Dopamine Discovery Day

August 30, 2012

Rikshospitalet — Store auditorium, Oslo, Norway

Organized by Linda H. Bergersen & Vidar Gundersen

Institute of Basic Medical Sciences & Centre for Molecular Biology and Neuroscience, Universtity of Oslo

- **1400: Introduction by Linda H. Bergersen**
- **1410: Alain Dagher (Montreal) "The role of dopamine in risky and impulsive behavior: a neuroeconomics approach"**
- **1445: Edward Fon (Montreal) "Function of Parkinson's Disease Genes in Mitochondrial Quality-Control"**
- **1420: Coffee**
- **1545: Albert Gjedde (Copenhagen) "Causes of the blessings and the curses of dopamine"**
- **1620: Øivind Hvalby (Oslo) "Dopaminergic modulation of glutamatergic transmission in the hippocampus in a rat ADHD model"**
- **1655 : Closing remarks**

↓ Abstracts and affiliations

“Dopamine Discovery Day”

Dopamine mediates brain mechanisms underlying fundamental and diverse behavioural phenomena such as pleasure, joy, love, motivation, habits and motor control, but dopaminergic dysfunction may lead to dyskinesia, addiction, compulsiveness or psychosis.

The presence of *dopamine* (3-hydroxytyramine) in the brain was published by Kathleen Montagu in August 1957 (Montagu KA 1957 Nature 180: 244). In November the same year, Arvid Carlsson et al. (1957 Nature 180: 1200) reported that L-dopa rescued behavioural deficits due to reserpine induced depletion of brain monoamines, and subsequently showed that the effect was associated with restoring brain dopamine levels, rather than levels of other monoamines (Carlsson A et al. 1958 Science 127: 471).

While *dopamine* was not discovered in one day, we take the opportunity of the 55th anniversary to organize the “Dopamine Discovery Day” – a symposium highlighting recent advances in research on dopaminergic mechanisms.

The organizers

The role of dopamine in risky and impulsive behavior: a neuroeconomics approach

Alain Dagher

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Dopamine is implicated in risky behaviors such as drug addiction and gambling. First, dopamine manipulations can make animals and humans impulsive. Second, dopamine has been identified as a learning signal that encodes reward prediction errors. Here we try to reconcile these two findings by measuring dopamine receptor levels in healthy subjects using positron emission tomography, and by reducing dopamine levels using a dietary manipulation (tyrosine depletion), in combination with behavioral tasks.

We show that striatal dopamine D1 receptor levels predict reward learning while striatal D2 receptor levels predict punishment learning. This is consistent with the known roles of D1 and D2 receptors in the direct excitatory D1-bearing pathway and the indirect inhibitory D2-bearing pathway. Reducing dopamine levels leads to an improvement in punishment learning.

We also measured loss aversion in healthy subjects using a gambling task. We provide evidence that the level of tonic dopamine is inversely correlated with loss aversion. Loss aversion also correlated negatively with behavioral impulsivity measures. Transient reduction of dopamine leads to an increase in loss aversion. In sum, loss aversion is under the control of dopamine tone, possibly acting via D2 receptors. This explains why tonic stimulation of D2 receptors with dopamine agonists, as in Parkinson's disease, may lead to addictive and impulsive disorders that rapidly resolve upon discontinuation of the medication. Thus, impulsivity can result from impaired inhibition secondary to tonic stimulation of the indirect basal ganglia pathway.

http://www.mni.mcgill.ca/neuro_team/mbic/alain_dagher/

Function of Parkinson's disease genes in mitochondrial quality-control

Edward Fon

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Parkinson's disease (PD) is a common, devastating neurodegenerative disorder. Both genetic and environmental models strongly implicate mitochondrial dysfunction in PD. In particular, *PINK1* and *Parkin*, two recessive PD genes, function in a common pathway regulating mitochondrial quality-control. In healthy mitochondria, PINK1, a mitochondrial kinase, is rapidly degraded in a process involving both mitochondrial proteases and the cytosolic proteasome. This process is highly dependent upon the membrane potential across the mitochondrial inner membrane ($\Delta\Psi m$), which drives PINK1 import into mitochondria. Indeed, mitochondrial damage that dissipates $\Delta\Psi m$ blocks PINK1 import and leads to its accumulation on the surface of mitochondria. PINK1 accumulation triggers the translocation of parkin, an E3 ubiquitin ligase, from the cytosol to mitochondria, where it mediates the elimination of dysfunctional mitochondria by autophagy (mitophagy). From these studies, a concept of PD pathogenesis is emerging whereby defects in PINK1 or parkin function reduce the efficiency with which damaged mitochondria, a major source of toxic reactive oxygen species, are eliminated. In particular, the control of PINK1 processing, localization and abundance serves a crucial cellular surveillance function, uniquely poised to signal mitochondrial damage and trigger the engagement of the parkin-mitophagy machinery. In this symposium, I will present recent work identifying the mitochondrial proteases responsible for PINK1 processing and a novel role for parkin in mitochondrial quality-control.

http://www.mni.mcgill.ca/neuro_team/neuronal_survival/edward_fon/

Causes of the blessings and the curses of dopamine

Albert Gjedde

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Dopaminergic neurotransmission and brain energy metabolism interact at cortical and subcortical sites in the mammalian brain. Dopaminergic volume transmission in cortex and striatum contributes to blood flow and oxygen consumption regulation by supporting the maintenance of spines and stimulating neuroplasticity, learning, and memory. The interaction changes with age but at different rates in different parts of the brain. The interaction is involved in neurodegeneration in ways that implicate mitochondria. As dopamine receptors and transporters are lost with age, extracellular increase of dopamine and impaired vesicular incorporation stimulate maladaptive plasticity and neurodegeneration through ROS generation and oxidant action from dopamine and its breakdown products. This action appears to depend critically on the sensation-seeking propensity of susceptible humans. At the intersection of these mechanisms lie the individual mitochondria that respond to circulatory contingencies, in part by uncoupling of oxidative phosphorylation.

http://inf.ku.dk/english/about/

Dopaminergic modulation of glutamatergic transmission in the hippocampal CA1 region in a rat ADHD model

Øivind Hvalby

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Dopamine plays an important role in synaptic plasticity and learning and is involved in the pathogenesis of various neurological and psychiatric disorders. We have examined the effect of dopamine agonists on NMDAR-dependent long-term potentiation (LTP) and found a region-selective reduction of the AMPA component in stratum oriens of the rat hippocampus CA1 (Herwerth M et al. 2012 Cereb Cortex). This layer-specific effect was caused by D4 receptor activation, which augmented the inactivation of synaptic NMDAR-mediated currents during LTP induction through a Ca^{2+}-dependent G-protein-independent mechanism. Experiments with ko mice showed that the effect occurs through NMDARs containing NR2B subunits. We have previously demonstrated a functional predominance of NR2B, a feature characteristic of early developmental stages, at CA3-to-CA1 synapses in a rat model of ADHD (Jensen V et al. 2009 Neuroscience). In addition, we find the reservoir of D5 receptors in CA1 pyramidal cells to be deficient in the ADHD rat (Medin T, Jensen V et al. unpublished). The dopaminergic modulation of AMPA receptors may be either enhancing or inhibiting, depending on conditions such as the neuronal activity level (Yuen EY, Yan Z 2011 J Biol Chem). As DA function and NMDAR function are linked in the hippocampus, the severity of symptoms of mental disorders may depend on dysfunctions of the dopaminergic and glutamatergic neurotransmitter pathways, which could be exploited therapeutically.

http://www.med.uio.no/imb/english/people/aca/oivind/index.html