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Depression and Adenylyl Cyclase: Sorting Out the Signals

Mark M. Rasenick

Departments of Physiology & Biophysics and Psychiatry, University of Illinois College of Medicine; and Jesse Brown VA Medical Center, Chicago, Illinois.

The article in this issue of *Biological Psychiatry* by Chen *et al.* (1) suggests that knockout of adenylyl cyclase 3 (AC3—*Adcy3*) leads to depression. The study knocks out AC3 three ways: globally, targeted to forebrain, or conditionally. In a comprehensive series of behavioral studies, the data from this study reveal a “depressive” phenotype. This thorough and thoughtful study was undertaken, at least in part, pursuant to the suggestion that *ADCY3* polymorphisms track with major depressive disorder (MDD). Consideration of this work, along with other mouse and human data, raises the question: What is our current knowledge of cyclic adenosine monophosphate (cAMP) and adenylyl cyclase in MDD?

A 1500-word commentary is insufficient to answer that question, but it can help to rephrase it. First, cAMP does appear to be attenuated in depression, and this is normalized by antidepressants. cAMP is diminished in peripheral tissue of human subjects with depression, and antidepressant treatment restores cAMP in human peripheral tissue and rodent models. Positron emission tomography studies also suggest that cAMP is diminished globally in the brains of humans with MDD (2). We have suggested that this is due to Gsα being unavailable to adenylyl cyclase in depressive states, and this is resolved following prolonged antidepressant treatment (3).

The situation with adenylyl cyclase and depression is more complex, as summarized in Table 1. Chen *et al.* (1) state that one of the reasons for their concentration on AC3 is that the genome association study cited in their article revealed *ADCY3* as a gene of interest. Although *ADCY3* registered as a major “hit,” *ADCY3* single nucleotide polymorphisms failed to achieve significance either in the MDD2000+ study or in a meta-analysis with two other studies totaling 5763 cases and 6901 controls. Two postmortem human studies that examined adenylyl cyclase (enzyme activity or protein expression) in MDD have suggested a reduction of AC4 (4) and gain of function for AC7 (5). *ADCY7* polymorphisms or AC7 gain of function has also been observed in female humans with MDD, and altered *Adcy7* yields female mice with a depressive phenotype (6). Polymorphisms in *ADCY5* appear to be causal for hereditary dyskinesia and for obesity, but there are no reports for altered mood in the small population examined so far. Polymorphisms of *ADCY3* have also been associated with obesity in two large human population studies [as are *Adcy3* knockouts in adult mice—as observed by Chen *et al.* (1)], but clear evidence for association of a single isoform of adenylyl cyclase with depression in humans remains lacking.

For mood-disorder models in mice, the potential roles of adenylyl cyclase are also complex. In addition to the data described in the study by Chen *et al.* (1), AC1/AC8 double knockouts show a similar depressed phenotype. AC8 knockouts are more “resilient” than wild-type mice in the presence of environmental stressors, and AC5 knockouts showed a similar “antidepressant” phenotype. This suggests a complex interplay between adenylyl cyclase and depression. It would have been interesting to determine whether antidepressant treatment in the AC3 knockout animals reversed some of the observed behaviors.

Chen *et al.* (1) posit that AC3 may play a unique role in depression as a result of modified synaptogenesis. Indeed, hippocampal volume, and for that matter whole brain volume, is significantly smaller in AC3 knockouts, and an earlier study with these animals [cited by Chen *et al.* (1)] showed profound disruption of learning and memory. The authors suggest that the localization of AC3 to primary cilia may be relevant for the lack of dendrite outgrowth and cite a study consistent with this idea.

Certainly, AC3 is highly enriched in primary cilia as well as cilia from olfactory cells (AC3 knockouts are anosmic). These structures, which are normally restricted to one per cell, are nonmotile because they lack the central microtubule pair seen in motile cilia. These structures are rich in G protein–coupled receptors and are often referred to as a cell’s antenna. AC3 knockout shortens primary cilia, and this appears to be related to diminished local cAMP within the cilia. Could diminished cAMP within the primary cilia lead to a global reduction in cAMP throughout the brain?

