Neurobiology of Disease: Obesity

SFN 2010 Annual Meeting Course:
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Clinical description and epidemiology

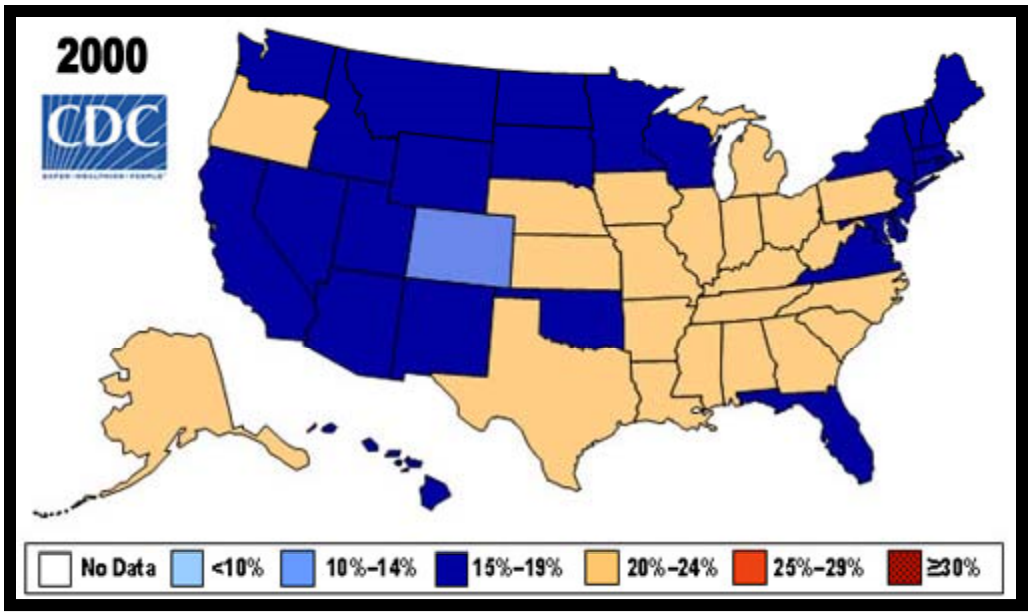
Stanford U, Steven Smith

- One female patient: Getting overweight although she was doing everything right, e.g. exercise, diet. But she was able to sleep only 3-4 hours a night and was highly susceptible to stress. ref to: Hypothlamus regulates body weight.
- Risks of obesity included: type 2 diabetes is high 57%, ___ gall bladder (30%) heart disease, and cancer..
- Generally: increased BMI, decrease lifespan
  - 30-45% bmi, reduce about 2-4 years of life.
- Factors: 1) Environmental, e.g. Food 2) Genetics variation, 3) Metabolic,,,
- Historical background: pituitary gland followed by hypothalamus: evidence: hypothalamus lesion: increase food intake up and obesity
  - Lateral hypothalamus lesion: Increase appetite,
  - Leptin deficiency: obesity resulting from increased appetite

