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REVIEW

The Role of Calcium in the Etiology of the Affective Disorders

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ABSTRACT—Calcium abnormalities are some of the more consistent findings in platelets of affective disorder patients. While medication status does not correlate with this finding, antidepressants do modulate intracellular calcium. This, in combination with reports that calcium channel inhibitors may have antidepressant potential, suggests that calcium may play an important role in this disorder. This paper reviews the specificity of calcium abnormalities for the affective disorders and also discusses possible mechanisms of action.

Keywords: Intracellular signaling, Calcium, Platelet, Serotonin, Affective disorder

1. Introduction

The serotonin neurotransmitter system has long been associated with affective disorders, both in terms of etiology and therapeutics. Specific serotonin reuptake inhibitors (SSRIs) are effective therapeutic agents, but require chronic rather than acute administration. In the search for more potent and faster-acting therapeutic agents, different classes of compounds have been tried with varying success. One of these classes of compounds involves calcium channel blockers. The relationship of calcium-modifying drugs to the affective disorders has received increasing attention due to the relatively recent findings of abnormal serotonin-2A receptor-mediated IP_3 (inositol 1,4,5-trisphosphate) and intracellular calcium pathways in the affective disorders. In this review, we will discuss these new developments and focus on the relationship between antidepressants, serotonin and calcium. Research in this area has been greatly facilitated by advances in intracellular calcium signaling techniques (1), which now allow questions about receptor-mediated intracellular calcium changes to be addressed. While most of this review will examine the evidence for calcium abnormalities in the affective disorders, we will also discuss modulation of calcium mobilization by antidepressant drugs and the role calcium changes may play in the affective disorders.

2. Background literature on calcium pathways

In order to understand the nature of the calcium abnormalities that may play a role in the affective disorders, it is helpful to be familiar with the biochemistry of the pathways involved. Activation of the serotonin-2A receptor, which is coupled to the phospholipase C pathway, results in cleavage of PIP_2 (phosphatidylinositol 4,5-bisphosphate) into IP_3 and DAG (diacylglycerol). IP_3 then binds to its intracellular IP_3 receptor, which causes an influx of calcium from intracellular stores in the endoplasmic reticulum (2). The emptying of these intracellular calcium stores is then thought to signal calcium influx from the external medium through channels in the plasma membrane (3). Thus the rise in intracellular calcium after receptor stimulation consists of two components, one from calcium stores inside the cell and a second component of calcium influx from outside the cell.

It should be noted that the resting (baseline) concentration of Ca^{2+} in the cytoplasm is relatively low at 10^{-7} M to 10^{-8} M, while $[Ca^{2+}]$ is 10^{-3} M outside the cells (4). Thus, opening plasma membrane calcium channels has the potential to contribute to a relatively large proportion of the intracellular calcium signal. The relative contribution of these two components differs according to the type of receptor activated. Additionally, both pathways are modulated by different classes of pharmaceutical and potential therapeutic agents. These are discussed below.

Store-regulated Ca^{2+} entry appears to be activated by protein tyrosine phosphorylation (3, 5). Part of the evidence for this is the observation that Ca^{2+}-store depletion evoked by thapsigargin (Ca^{2+}-ATPase inhibitor) leads to a rise in tyrosine phosphorylation, but this has not been confirmed by all studies (6). Of interest in this regard is the observation that Ca^{2+}-ATPase is regulated by tyrosine phosphorylation as well as by cAMP-dependent phosphorylation (7). Babnigg et al. (8) have reported that calcium entry, following store depletion, is dramatically lower in fibroblasts which lack the nonreceptor tyrosine kinase c-src. The level of capacitative calcium entry in Src^- cells was restored to nearly normal levels by transfecting Src^- cells with c-src. These data suggest that c-src may play a major role in regulation of store-operated calcium channels. Refilling of the calcium stores has been proposed to result in the activation of a tyrosine phosphatase, and thus termination of Ca^{2+} influx (3).

A number of biochemical pathways may regulate calcium release from intracellular stores. IP_3 receptors which are responsible for calcium release from intracellular sites, appear to be regulated by tyrosine phosphorylation (9, 10), a pathway already described above. Cyclic GMP, nitric oxide and cytochrome P-450 inhibition have additionally been reported to affect intracellular calcium mobilization or influx (11–14).

Thus abnormalities in a number of biochemical pathways may result in altered receptor-mediated rises in intracellular free calcium. Since these pathways are expected to be widely involved in calcium mobilization across cell types, an abnormality in, for example, src-mediated tyrosine phosphorylation would be expected to affect more than one class of receptor-mediated calcium mobilization. In this case, multiple receptor-mediated calcium abnormalities should be seen, which would be expected to correlate with the known src distribution pattern. Therefore, when evaluating calcium abnormalities in the affective disorders, it is important to test the receptor and cell specificities of the abnormalities. This has the potential to give valuable information on the underlying aberrant mechanisms.