Although the role of primary cilia in the central nervous system is not understood, defects in primary cilia are implicated in many diseases, including learning and memory. Hippocampal volumes are decreased in humans with ciliopathies, and these subjects also show stunted brain development. Chen *et al.* (1) show that the AC3 knockouts sport markedly pruned dendrites, which suggests that an AC3 knockout would have a marked decrease in the number of synapses and, presumably, a plethora of deficiencies in addition to those related to mood. In addition, primary cilia may organize information flow in G protein–coupled receptor signaling. Certain Gs-coupled receptors (e.g., the 5HT6R serotonin receptor and DRD1 dopamine receptor) that might activate ciliary AC3 show a complex flow of information wherein ciliary and nonciliary receptor localization provides distinct responses to the same agonist (Figure 1) (7).

It is at this juncture that the trail becomes unmarked. If AC3 is restricted to primary cilia, it is inherently extrasynaptic. AC5 and AC6 are also reported to be present in cilia, albeit not with the exclusivity of AC3. cAMP is a negative regulator of the developmental orchestrator sonic hedgehog, and a lack of balance in developmental programs could result in the diminished brain size seen in AC knockouts (1). Under such circumstances, it would be anticipated that a “depressed” phenotype would be one of many deficits seen in these animals. The Storm group has seen deficits in learning and memory of AC3 knockouts [see references in Chen *et al.* (1)]. In addition, the constitutive knockouts were anosmic, presumably as a result of a loss of AC3 in olfactory cilia. The conditional knockouts were not anosmic, suggesting a slow turnover of AC3 in these structures. Furthermore, the AC3

knockouts were obese as adults, and this is consistent with AC3 polymorphisms and adult obesity seen in both Swedish and Chinese populations.

As stated above, deficient cAMP is associated with depression and elevated cAMP with antidepressant action. Although elevating cAMP with phosphodiesterase inhibitors has been postulated as having an antidepressant effect, this does not help to parse the contribution to depression etiology or therapy of the nine discrete AC isoforms. These enzymes, which fall into four groups (AC1, AC3, AC8; AC2, AC4, AC7; AC5, AC6; and AC9), have in common only activation by G α and, albeit less so for AC9, by forskolin. Depending on the isoform, Ca²⁺ can be stimulatory or inhibitory, G $\beta\gamma$ can inhibit or activate, and G α or G α can inhibit or act as a buffer for G $\beta\gamma$. Add to this a panoply of regulation by various kinases, and it is clear that adenylyl cyclases not only produce cAMP but also act as a regulatory switchboard.

In addition to multifarious regulation, some of the AC enzymes show scaffolding properties allowing the juxtaposition of proteins that subserve both signaling and structure (8). G protein-coupled receptors, G proteins, and adenylyl cyclase display remarkable heterogeneity of localization with respect to cytoskeletal components and plasma membrane microdomains (9). This localization appears to be quite relevant to the process of cellular signaling and is influenced by extended treatment with antidepressants (3). In fact, antidepressants, but not antipsychotics or mood-stabilizing drugs, partition gradually into the cholesterol-rich, cytoskeletal-associated regions of the plasma membrane known as lipid rafts (10). This process may be relevant to their latency of clinical efficacy.

One final note concerns the building block of the cilia that house AC3. Primary cilia are composed of microtubules and lack the central microtubules of motile cilia. G α regulates microtubule dynamics and neurite outgrowth, which may also relate to some of the observations in the study by Chen *et al.* (1).

Even though this commentary is brief, an attempt to summarize is made with trepidation. The myriad studies in mice and humans certainly suggest roles for adenylyl cyclase and cAMP in depression and antidepressant response. We may begin to know these roles only as new and more sophisticated investigational tools are developed.