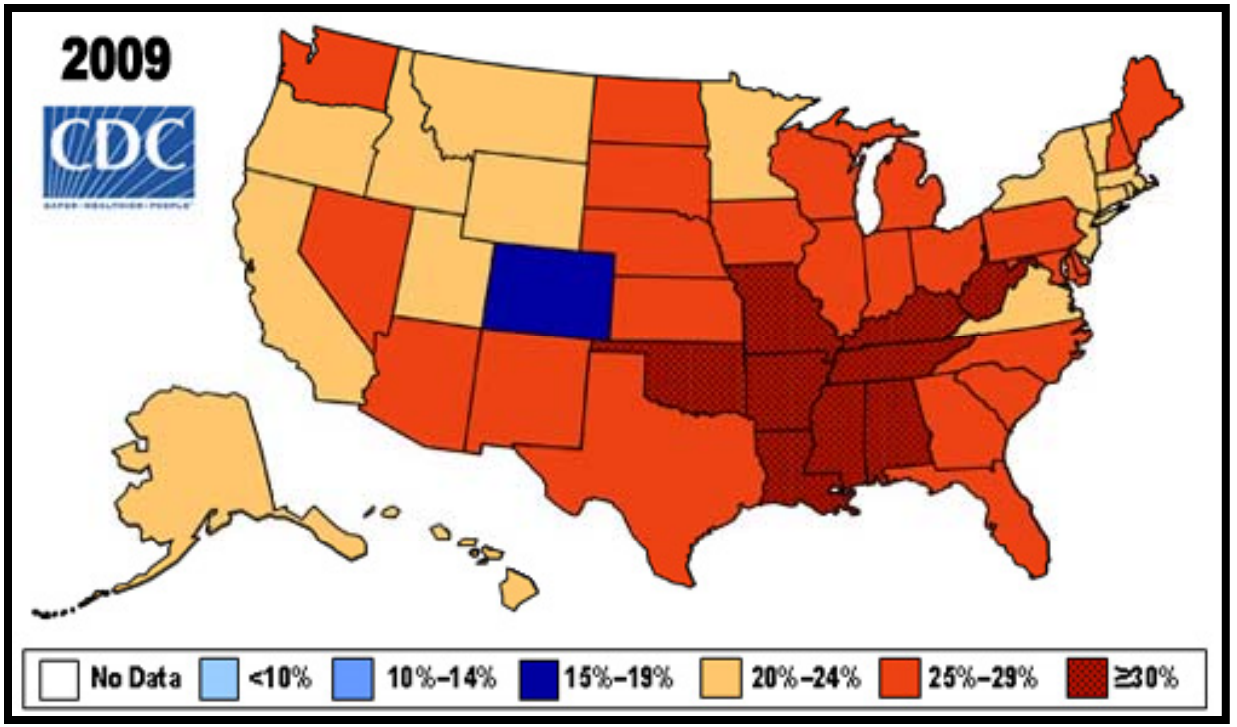
- Conclusion: Brain is the dominant player in obesity

BMI in the USA

- BMI for obesity_25-29.9 bmi is overweight; over 30 BMI, obese: Many east and middeast states have high BMI of more than 24. US is one of the developed countries that has the highest population with BMI of more than 30.
- Generally: increased BMI, decrease lifespan
  - 30-45% bmi, reduce about 2-4 years of life.



US Obesity Trends: Percent of Obese (BMI>30) in the US in 2000 and 2009 (source: CDC)



Utah	23.5 %
California	24.8%

White lowest, BLK and Hispanic highest

Neural systems mediating energy balance:
Hans-rudi Berthound, PhD. LSU

- Energy intake = energy expenditure
  - Error rate for this balance is about 1% resulting in a 30 gm weight accumulation in one's life time.
- Environmental and lifestyle signals are sent to brain which modifies feeding behavior:
  - Ingest sends taste to homeostatic regulator (brain). E.g. the gut-brain communication regulator is mediated by leptin signal.
  - There are several regulators such as hypothalamus nuclei, leptin, NPY, GAPA neurons which mediate signals to POMC.
- Behavioral controls are mediated by several organs and tissues (e.g. brainstem, spinal cord, muscle, adipose tissues), and several systems such as neurotransmitter, metabolism, hormones, synaptogenesis, membrane excitability, etc…
- Neuroeconomics..making optimal decisions (Hare et al, J. Neuroscience, 2008).
- Many brain areas are involved in obesity: cingulate, amygdala, insular striatum, thalamus, accumen nuclei, motor cortox, hippocampus, etc….. And neurons involving in representation, reward, learning, memory, motor cotex, energy balance
- Top down control: the notion that expensive wine tastes better even through it the same wine (Plassmann et al, PNAS 2008 experiments).
- Bottom up control: the value of food is dependent on metabolic need
- Leptin regulate food smell: e.g. leptin deficient mice found food fasters suggesting that leptin deficiency enhanced smell sensory.
- Ghrelin controls hippocampal synapse and memory performance (Diano et al, Nature Neuroscience, 2006)

Gut peptide signaling in feeding control
Gary Schwartz, PH.D., Abert Einstein College of Medicine

- Gut-endocrine system is the **gut-brain axis** (gut-brainstem) which regulates sensory inputs and motor outputs.
  - Gut sensory
  - Gut peptide
  - Gut is innervated by sensory fibers
- Transmission to brain involved many factors
  - Gut peptides can signal gut sensory neurons (endocrine neurons), nodes on ganglion
  - Gut vagal afferent fibers are sensitive to meals
  - Experiment: Gut peptide CCP: lack of CCK mice are obese resulting from hperphasia
  - Transmission from gut to brain can be summarized as: gut----vagus nerves----brainstem---hypothalamus, amydgala, limbic systems
    - **Caudal brainstem:**
  - gut peptides and gut neural signalling are important in feeding
    - Viral trace starting at the gut can be found in the app/NTS, IPBN, PVN nuclei and so on.
    - Gut vagal afferent fibers mediates satiety effects of gut peptides
    - Functional leptin Receptors are found at multiple nodes of t he gut-brain axis
  - Leptin acts at eh brainstem to suppress feeding input (???)
- **Future direction.**
  - A. Taste in the gut med gut peptide release?
    - Tongue? Ghelin signaling in tongue...
  - B. Gut pept signaling is dynamic
  - C. Gut pept I. Feeding reward....

