

Appendix A14.19

Calcium Dysregulation in Bipolar Disorder: Potential Role of Mitochondrial-ER calcium Sequestration Machinery

As discussed above, calcium is a very common signaling element, and plays a critical role in the CNS by regulating the activity of diverse enzymes and facilitating neurotransmitter release (Szabo et al., 2003). Importantly, excessively high levels of calcium are also a critical mediator of cell death cascades within neurons, necessitating diverse homeostatic mechanisms to regulate intracellular calcium levels very precisely. Acting via intracellular proteins such as calmodulin and enzymes such as protein kinase C (PKC), calcium ions influence synthesis and release of neurotransmitters (Parnas and Segel, 1989), receptor signalling (Rasmussen, 1986), the action potential (Packer and Frishman, 1984, 1982), and neuronal periodicity (Matthews, 1986).

Calcium is generally mobilized in one of two ways in the cells; either by mobilization from intracellular stores or by selective diffusion across plasma membrane ion channels, and certain receptors (e.g. NMDA). Indeed the calcium flux through NMDA receptors has been implicated in various forms of excitotoxicity and, as we discuss later, may play a central role in the impairments of plasticity observed in BPD. Ca^{2+} released intracellularly is regulated both positively and negatively, resulting in the generation of dynamic Ca^{2+} waves. Once intracellular Ca^{2+} levels are increased, this triggers/activates a number of proteins (e.g. AC type I, CamKinases, PKC, calpain (protease), calcineurin (a protein phosphatase)). In neurons, Ca-dependent processes represent an intrinsic, nonsynaptic feedback system that provides the competence for adaptation to different functional tasks (Szabo et al., 2003). Regulation of intracellular Ca^{2+} could be of particular relevance to the study of psychiatric disorders because the same elevation of $[Ca^{2+}]_i$ may facilitate or inhibit a given function, depending on the target enzyme, the phase of the cell cycle, the intracellular effector protein, and the Ca^{2+} -dependent process. In addition, higher or more sustained increases of $[Ca^{2+}]_i$ may inhibit the same function that smaller elevations facilitate (Torok, 1989) that elevated $[Ca^{2+}]_i$ can produce excessive activation of some systems and inhibition of others.

Interestingly, impaired regulation of Ca^{2+} cascades has been found as the most reproducible biological measure abnormalities described in bipolar disorder research. For this reason, mechanisms involved in Ca^{2+} regulation have been postulated to underlie aspects of the pathophysiology of bipolar disorder. To date, fifteen studies have consistently revealed elevations in basal intracellular Ca^{2+} levels in platelets, lymphocytes, or neutrophils of patients with BPD. By contrast, there are only 4 negative studies. Although this may represent (in part) the phenomenon of publication bias, the elevation in basal Ca^{2+} represents one of the most replicated finding in BPD research. Higher platelet intracellular Ca^{2+} elevations have also been also found

in response to stimulation with thrombin, platelet activator factor (PAF), serotonin, dopamine and thapsigargin. In lymphocytes, the same higher elevations were observed when the cells were stimulated with phytohemagglutinin, concavalin A, thrombin and, as in platelets, with thapsigargin and serotonin. There is, however, considerable evidence that a variety of circulating factors may influence the activity of blood cells and elements, and BPD patients are known to have numerous neurohormonal abnormalities (e.g. catecholamines and cortisol levels); furthermore, many of these studies did not employ extensive a prolonged medication washout period, raising the possibility that the elevations in Ca^{2+} in circulating cells are simply secondary manifestations. In an elegant series of studies, Warsh and colleagues have utilized Epstein-Barr-virus-immortalized B lymphoblasts, having grown these cells in culture (and away from the patients' confounding circulating environment) for weeks. They found that even in the immortalized lymphoblasts, BPD patients showed elevated basal Ca^{2+} concentration compared to healthy subjects or patients with other psychiatric disorders. In an extension of these studies, they investigated the components of the storage-operated Ca^{2+} entry (SOCE), and found a reduction in the protein expression of the TRPC7 gene (whose gene product is implicated in SOCE functioning), in BLCLs from a subgroup of BPD I patients (Yoon et al., 2001).

Most recently, Kato and associates (2003) investigated cytosolic and mitochondrial Ca^{2+} responses to platelet-activating factor, carbonyl cyanide m-chlorophenylhydrazone (CCCP), a mitochondrial uncoupler that abolishes mitochondrial Ca^{2+} uptake; and thapsigargin in lymphoblastoid cells from BPD subjects. They found that the thapsigargin-induced cytosolic Ca^{2+} response was significantly higher in patients with BPD, effects which were not seen when the effects of Ca^{2+} influx from outside the plasma membrane was eliminated using Ca^{2+} -free measurement buffer. By contrast, response to thapsigargin tended to be higher in patients with bipolar disorder when at the Ca^{2+} -free conditions. Furthermore, CCCP-induced Ca^{2+} responses differed significantly between mitochondrial DNA 5178/10398 haplotypes that had been previously reported to be associated with bipolar disorder (Kato et al., 2003). Together, these results clearly suggest that the mitochondrial-ER calcium regulation system contributes to the Ca^{2+} abnormalities seen in BPD.

Overall, these findings are of great importance in view of the growing body of evidence demonstrating the potential toxic effects of elevated intracellular Ca^{2+} in neuronal and glial cerebral cells. In fact, recent studies have demonstrated that both the subcellular compartmentalization of Ca^{2+} and the source of the Ca^{2+} may be a greater determinant of neurotoxicity than the absolute intracellular Ca^{2+} levels per se (Sapolsky, 2000b), and there are major relationships between Ca^{2+} released from IP3-sensitive endoplasmic reticulum (ER) stores, and mitochondrial Ca^{2+} uptake (Mattson et al., 2000). We now turn to the evidence demonstrating that BPD is accompanied by impairments of cellular plasticity and resilience.

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