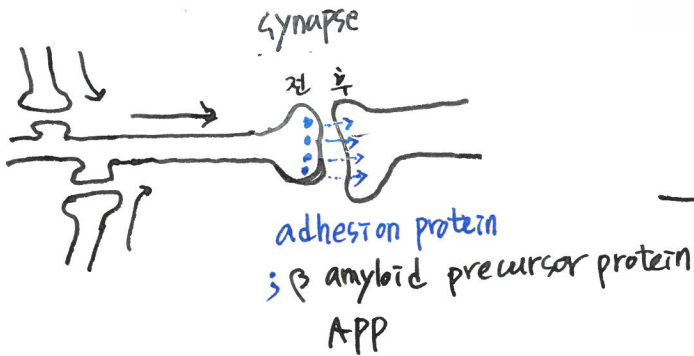
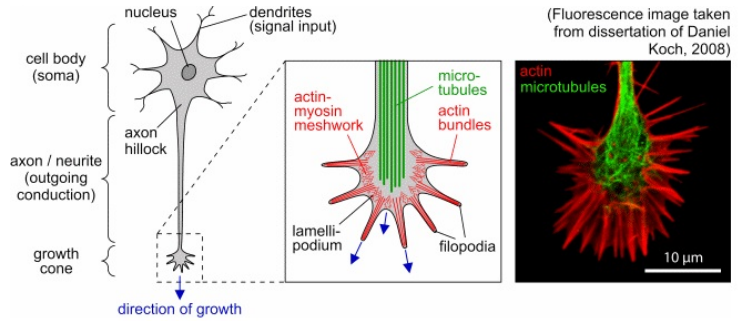


- 치매 환자의 neuron 상태
① 세포 외부: 벡타라이저로 엮힌 단백질 덩어리 관찰됨 by Alzheimer 100명전



- ② 세포 내부: Tau 단백질이 뭉쳐 엉겨붙은 상태





APP는 synapse 간의 연결에 매우 중요
+ 세포분화, 세포분화 등에 관여
⇒ synapse 간의 신호전달이
제대로 이루어지지 않는 것이 바로
"치매" 이다.

[4강의 핵심 주제]

1 $A\beta$ (Amyloid β), Tau

* 핵심은 '순서'

APP 중 $A\beta$ 자르는 순서 2 가지가 있다.

∴ amyloid β precursor protein

• APP 중 $A\beta$ 자르는 가위 3종류
(secretase)

α normal
 $\beta \rightarrow A\beta$ 생성
 γ 정상

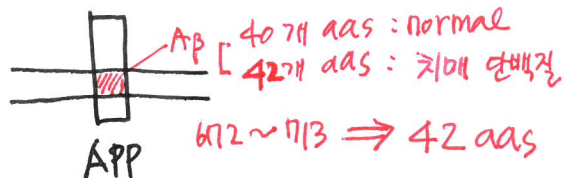
$\alpha \rightarrow \gamma$: **정상**
 $\beta \rightarrow \gamma$: **치매**

2

생각은 Ca^{++}
죽음도 Ca^{++}

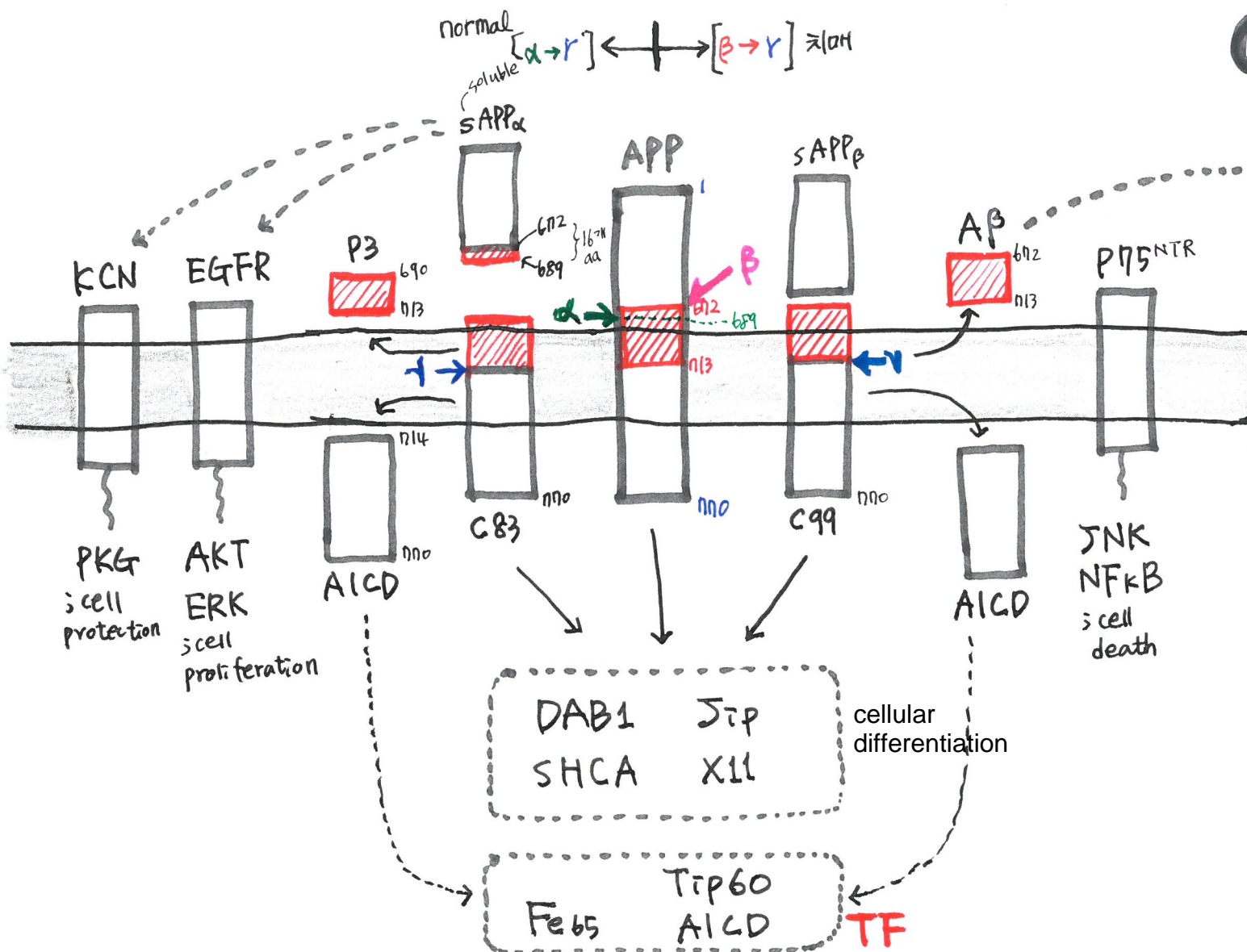
∴ Ca^{++} 농도를 조절하지 못함
→ glutamate 농도 조절 X
→ Death

