Module:
Biological Foundations of Mental Health

Week 5
Reward, emotion & action

Topic 2
The structure and function of the Basal Ganglia – part 3 of 5

Dr Frank Hirth
Department of Basic and Clinical Neuroscience

Lecture transcript

Slide 2

Now let's look at a very important modulator of the direct and indirect pathway. And this is dopamine. There are other neural modulators, but we are looking at dopamine now because we know most about it and it's one of the most important neural modulators of basal ganglia activity. The dopamine input arises from another part of the substantia nigra, which is called pars compacta, here in this scheme, abbreviated SNC.

As you can see, we have two connections to the striatum. One connecting to the direct pathway, and one connecting to the indirect pathway.

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It is now important to understand the modulatory activity of dopamine by looking at the dopamine receptors that are expressed and active in the direct versus indirect pathway. As you can see in the scheme, the direct pathway expresses D1 receptors, whereas the indirect pathway expresses D2 receptors. And it is because of the different nature of these D1 and D2 receptors that we have different responses to dopamine signalling.

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Now the D2 signalling suppresses the firing in indirect pathway neurons...

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...which is outlined here.

Now let's look at D2 signalling. D2 signalling suppresses firing in the indirect pathway neurons. How is that achieved? Because of this peculiar activity of the D2 receptors. It results in the reduction of inward, depolarising currents, and the increase of hyperpolarising currents, and therefore diminishes the spiking in the indirect pathway.

As a consequence, you have less activity of the GPI. That means dopamine signalling via D2 receptors diminishes indirect pathway activity, and as a result, dopamine acting on D2 reduces the indirect pathway inhibitory effect, and thus facilitates movement.

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Now let's look at D1 signalling pathway when it receives dopaminergic input. In contrast to the D2 dopamine receptor, the D1 receptor acts differently. Dopamine input enhances calcium currents and reduces potassium currents. The effect of this is to increase the spiking of the neurons in the striatum. That is, it facilitates striatal signalling on the output nuclei.

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That, of course, causes an inhibition of the output nuclei. And as shown here, dopamine acts on D1, and thereby facilitates the movement in the presence of strong cortical drive.

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So let's summarise the dopamine effects on the direct and indirect pathway. Keep in mind that this is due to the fact that D1 and D2 receptors respond differently to dopamine. That is, the very same neurotransmitter can have opposite effects. Dopamine signalling through D2 receptors in the indirect pathway suppresses striatal inhibitory activity. Dopamine signalling through D1 receptors in the direct pathway facilitates strong phasic inputs, it suppresses weak inputs. Thus, dopamine modulates impact of direct and indirect pathway activity via different differential action of D1 and D2 receptors.

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This is once more illustrated in this slide here. Remember, the overall activity of the indirect pathway suppresses action. The overall activity of the direct pathway facilitates action. Now dopamine modulates their impact. And at the bottom, you can see very recent experiments, the results of very recent experiments, which illustrate that. In the lab of Anatol Kreitzer, they used optogenetics to activate either the D1, which is the direct pathway, or the D2, the indirect pathway. Now you will learn later about optogenetics, but for now, let's summarise what optogenetic does.

You can express a factor in a neuron that allows you to activate that neuron by a pulse of light. And you can see, on the left bottom side, there are two sources of light that shine onto the striatum, STR. Now in the middle, the circular line shows when the activity of D1, the direct pathway, has been modulated. Wherever you see a grey dot, the light was off. Wherever you see a red dot and connections between the red dot, the light was on. That means the light was switched on and hence the neurons of the direct pathway were activated. You can clearly see whenever the light was on, this mouse was running around in the arena, which clearly emphasises the role of the direct pathway in facilitating movement and thus action.

Now on the right-hand side, you see a similar experimental set-up. But now, light activates the D2 receptor, which, as you know, is expressed in the indirect pathway. In grey, the light is off. In green, light is switched on, and thus, activates neurons of the indirect pathway. You can clearly see that when you switch the light on and thereby activate the neurons of the indirect pathway, you immediately stop movement and thus inhibit action. This study, which was published in 2010 by Anatol Kreitzer's lab, is a very elegant demonstration of the major output of the direct and indirect pathway.

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And this work is beautifully illustrated in this video, which you can actually download yourself and have a look at. It illustrates what happens when you activate, via optogenetic activation, the indirect pathway. It suppresses action and thus inhibits motor behaviour. Now as you can see from this study, when you artificially activate the indirect pathway, you suppress action and thus inhibit motor behaviour. You can well imagine that any problems with the activity of the direct pathway or the indirect pathway can be related with disease, and this is indeed the case.