

## シグナル伝達医学講演会

# 強迫的な報酬探索行動を司る皮質線条体路の神経可塑性

Cortico-striatal synaptic plasticity underlying compulsive reward seeking

## 原田 征弥 先生

University of Geneva MD/PhD student



日時： 2020年10月27日（火）午後5時～午後6時半

場所： Zoom (Meeting ID 885 2243 8759 Pass 6buuYU)

Drug seeking despite negative consequences is a one of defining symptoms of addiction. Increase dopamine levels in the mesolimbic system may constitute the initial trigger. Optogenetic self-stimulation of VTA DA neurons (oDASS) has thus been proposed as a model of addiction. Indeed, lever pressing to turn on a laser aimed at ChR2 expressing DA neurons is strongly reinforcing. Clinical observations indicate that drug-seeking even with the risk of harmful consequences occurs only in a fraction of users after prolonged drug consumption. Here, mice carried out a seek-take chain in order to selectively study compulsive seeking behaviour. Once reward seeking was fully established, a probabilistic punishment of the seeking lever led to the emergence of two classes of mice; those that persevered and those that renounced oDASS. Ex vivo characterization of three distinct cortico-striatal streams demonstrated a selective potentiation of excitatory synapses of the orbito-frontal cortex (OFC) to dorsal striatum projection in persevering mice. Photometry experiments revealed that a specific subregion of the dorsal striatum (DS) which receives input from the OFC was hyperactive at the end of seeking behaviour in persevering mice. Furthermore, chemogenetic inhibition of the OFC attenuated the compulsivity and flattened the calcium signal in the DS. Finally, to establish the causal link between the hyper activity in the DS and compulsivity, we dampened the DS activity in a time locked manner. It faded the compulsive reward seeking. In summary, our data indicate that synaptic potentiation at OFC-DS pathway sparks hyper activity in the DS in a specific timing which promotes compulsive reward seeking.

### References

O'Connor EC, **Harada M** et al. Stochastic synaptic plasticity underlying compulsion in a model of addiction. *Neuron* (2015)

Deguchi Y, **Harada M** et al. Cortico-striatal synaptic plasticity underlying compulsive reward seeking. *Cell Reports* (2016)

Pascoli V, **Harada M** et al. Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. *Nature* (2018)

主催：シグナル伝達医学研究展開センター（担当：薬理学分野 078-382-5443）