(Ca^{++} 농도균형을 잡음 → '생각'
 Ca^{++} 농도균형이 깨어남 → 'death')



○ Amyloid β : Amyloid protein 중 β ($A\beta$)
가장 위험

$A\beta_{42} \uparrow / A\beta_{40}$: 치매



KCN : potassium cyanide
 PKG : protein kinase G
 = cGMP-dependent protein kinase
 EGFR : Epidermal growth factor receptor
 AKT : v-Akt Murine Thymoma Viral Oncogene
 /PKB (Protein Kinase-B)
 ERK : extracellular signal-regulated kinases
 =MAPK (mitogen-activated protein kinases)
 AICD : Amyloid precursor protein intracellular domain
 sAPP : soluble amyloid precursor protein alpha
 APP : amyloid precursor protein
 p75NTR : p75 neurotrophin receptor
 JNK :c-Jun N-terminal kinases
 NF- B : nuclear factor kappa-light-chain-enhancer of
 activated B cells

ROS : Reactive oxygen species
ABAD : amyloid-beta peptide alcohol dehydrogenase
Bid: Bax-like BH3 protein
BAD : Bcl-2-associated death promoter
Cyt C : cytochrome C
Apaf1 : Apoptotic protease activating factor 1

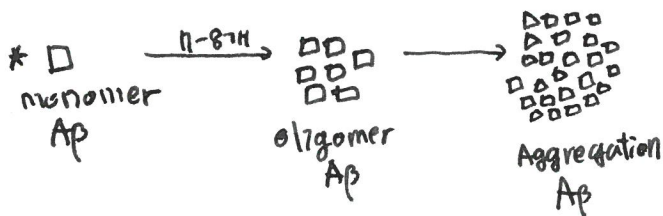
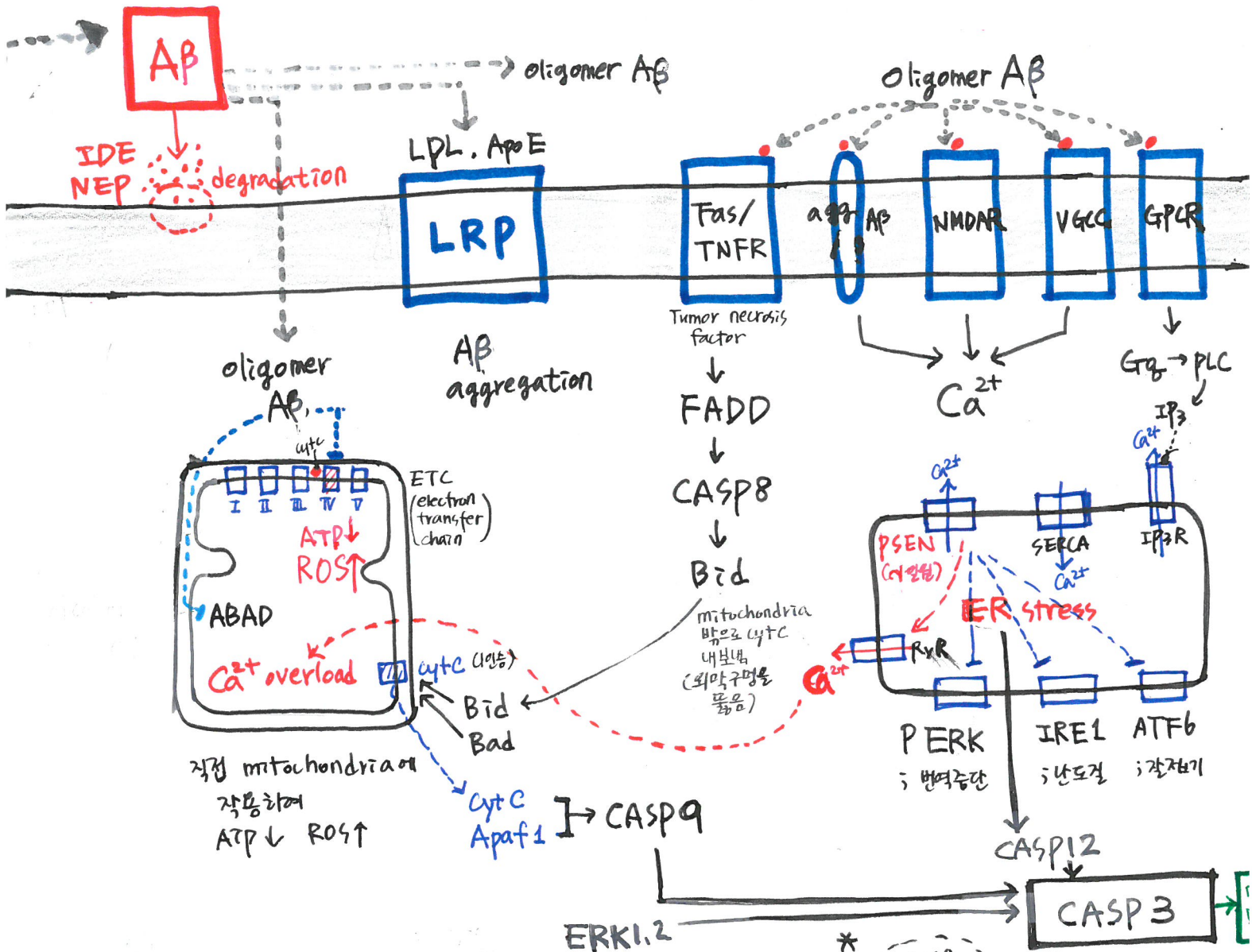
LPL : Lipoprotein lipase
LRP : Low density lipoprotein receptor-related protein
Fas :TNFRSF6
TNFR : tumor necrosis factor receptor
FADD : Fas-associated protein with death domain
Caspases : cysteine-aspartic proteases.

