

- Second Messenger -

The Prostate Apoptosis Response 4 (PAR-4)

A new role for an old protein in depression

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Issue A new role for an old protein has been discovered, and it is critically important to the functioning of dopamine D2 receptors.

Actions Learn how this protein affects the function of D2 receptors at the molecular level and how it relates to depression.

Benefits Understanding the function of PAR-4 at D2 receptors provides a view into the future of research on the pathophysiology and treatment of depression.

Although dopamine has received much attention in the pathophysiology of psychosis and addictive disorders, it is a somewhat neglected neurotransmitter when it comes to affective disorders. The focus, of course, has been on serotonin and norepinephrine for affective disorders. However, a recent paper in the journal *Cell* brings dopamine into the spotlight with respect to the pathophysiology of depression.

Dopamine receptors are G-Protein-coupled receptors

By way of background, neurotransmitters, the first messengers of neurons, effect neurotransmission by binding to specific proteins on the surface of cells called receptors. There are two broad classes of receptors for neurotransmitters: ionotropic and metabotropic. Ionotropic receptors are gated ion channels (e.g., the nicotinic acetylcholine receptor). When the receptor is activated, the channel opens, allowing a certain type of ion to enter the cell. This process is fast (of the order of milliseconds). Metabotropic receptors require the production within the cell of a molecule, the "second messenger," to propagate the signal of the "first messenger," the neurotransmitter. This process is relatively slow (of the order of seconds). The receptors for dopamine fall into the latter class, the vast majority of which are the so-called 7-transmembrane spanning (7-TMS), G-protein-coupled receptors. These receptors, which are around 350 to 500 amino acids in length, span the membrane 7 times, resulting in the formation of 3 outer loops and 3 inner loops. The third inner loop is generally where the G-proteins (GTP-binding proteins) couple to stimulate or inhibit second messenger synthesis. However, as we shall see, there are more elements in addition to G-proteins involved with signal transduction at these receptors.

Based on structural homology and second messengers associated with them, the dopamine receptors are divided into two broad classes: D1-like and D2-like. The D1-like receptors are D1 and D5, while the D2-like are D2 (which comes in a short and long form), D3, and D4. D1-like receptors are mainly coupled to the stimulatory form of a G-protein, called G_s, that causes the elevation of intracellular levels of the classical second messenger cyclic AMP (cAMP) by activation of the enzyme adenylate cyclase. This is the most proximal event that in turn causes the activation of a protein kinase, called Protein Kinase A (PKA). On the other hand, the D2-like receptors do the opposite with respect to intracellular levels of cAMP, by coupling to the inhibitory G-protein, called G_i.

The key subtype is the dopamine D2 receptor

Of all the dopamine receptors, it is the D2 receptor that appears to play an important role in psychosis, motor function, and reward mechanisms. Antipsychotic drugs block these receptors (among others). Many years ago, researchers established that blockade of D2 receptors by antipsychotic drugs correlates with clinical potency in treating schizophrenia. This blockade, at least for the older generation drugs, also relates to their extrapyramidal side effects. Finally, these receptors also play an important role in dopamine's rewarding effects, although other dopamine receptor subtypes are likely involved too. The prominent feature of anhedonia in many depressed patients is most likely due to low dopamine at its receptors in the brain, particularly in the nucleus accumbens. Other possible clinical features of low DA in depression are lack of interest, difficulty concentrating, lack of motivation, and fatigue.