Environmental and developmental influences of obesity
Tracy L Bale, U. Of Pennsylcania

- Dutch Winter and Swedish famine: Offsprings of starving people had low risks of cardiac diseases, obesity etc..

Epigenetic Mechanism of Obesity

xxxObese mothers produced offspring susceptible to obesity:

Although having having either parent obese parent is an independent risk factor for childhood obesity, **the impact of diet-induced maternal obesity on adiposity and metabolism in offspring are well established**.

- HF diet: increased obesity, female offspring are likely to display high anxiety and stress.
- Female mice fed with hi fat diet during pregnancy produced offspring with increased weight, longer body length, reduced insulin sensitivity.
- .

- Recent study by Ng. et al (Nature 2010) was the first report in mammals of non-genetic, intergenerational transmission of metabolic genes of a HFD from father to offspring.
  - This study found that HFD-induced Spragque-Dawley fathers produced F1 female offspring with beta-cell dysfunction, ,had early onset of impaired insulin secretion and glucose intolerance that worsen with time,
    - (once grown) altered the expression of 642 pancreatic islet genes belonging to 13 functional clusters including the cation and ATP bining , skeleton and intracellular transport clusters ($P < 0.01$);
    - AND calcium-, MAPK- and Wnt-signalling pathways, apoptosis and the cell cycles $P<0.05$).

CRF is the key stress mediator in the brain: High fat diet, hi CRF level causing hi stress

When mice were refed with control diet, CRF gene expression returns to normalObesity may be maternal transfected with offspring received obese causative genes form mothers and also suggest that miRNA regulation may be involved in obesity regulation

Human physiology of reduced body weight

Rudy Leibel MD, Columbia U

- Type 2 diabetes are preventable by decreased wt gain, and it can be reversible by a modest decrease in wt.
- However, formerly obese persons are different than Never Obese persons in that they are more susceptible to environmental conditions including 1) more susceptible to cold and other factors.
- Xxxx????

Sunday: New advances in Calcium Signaling in Neuronal function and disease: Solomon H Synder, ""Inositol as molecular messengers."

- IPs are synthesized by 3 inositol hexakisphosphate (IP6) kinases (IP6Ks). Hexakisphosphate kinase-2 (IP6K2) is an enzyme that catalyzes the production of inositol pyrophosphate diphosphoinositol pentakisphosphate (IP7). IP7 is a physiologically occurring inositol pyrophosphate with 7 phosphates.
- Inositol pyrophosphates (IP3, IP7, IP8) involved in many biological processes: 1) release intracellular calcium (IP3), 2) apoptosis (IP7 via IP6K2) 3) endocytosis (IP7, IP6, with the IP7 contribute the phosphate to ATP synthase, 4) telomere length maintenance (IP antagonizes phosphoinositide 3-kinase related proteinase kinases Tel1 and Mec1 to shorten telomeres), and 5) chemotaxis (IP7 competes with chemotaxis mediator domain, PH domain, binding twith ptdlns(3,4,5)P3. IP7 reduction enhances PH domain membrane translocation and augments downstream chemotactic signaling activity.
  - Bhandari R Juluri KR, Resnick AC, Snyder SH, PNAS 2008: Ko of IP6K1 reduced production of I)P: mice were more. Insulin resistance with a lower circullatory insulin but they did not become diabetic Males were sterile from defects in spermiiogenesis. When fed with the normal diet, the IP6K1 ko mice became thin because gsk3 beta inhibited

IP7 role in vesicular trafficking:

_1) yeasts with IP6K deletion showed defects in vesicular endocytosis and vacuoar morphology. 2) clathrin-associated proteins regulating endocytosis and exocytosis bind to IP6 and IP7, 3) IP7 pyrophosphorylated the beta-3 subunit of Adaptor protein AP3.