PSEN : Gamma secretase PSEN1 (presenilin-1), nicastrin,
 APH-1 (anterior pharynx -defective 1), PEN-2 (presenilin
 enhancer 2) 4 가
 SERCA : sarco/endoplasmic reticulum Ca²⁺-ATPase
 PERK : protein kinase R (PKR)-like endoplasmic reticulum kinase
 IRE1 : inositol-requiring enzyme 1
 AFT6 : Activating transcription factor 6

NFT : Neurofibrillary tangles
PHF : paired helical filaments

[Aβ Cascade]

(단량체) 원래 세포막에 박혀있던 존재 → 'β' → 'r' 순으로 갈라져 'Aβ' 자유됨 → 모든 곳에 간다. 문제 일으킴

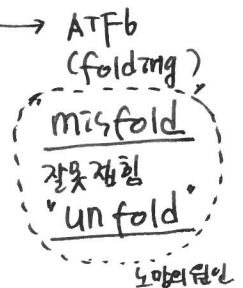


* ER stress : endoplasmic reticulum stress
misfolded unfolded protein ER

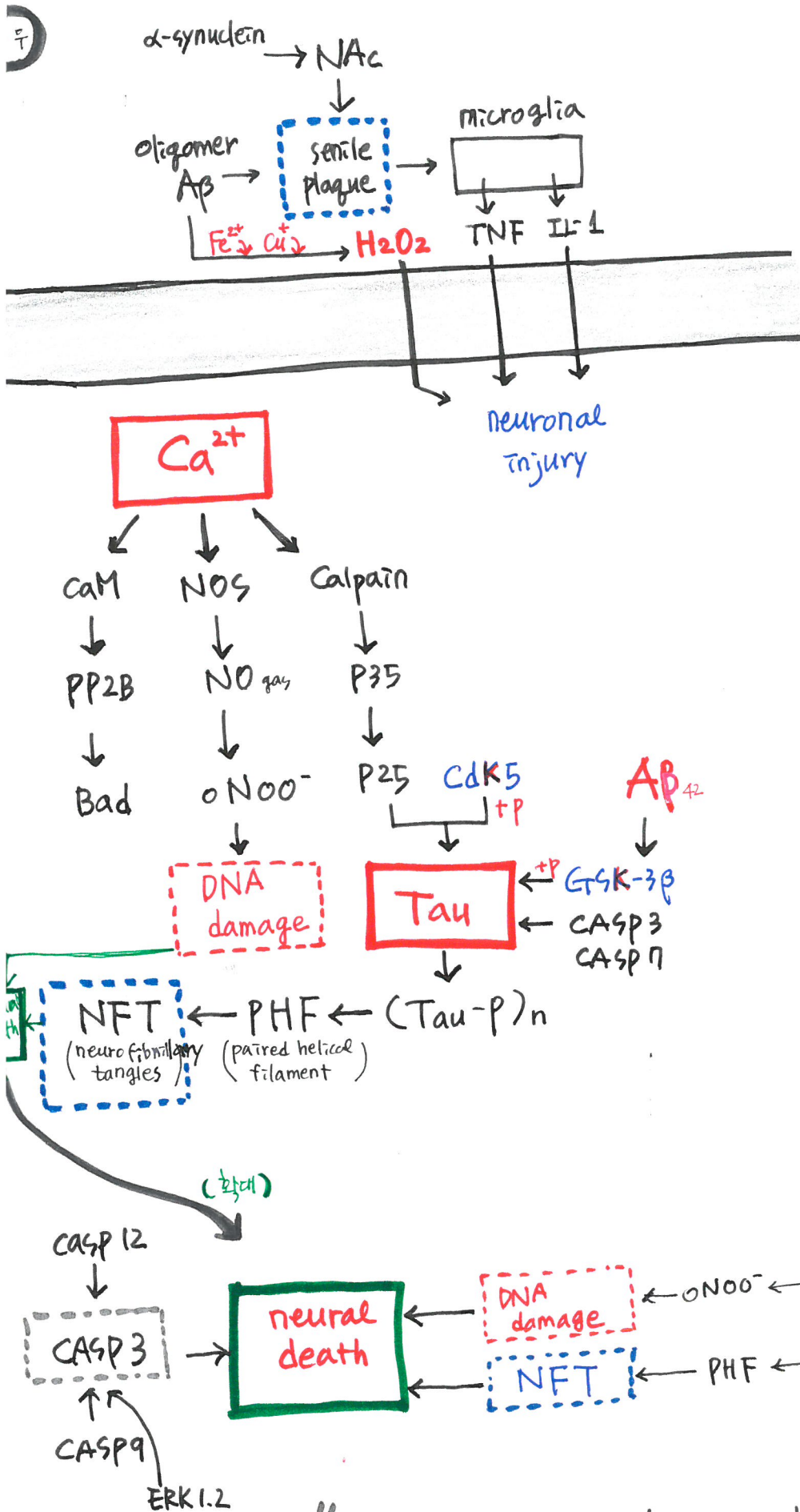
* ER stress 의 이유는?