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References

1. Chen X, Luo J, Leng Y, Yang Y, Zweifel LS, Palmiter RD, Storm DR (2016): Ablation of type III adenylyl cyclase in mice causes reduced neuronal activity, altered sleep pattern, and depression-like phenotypes. *Biol Psychiatry* 80:836–848 [PubMed: 26868444]

2. Fujita M, Hines CS, Zoghbi SS, Mallinger AG, Dickstein LP, Liow JS, et al. (2012): Downregulation of brain phosphodiesterase type IV measured with ¹¹C-(R)-rolipram positron emission tomography in major depressive disorder. *Biol Psychiatry* 72:548–554 [PubMed: 22677471]
3. Czysz AH, Schappi JM, Rasenick MM (2015): Lateral diffusion of Gαs in the plasma membrane is decreased after chronic but not acute antidepressant treatment: Role of lipid raft and non-raft membrane microdomains. *Neuropsychopharmacology* 40:766–773 [PubMed: 25249058]
4. Reiaich JS, Li PP, Warsh JJ, Kish SJ, Young LT (1999): Reduced adenylyl cyclase immunolabeling and activity in postmortem temporal cortex of depressed suicide victims. *J Affect Disord* 56:141–151 [PubMed: 10701471]
5. Joeyen-Waldorf J, Nikolova YS, Edgar N, Walsh C, Kota R, Lewis DA, et al. (2012): Adenylate cyclase 7 is implicated in the biology of depression and modulation of affective neural circuitry. *Biol Psychiatry* 71:627–632 [PubMed: 22264442]
6. Hines LM, Hoffman PL, Bhave S, Saba L, Kaiser A, Snell L, et al. (2006): A sex-specific role of type VII adenylyl cyclase in depression. *J Neurosci* 26:12609–12619 [PubMed: 17135423]
7. Marley A, Choy RW, von Zastrow M (2013): GPR88 reveals a discrete function of primary cilia as selective insulators of GPCR cross-talk. *PLoS One* 8:e7085
8. Dessauer C (2009): Adenylyl cyclase-A kinase anchoring protein complexes: The next dimension in cAMP signaling. *Mol Pharmacol* 76: 935–941 [PubMed: 19684092]
9. Allen JA, Halverson-Tamboli RA, Rasenick MM (2007): Lipid raft microdomains and neurotransmitter signalling. *Nat Rev Neurosci* 8:128–140 [PubMed: 17195035]
10. Erb SJ, Schappi JM, Rasenick MM (2016): Antidepressants accumulate in lipid rafts independent of monoamine transporters to modulate redistribution of the G protein, Gαs. *J Biol Chem* 291:19725–19733 [PubMed: 27432886]

Figure 1.

Adenylyl cyclase, primary cilia, depression, and antidepressants. A neuron is depicted, and both primary cilia and dendrites are shaded and expanded. Adenylyl cyclase 3 (AC3) is shown in the cilium, wherein the G protein, G_{α} , is activated by 5HT6R (the only cilia-localized 5-hydroxytryptamine receptor) and subsequently activates AC3 to produce cyclic adenosine monophosphate (cAMP). Primary cilia are nonmotile, but they do change in length, presumably as a result of the elongation and disassembly of their microtubules, a process influenced by G_{α} . Although a neuron is depicted here, most cells, including glia, contain primary cilia. In the dendrite, a typical postsynaptic response to an agonist activating a Gs-coupled G protein-coupled receptor (GPCR) is shown. Adenylyl cyclase activity is damped in depression, at least in part as a result of G_{α} being ensconced in lipid rafts (3), where it is less able to activate adenylyl cyclase (9). Antidepressant treatment gradually translocates Gs— from lipid rafts, where it enjoys a more facile relationship with forms of adenylyl cyclase other than AC3. Although this scheme is depicted in a dendrite, glia can be similarly affected. The relationship between signaling in primary cilia and the rest of the cell may be most germane to the neurobiology of depression and to depression therapeutics. ATP, adenosine triphosphate; PPi, inorganic pyrophosphate. (Illustration by Molly Huttner. © 2016.)

Table 1.

Roles for Adenylyl Cyclase Isoforms in Human Depression and Mouse Models

Isoform	Manipulation or Measurement	Observation	Species
AC3	Knockout	Depressant	Mouse Human polymorphism
AC5	Knockout	Resilience	Mouse
AC8	Knockout	Resilience	Mouse
AC1, AC8	Knockout	Depressant	Mouse
AC7	Upregulated	Depression	Human postmortem Mouse (females)
			Human polymorphism (females)
AC4	Diminished	Depression	Human postmortem

Table indicates the isoform of adenylyl cyclase knocked out in mice or examined in humans (expression by messenger RNA or protein detection and polymorphisms by gene sequencing).