Snyder continued:

- Amphetamine-DA pathway: Ip7 inhibit Akt, stmulate GSK 3alpha/beta
  ip6k activate Akt

- Ip6k works with p110/p85 to produce pip3 from pip2 to make Akt

Sunday: New advances in Calcium Signaling in Neuronal function and disease:

Takayuki Michikawa: *Structure and function of 1,4,5-trisphophate receptor*

- Ip3 only memeber of the ipfamily that targets a calcium channel
  Ip3 receptor is a calc channel.
  Ip3 involves in a variety of diseases..\
- Why?
  - Ip3 links cal channels(2) on the cytosol side and then links with other kinases to form complex for cal internAlization ..
- Ip3 binding core..
  - Ip3 binding suppressor doamain makes isoforms with different affinity for different ip3 receptors..
  - NGf acts via ip3 signaling
- Ip3r1 signaling is involved in sca15 sca16 by point mutations\
  - Er stress impairs ip3r1 mediated release.
  - Loss of ip3r1 fcn enhances er stress induced neuronal death...
  - Grp78 interacts wit ip3r1 but the interaction is weaker in HD.

Sunday: PM special Lecture:
S. Arber, Biozentrum, U. of Basel*: Connecting Motor Circuits*

- Central Pattern Generators: CPGs
  - Central primary generators
    - Brain and brainstem have sensory feedback with more than 100 premotor sources to activate a single neuron.
  - Early target derived signals specify each motor neuron via axonal outgrowth.
    - E.g. Pea3 is a (ETS family) transcription factor spinal cord circuit assembly. Pea3 regulate Sema3. Sema complex can modify motor neuron signaling.
- Retrograde signaling and specification:
  - Peripheral nt3 (neurotrophin 3) mediates the formation of proprioceptive afferent-motor neuron connection via regulation of Er81 expression. It increases gene expression, including ETS transcription factors such as Er81 and Pea3.
  - KO of nt3 gene results in the elimination of ETS transcription factors (Er81 and Pea3) expression.
  - When crossed with Bax ko mice, Nt3(-/-)/Bax(-/-) offspring 1)abolish the generation of DRG neurons found in Bax(-/-) resulting from the lack of Er81 transcription factor and suggest that NT3/Trk signaling is important for DRG neuronal generation, 2) defect in priprioceptive axon projections.
  - (NT3___Schwann cells regeneration)

- Ipsilateral and Bilateral Projection:???no note

xxxxUse viruses with specific promoter to trace neuronal pathways

- Wonder trace PK neurons to brainstem neurons using specific promoter???

Sunday Posters

- K16 250.28 Generation of induced pluripotent stem cells from Parkinson and Huntington disease patients. W. ZHOU*; C. R. FREED. Univ. Colorado Denver.
  - *Used adnovirus vectors expressing cmyc, klf4, oct4, and sox2 separately. Generated human iPS cells from human skin fibroblast cells.*
  - *Were able to generate iPS cells from one idiopathtic PD patients and two HD patients with 70 and 180 CAG repeats.*
  - *Confirmed that all iPS cells expressed human embryonic stem cell markers (Alk. Phosphatse, nanog, oct4, SSEA-3, TRA-160 by immunofluorescent staining.*
  - Were able to differentiate iPS cells into a population of different neuron types.
  - **Methods:**
    - Dissociated human iPS cells were lay on a mouse PA6 stromal cell layer in ES medium without (bFGF)..non-essential aa, Na Pyruvate, P/S, L-gln, 0.1 mM beta mercaptoethanol (NO 4 ng/ml bFGF) at 1000 iPS cells per well (12-well plate. The iPS were differentiated for 14-16 days.
    - Differentiated cells were fixed and stained with betaIII-tubulin, MAP2, and TH.
- 250.17/K5 **M. D. NEELY, A. M. TIDBALL, P. HEDERA, K. C. ESS, A. B. BOWMA** Development of an hiPSC model for the study of gene-environment interactions in Parkinson's disease (13:00 - 14:00)
  - Generated iPS cells from two brothers carrying the PARK2 mutations: one developed PD symptoms at age 12), the other now 41 yrs old did not.
  - **Differentiated DA neurons from these iPS and investigated the effect on mitochondrial toxins and metals. Could not get in to see the details!**
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253. Ataxias
Theme C: Disorders of the Nervous System

4:00 O1 253.4 A novel ankyrin domain-containing protein Stim prevents cerebellar Purkinje cell loss caused by an alanyl-tRNA synthetase mutation in mice. S. HOU*; J. LEE; S. ACKERMAN. The Jackson Lab., Korea Res. Inst. of Biosci. & Biotech.