너무 많이 만들어 지게 문제다.

- ⇒ ① 적게 만든다 (TF ↓)
- ② 불량품 제거 (IRE1)
- ③ 정품 만들기 (ATF6)



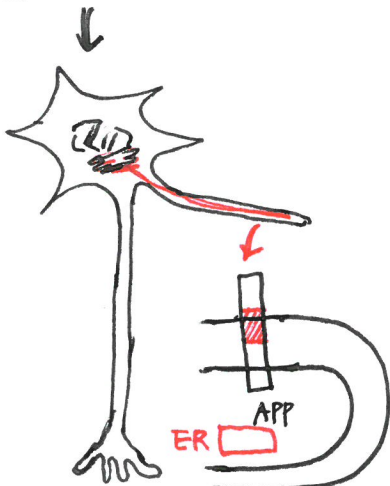
노아비원인
1차구조 → 2차 α-helix
β-sheet
3차구조



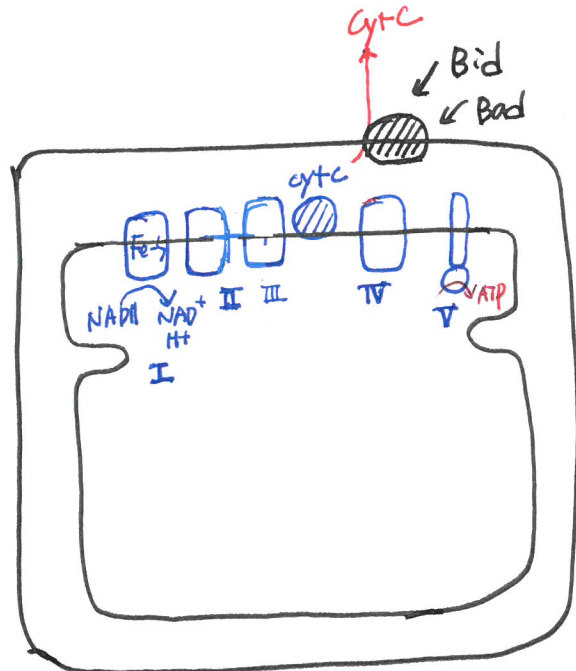
"Cancer is dysregulation of normal pathway."

"방조는 죽는다"

(선명)