Without PAR-4 dopamine D2 receptors don't function well

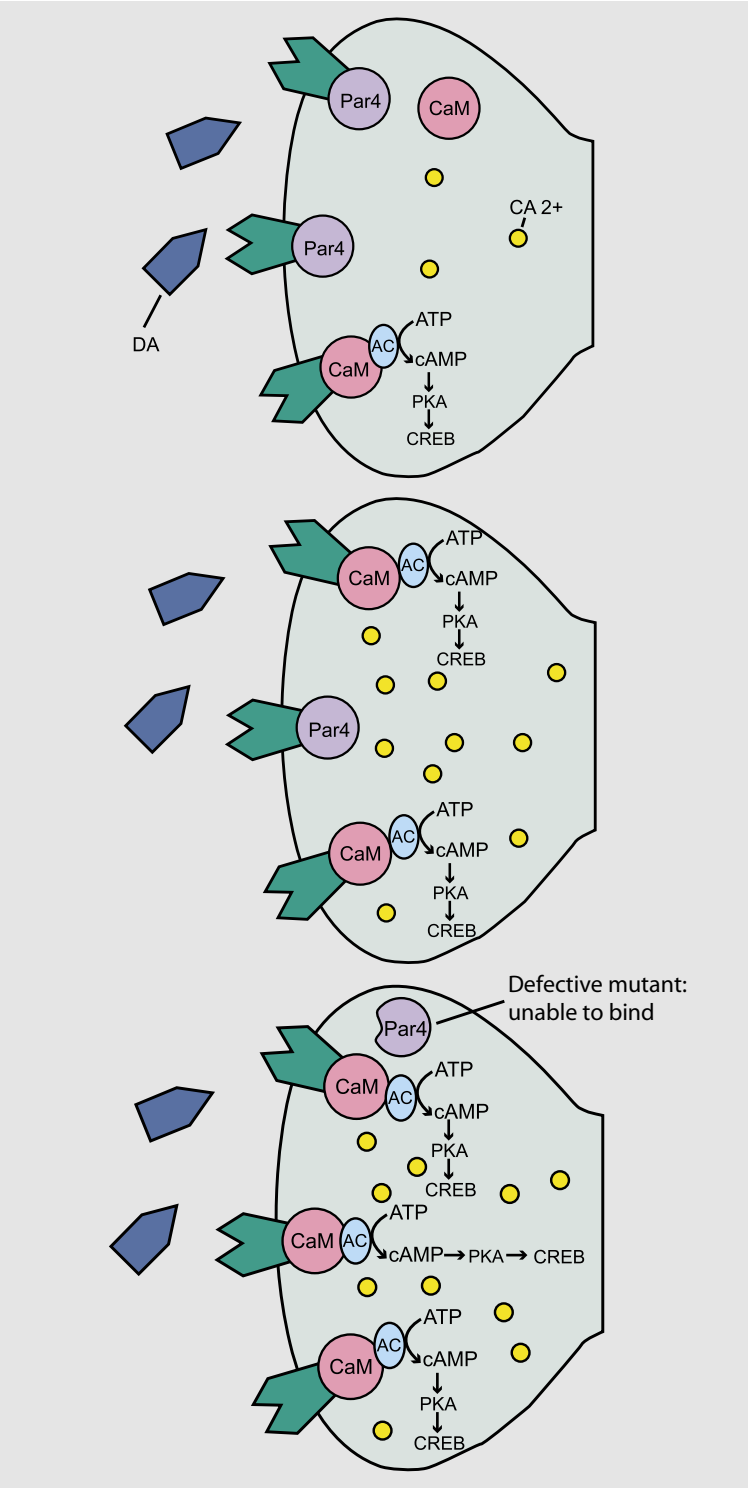
So, what does the prostate have to do with it? As with many molecules that are discovered in the body, their given names usually reflect where they are first found and what they do there. However, it is also the case that the initial site of discovery of the molecule is just its first location and its initial function is just its first. Such is the case for the Prostate Apoptosis Response 4 protein or PAR-4, for short.[1] It was initially found in prostate cancer cells and was shown to be involved with apoptosis or programmed cell death. However, subsequent research has shown that it is present in other cell types, from males and females, and in particular, in neuronal cells, where it is found prominently in synaptic regions.

Previous work on PAR-4 in brain shows that, as is the case in prostate, it is involved with processes of programmed cell death. However, Park et al.[2] have just reported that this protein binds to the third inner loop of the D2 receptor and that this direct interaction modulates D2 receptor signal transduction. PAR-4 appeared to bind specifically to the D2 receptor, as it had negligible binding to the D3 receptor. In addition, PAR-4 immunoreactivity was found in areas rich in DA inputs (e.g., striatum), where it co-localized with D2 receptors, mostly in the neuronal soma and processes. Interestingly, calmodulin (CALcium MODULated proteIN), which senses intracellular calcium levels and modulates the function of proteins, competes with PAR-4 for binding to the third inner loop of the D2 receptor in a calcium-dependent manner (figure 1). In experiments with cultured cells expressing the D2 receptor, these researchers showed that a dopamine agonist (quinpirole) causes inhibition of cyclic AMP production mediated by an activator of adenylate cyclase called forskolin. However, when PAR-4 was "silenced," quinpirole was no longer able to inhibit forskolin-mediated cAMP production.

These researchers then created a mutant mouse that lacked the part of the PAR-4 gene that codes for the binding motif necessary for the PAR-4 protein to bind to the third inner loop of the D2 receptor. When they cultured striatal neurons from these mutant mice, they found that there was an up-regulation of DA-mediated cyclic AMP formation.

Most interestingly, however, were the *in vivo* experiments with these mutant mice. In several animal behavioral tests that are used to test compounds for antidepressant activity (e.g., Porsolt's forced swim test and the tail suspension test), these mutant animals behaved as though they were more "depressed" than the control mice.

Figure 1



The bottom line—If we can extrapolate from mice to men, the implications of this research are great. Park et al. have discovered a novel site that could be the target of a new class of antidepressant drugs. For example, a drug that is able to mimic the effects of PAR-4 at the third inner loop of the D2 receptor could be a novel antidepressant drug. This drug might also be useful to treat Parkinson's disease. One could also speculate that faulty functioning of PAR-4 can lead to depression.

References

1. Sells SF, Wood DP, Jr., Joshi-Barve SS, Muthukumar S, Jacob RJ, Crist SA, Humphreys S, Rangnekar VM. Cell Growth Differ 1994;5:457-66.
2. Park SK, Nguyen MD, Fischer A, Luke MP, Affar el B, Dieffenbach PB, Tseng HC, Shi Y, Tsai LH. Cell 2005;122: 275-87.