- *sti = sticky = mice homogeneous mutation resulting from missesnse mutation of the editing domain of alanyl tRNA resulting in the accumulation of misfolded proteins. The gene was mapped to chromosome 2 and containing a novel ankyrin repeat domain within the Stim critical region, Stim gene.*
- *In sticky mice, PK cell death starts at 3 weeks postnatal.*
- ***Stim** rescues this phenotype by preventing misfold proteins from accumulating in sti/sti PK cells....*
- ***Methods:** gfp fused proteasome substrate to examine proteasome activity in vivo. Found that expression of Stim respored normal proteasome homeostasis, rescuing PK cell death in sti/sti cells.*
  Stim is an ankyrin containing protein Ankrd16

- O2 253.5 Cytosolic carboxypeptidase 1 (Nna1/CCP1) deficiency alters peptide levels and induces autophagy in the brain of the Purkinje cell degeneration mouse. I. BEREZNIUK*; J. SIRONI; L. D. FRICKER. Albert Einstein Col. Med., Albert Einstein Col. of Med.
  - *Study pcd mice (PK degeneration): The disease is adult-onset degeneration of specific neurons: PK, retinal photoreceptor cells, mitral cells of the olfactory bult, and selected t halamic neurons.*
  - *Due to the deletion of exon 5 of the cytosolic carboxypeptidase 1. Carboxypeptidase 1 is an amminopeptidase,*
  - *Using quantitative peptidomics approach (?): found many peptides derived from cytosolic and mito proteins are increased.*
  - *Proteasome is normal in pcd mouse brains*
  - *Stained with autophagsome marker showed hi levels of autophagy.*
  - *Speculated: elevated autophagy resulted form decreased level of aa in the pcd brain?This enzyme acts downstream of the proteasome to break down ubiquitunated proteins...*
  - *Results suggested "that cytosolic carboxypeptidase 1 cleaved proteasome products into aa." Lack of carboxypeptidase 1 caused a decrease in the level of aa in the pcd mouse brain.*

Session Title: Experience-Dependent Synaptic Plasticity and Neurogenesis in the Degenerating and Injured Brain

Carl W. Cotman: Mechanisms of experience dependent neuroplasticity and the role of neurotrophic factors in animal models of Alzheimer's disease

- Exercise regulates hippocampal performance in APP transgenic mice (double mutant forms of APP)
  - Five months of volunteer exercises (cage with and without a running wheel): increased Watermaze performance, decrease extracellular amyloid beta plaques in frontal cortex, hippocampus, decrease Abeta1-40 and Abeta1-42).
  - Block BDNF during exercise reduce exercise-induced learning.
  - Stress resistance....
  - Increased Growth factors.. Bdnf, vegf, ngf, gdnf, igf
  - Dietary enrichment plus exercise improved learning
  - Exercise Plus antioxidants produced great benefit to learning and others...
  - Exercise Reduced caspase 3 and it's cleavage product and stimulates neurogenesis
  - MULTIPLE PAHTWAYS MAY BE ACTIVATED TO REGULATE AMYLOID LEVELS:
    - EXERCISE INDUCED UPREGULATION OF PROTEASOME ACTIVITY THAT CAN MEDIATE THE DEGRADATION OF THE PROTEOLYTIC FRAGMENTS OF APP.
    - LIKELY: EXERCISE MODULATED APP METABOLISM DIRECTLY BY INCREASING NEURONAL ACTIVITY SUCH AS ACTIVATION OF OF PKC, MAPK (MITOGEN-ACTIVATED PROTEIN KINASE), AND PHOSPHOLIPASE C. THESE PAHTWAYS WERE WELL KNOWN TO ENHANCE APP PROCESSING. Several evidence supporting this idea of increasing neuronal activity enhance APP processing:
      - M1 MUSCARINIC AGONIST TREATMENT DECREASES Abeta LOAD IN A TRIPLE TRANSGENIC MODELS OF AD.
      - Exercise increased cholinergic activity, and has been linked to exercise –induced plasticity.
        xx
- Human studies: less clear
  - Descriptive studies showed marked improvement, but few studies showed enlarge volume
  - Aerobic exercise improved executive function and glucose utilization
  - Moderated intensity improved memory and Lower amyloid beta levels in human
  - One needs to exercise 3 to 4 times a week are enough
  - Exercise increased BDNF levels and reactivated Brain

Some studies showed that marathon run is not beneficial, damage heart, low memory retention

Session Title: Experience-Dependent Synaptic Plasticity and Neurogenesis in the Degenerating and Injured Brain