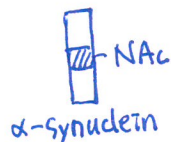
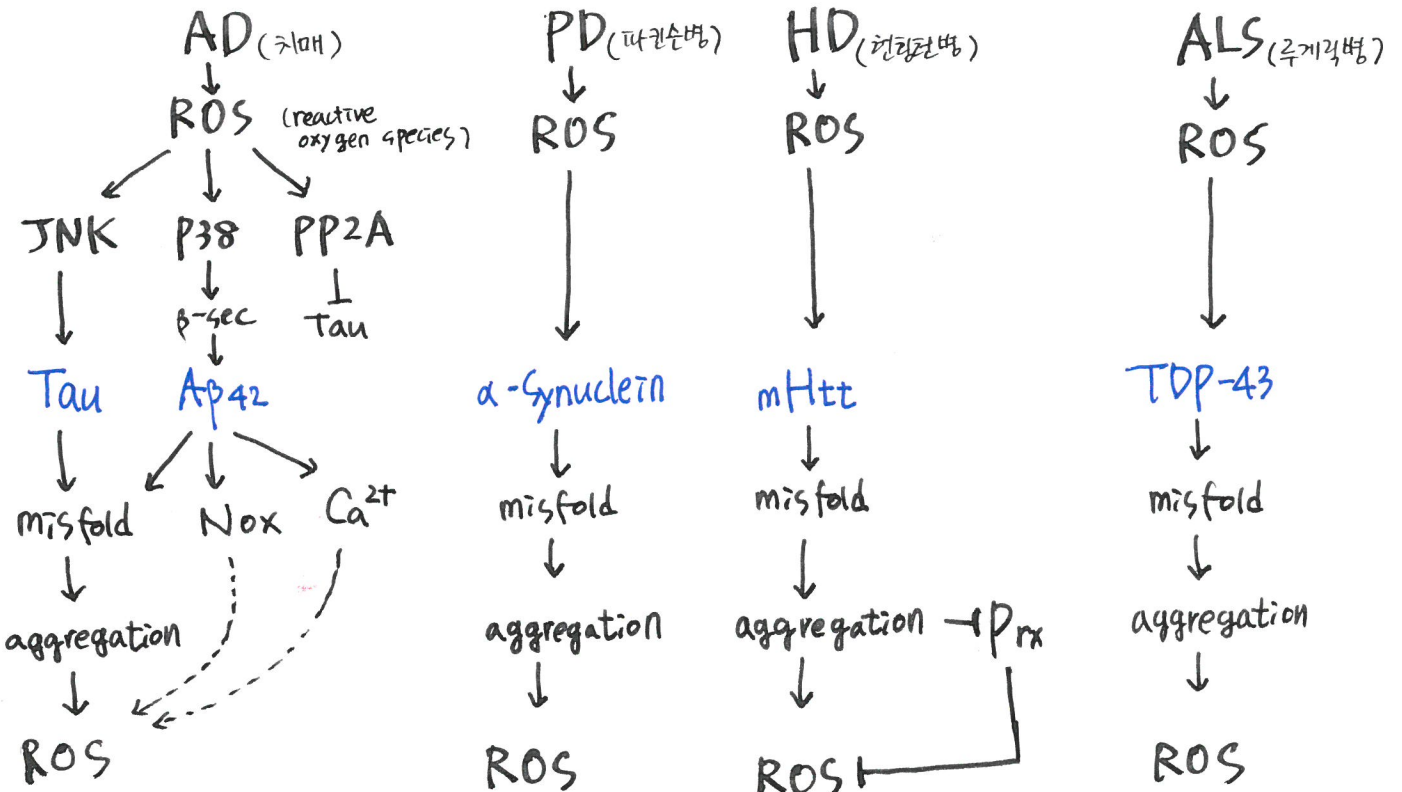


SER이 dendrite 끝까지 와있음



- ① 미토콘드리아 내막에서 cytC 분리
- ② Bid, Bad 작동해서 미토콘드리아 외막에 구멍 뚫고
- ③ cytC 유출 ↑
- ④ cytC Apaf1 → CASP9 작동

[AD, PD, HD, ALS 기전] : ROS → 'misfold'에서 기원

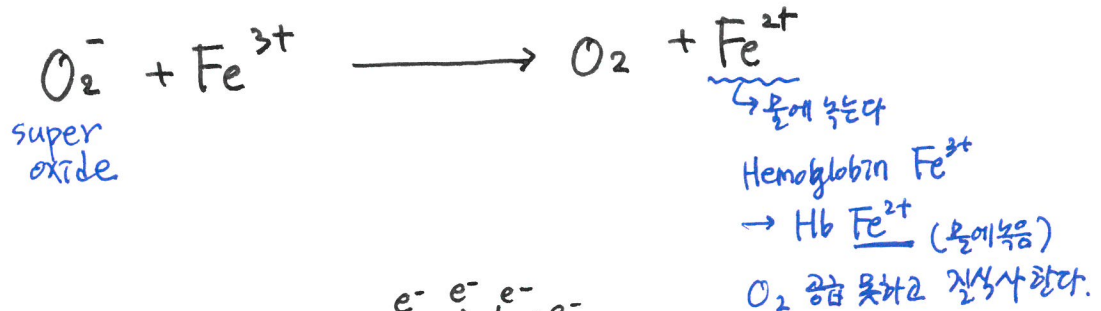
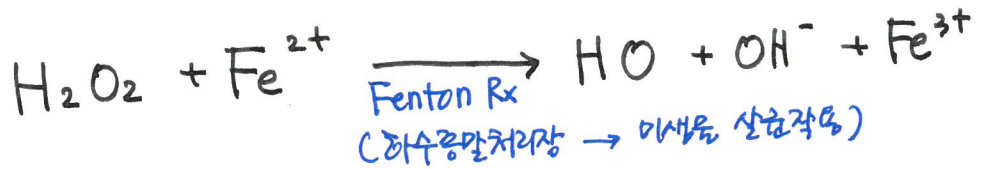
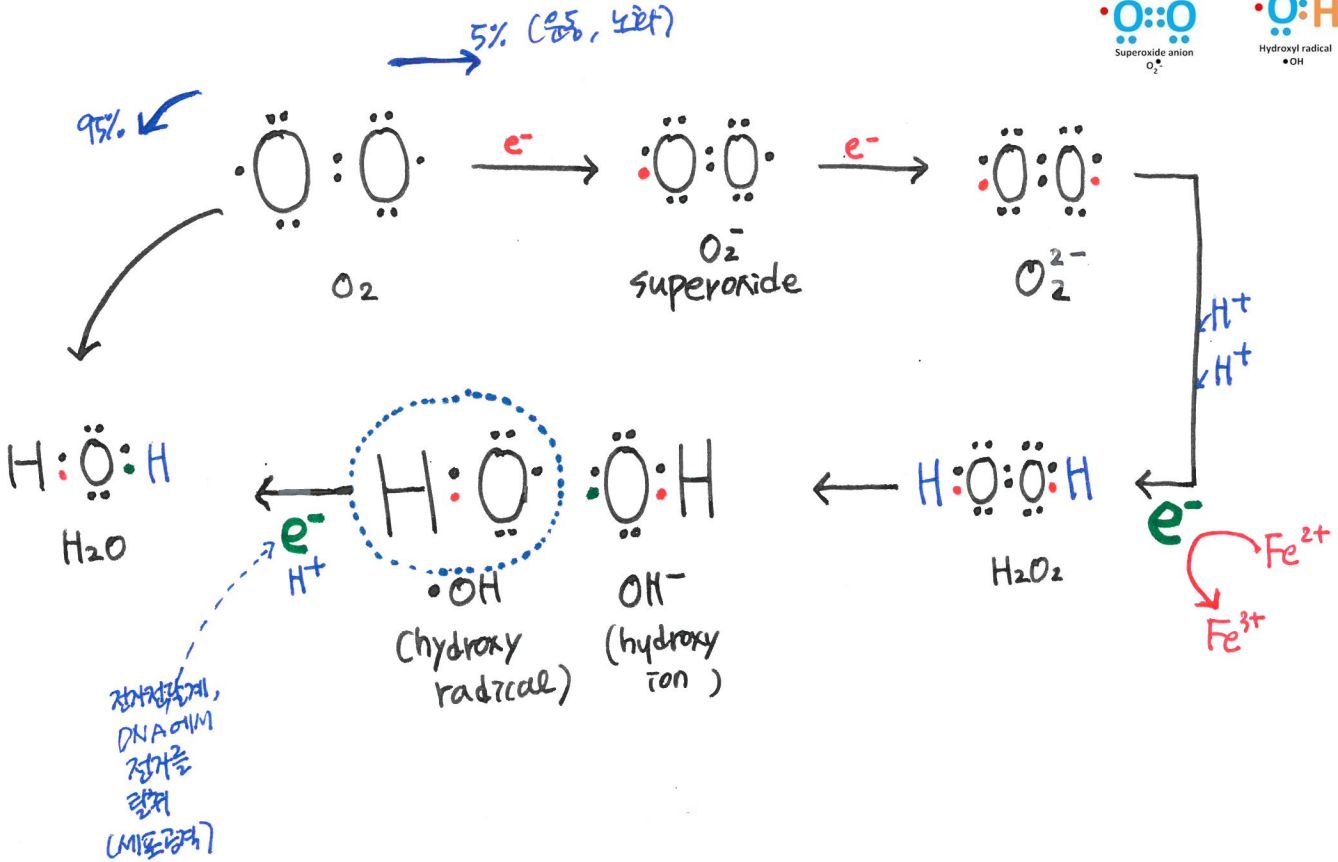
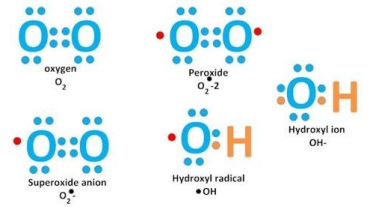


AD : Alzheimer's disease
 PD : Parkinson's Disease
 HD : Huntington's disease
 ALS : Amyotrophic lateral sclerosis

[Fe²⁺]가 치매에 중요한 요인이라는 연구가 진행되고 있다.
; 호흡은 산소가 물로 바뀌는 과정

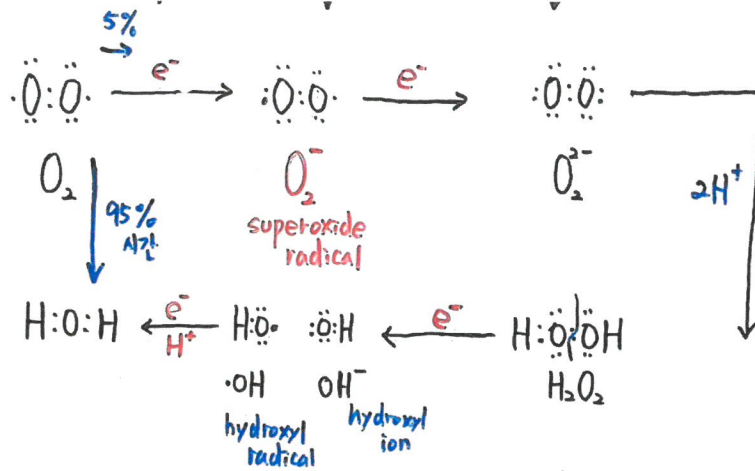
Reactive Oxygen Species (ROS)