Giselle Petzinger : The effects of intensive exercise on synaptic function in the striatum of the MPTP-lesioned mouse model of Parkinson's disease

- PD:1% of over 50.
  - Pathology: 40% of dop neuron loss in SNc, 80% dopamine loss
  - Symptoms: Slow, stiffness, trembles
- Intensive exercise and synaptic fcn:
  - Exercise does not change the level of DA but increased rate of DA release.
  - Exercise does not change the number of DA neurons but increased D2 receptor number.
  - Exercise ____alter DA and glutamatergic neurotransmissions-(or **activity- dependent neuroplasticity**)
  - Activity-dependent neuroplasticity is modifications within the CNS in response to physical activity that promotes a skill acquisition process.
    - Intense treadmill exercise of MPTP lesion mouse PD model: examined the effect on activity-dependent neuroplasticity in the striatum regarding to the DA and Glu neurotransmission:
    - Model: MPTP treated at 20 mg/kg at 2 hr interval for a total of 80 mg/kg. At this concentration, about 60-70% of DA will die after 5 days post-lesioning.
    - Animals were exercised on motorized treadmill for 30 days (5 days per week).
      - Improved motor task and balance,
    - Exercise effect on DA neurotransmission:
      - increased dopamine available b y increase stimulus-evoked release and decrease DA decay. DA release was most pronounced in the dorsolateral striatum (a region required for motor function).
      - Increased expression of DA D2 receptor mRNA and down regulation of DAT resulting in increased DA signaling.
        - » Down regulation of DAT resulting in increased synaptic DA for DA receptor binding
    - Exercise effect on Glutamatergic neurotransmission:
      - Reduced the amount of glut available for release (immunoelectron microscopy found reduced immunolabeling of synaptic glutamate).
      - Increased GluR2 and phosphorylation which lead to reduced synaptic strength and thus reduce glutamatergic hyperexcitability found in reduced DA neurons.
- Activity-dependent neuroplasticity and PD
  - Subjects: PD symptoms of no more than 3 years from initial diagnosis..exercise 3 times per weeks for 8 weeks.
  - After 24 sessions of specialized treadmill training (Body-weight support treadmill training), subjects showed improved walking performance, incrased gait velocity, stride length, step length, hip and ankle joint excursion, improved wt distriubtion during sit—to-stand.
  - Showed reversal of cortical hyper-excitability.

Posters: Human ESCs and iPSCs

- 331.1 Transplantation of human iPS derived dopaminergic neurons to a primate model for Parkinson disease. T. KIKUCHI*; A. MORIZANE; D. DOI; H. ONOE; T. HAYASHI; T. KAWASAKI; J. TAKAHASHI. Inst. Frontier Med. Sciences, Kyoto Univ., Dept. of Cell Growth and Differentiation, Ctr. iPS Cell Res. and Application, Kyoto Univ., Functional Probe Res. Laboratory, RIKEN Ctr.
  - *Human iPS cells cultured with Shh, FGF-8 and then matured With ES medium containing GDNF, BDNF, ascorbic acid, dbcAMP for 27 days could generate functional DA neurons that can alleviate MPTP treated symptoms on Monkeyx*
- 331.11 Sorting and transplantation of neural progenitor cells derived from human pluripotent stem cells. D. DOI*; T. KIKUCHI; A. MORIZANE; J. TAKAHASHI. Ctr. For iPS Cell Res. and Application, Kyoto Univeisity, Inst. for Frontier Med. Sciences, Kyoto Univ.
  - iPS neural progenitors cellls can be sorted by magnetic or by immunofluorescent labeling. Brief method: iPS cells cultured in Ps, BDNF..20 ng/ml, GDNF..2 ng/ ml, ascorbic acid 200 uM, dorsomorphin 2 uM, Y27632 10 uM, Sb43532 10 uM, were labeled with Corin, a cell plate marker for neural progenitor cells...GMEM, NEAA, sod pyruvate
  - Grow for 14 days, then treated with growth factors for another 14 days...
- B26 331.12 Protein tagging in human pluripotent stem cell-derived neural stem cells. J. M. DOERR*; J. SCHMIDT; I. POSER; A. A. HYMAN; P. KOCH; O. BRÜSTLE. Reconstructive Neurobiologie, Max Planck Inst. for Mol. Cell Biol. and Genet.
  niv. Hosp.
  - Tagged iPS cells with FLAG tag and a neuron specific marker. The tag was able to carry through the differentiation stage to neural population