• = unpaired electrons



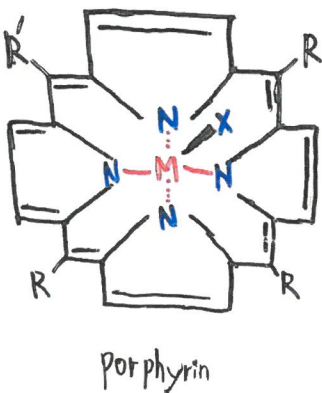
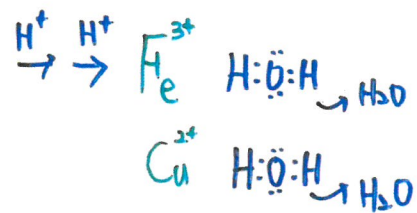
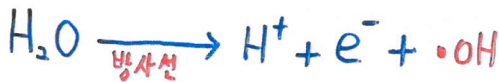
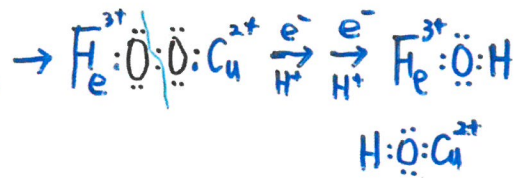
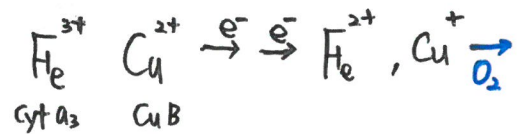
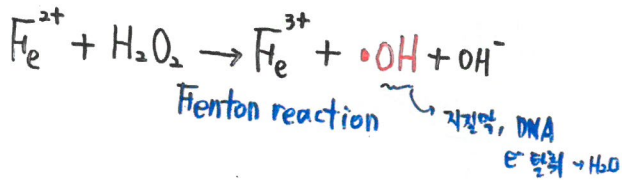
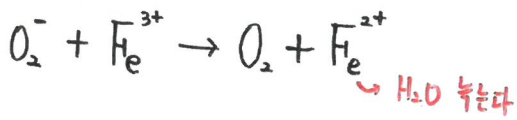
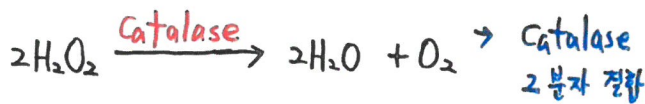
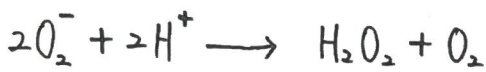
* 미토콘드리아 내막 TV protein cytc [O₂] 4개의 전자를 받을 때 까지
가두었다가 H₂O 만든다.
ROS (활성산소) 가 빠져나오게 되면 세포 속에서 난동을 부린다
→ 노화.

(참고) 제 9회 1999년 유수생물 제 5강 내용 중 "활성산소" 관련 내용

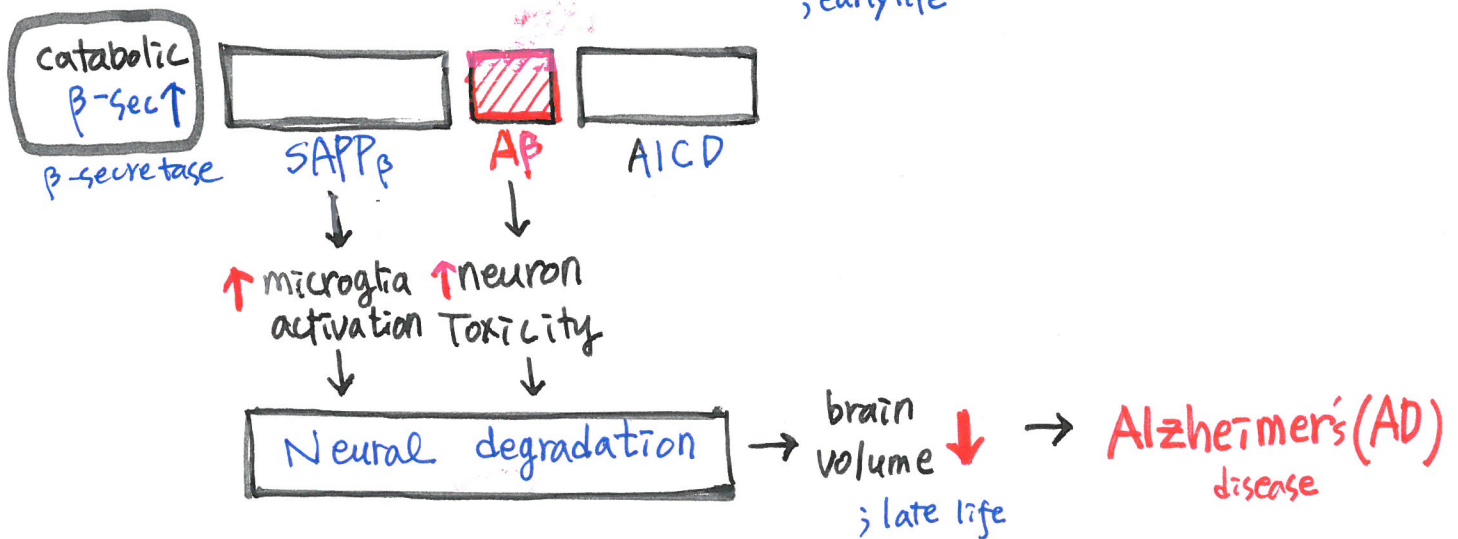
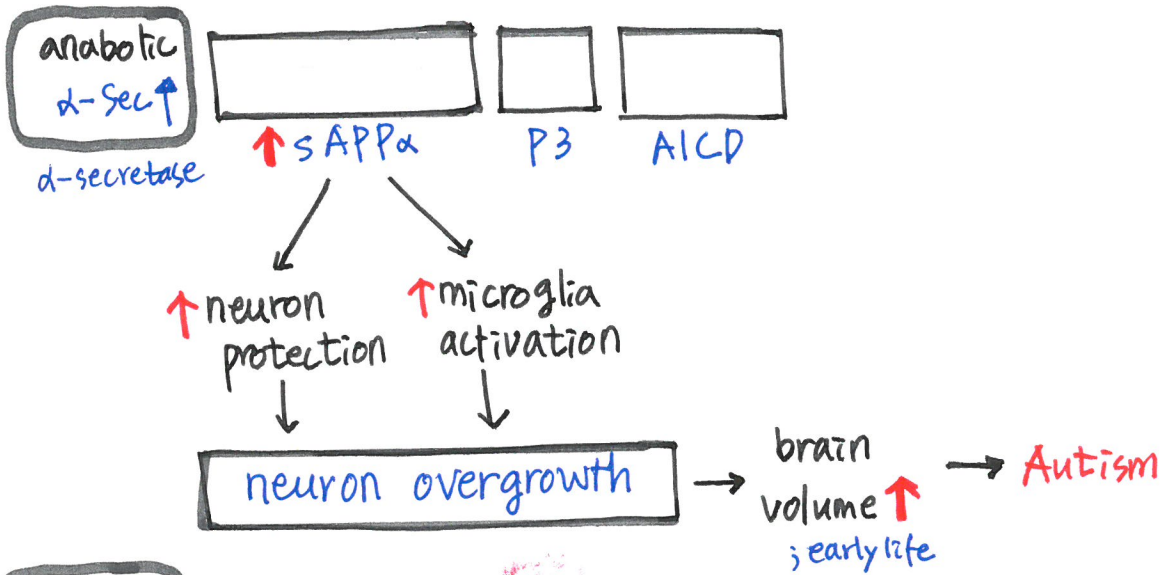
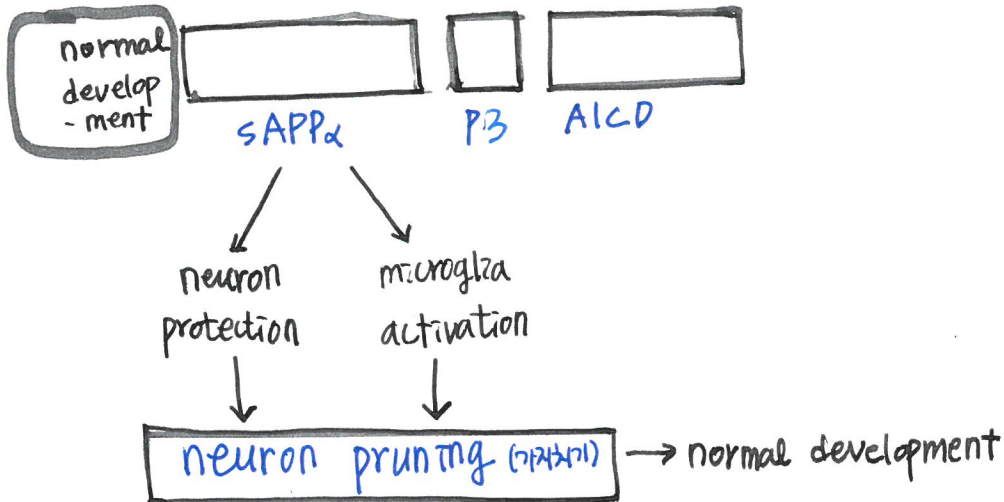
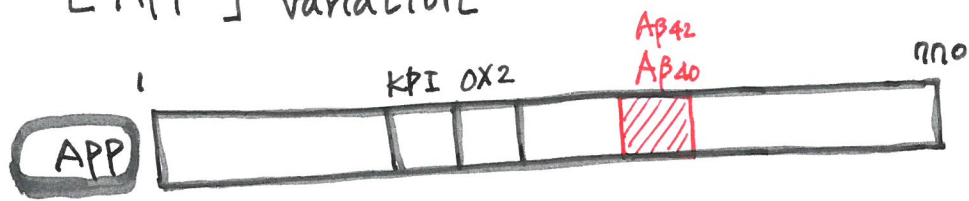


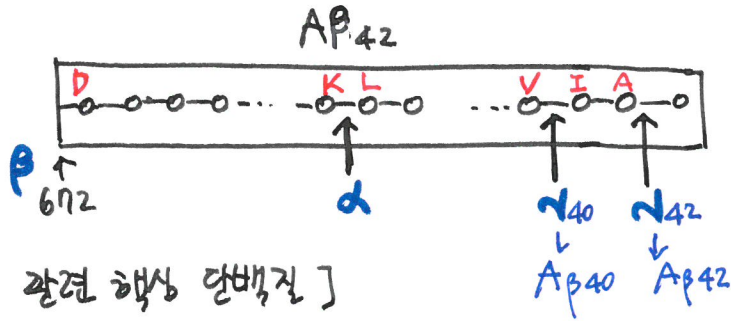
reactive oxygen speices

ROS $O_2^{\cdot -}$, O_2^{2-} , OH^- , $\cdot OH$
↑ start ↓ 주위



[APP] variation





[치매 관련 핵심 단백질]

[Apo E
GSK-3β
Cdk 5]

최신 연구들에서 치매와
관련있는 단백질로 연구되고 있음