With regard to receptor-specific calcium abnormalities, receptor polymorphisms may contribute to altered calcium responses. In the case of the serotonin-2A receptor, ^{452}Tyr, a naturally occurring amino acid substitution, is associated with a smaller peak amplitude in Ca^{2+} mobilization after stimulation with serotonin, as well as a longer peak latency and longer half-time compared to ^{452}His individuals (15).

Additionally, there is evidence that receptors may interact synergistically to enhance intracellular calcium mobilization. Kagaya et al. (16) have reported heterologous supersensitization between serotonin-2 and alpha-2 adrenergic receptor-mediated intracellular calcium mobilization in human platelets. The data of Roevens et al. (17) have supported these findings. The synergistic action seems to result from changes in intracellular signaling components rather than from an effect on affinity of the receptors for agonist. This may be relevant for the changes seen in the affective disorders since, as discussed below, there is often more than one type of enhanced receptor-stimulated calcium response in these patients. Receptor synergism is one area that requires careful examination.

The complete sequence of steps involved in termination and desensitization of the calcium signal inside the cell are not completely known, but most likely involve a number of components. Abnormalities in these pathways may be reflected in changes in peak height or shape of the calcium mobilization curve.

Termination of signal involves calcium pumps that are responsible for removing intracellular free calcium during recovery from stimulation (18). Differences in desensitization may affect peak height and shape. According to Kagaya et al. (19), desensitization of serotonin-2 receptor-mediated calcium mobilization may involve protein kinase C-mediated feedback. Inhibition of protein kinase C can acutely enhance the plateau phase of the serotonin-mediated calcium response, as well as the peak response level. Serotonin itself may desensitize serotonin-2 receptor-mediated calcium mobilization. It is possible that this is achieved via the protein kinase C mechanism described above, since serotonin-2 receptor stimulation by serotonin would activate protein kinase C. However, Kagaya et al. (20) suggested that the mechanisms of serotonin- and phorbol ester-induced desensitization of serotonin-2 receptor-mediated $[Ca^{2+}]_i$ mobilization may be different, since H-7 (protein kinase C inhibitor) only slightly affected serotonin-induced desensitization. The desensitization calcium curve is also different from the curve for the ^{452}His/^{452}Tyr variant of the serotonin-2A receptor, which has a blunted peak amplitude (characteristic of desensitization) but an enhanced half-time when compared to the ^{452}His/^{452}His variant (more frequent genotype) (15). Ozaki et al. (15) showed that serotonin-induced desensitization did not change the

half-time for $[Ca^{2+}]_i$ mobilization, irrespective of whether the genotype was ^{452}His/^{452}His or ^{452}His/^{452}Tyr. They also showed that phorbol 12,13-dibutyrate decreased the half time for $[Ca^{2+}]_i$ mobilization in the ^{452}His/^{452}Tyr but not ^{452}His/^{452}His variant. Kagaya et al. (20) have suggested that desensitization of serotonin-2 receptor-stimulated calcium response involves a calmodulin pathway since W-7, a calmodulin antagonist, inhibited serotonin-induced desensitization of the calcium response. It should be noted that W-7, in addition to being a calmodulin antagonist, is also a competitive inhibitor of the serotonin transporter (21). Inhibition of serotonin uptake would be expected to enhance release of cellular serotonin, which would appear to inhibit the desensitization of serotonin-stimulated calcium mobilization. In the Kagaya et al. (20) study on glioma cells, experimental controls showed that serotonin uptake inhibition probably did not play a role. However, in the case of platelets that are known to store large quantities of serotonin, inhibitory effects of calmodulin antagonists on serotonin uptake may cause misinterpretation of desensitization data.

3. Evidence for calcium abnormalities in the affective disorders

Clinical evidence for aberrant calcium mobilization in patients with affective disorder can be placed into two groups. The first is the study of calcium mobilization in platelets, generally via the serotonin-2A or thrombin receptors. The second group of studies, which have been less numerous to date, involves other peripheral blood cells such as lymphocytes and neutrophils. Clinical studies on brain have not been available, simply because of the requirement for fresh, viable cell preparations in calcium mobilization studies, which makes post-mortem samples not suitable.

As shown in Table 1, the majority of studies found an enhanced serotonin-mediated intracellular calcium response in blood cells of patients with bipolar or depressed affective disorder. Only 1 study out of 10 observed a normal platelet calcium response to serotonin (33). Four studies out of 7 found a normal platelet calcium response to thrombin, the other 3 showing elevated thrombin signaling (25, 28, 33, 34). Only one study found a reduced lymphocyte Ca^{2+} response (to phytohemagglutin), but this was the only study for phytohemagglutin (32). Taken together, these findings for bipolar or depressed patients are remarkably consistent given the general variability inherent in clinical psychiatric studies. Unipolar patients, by contrast, appear to be different from bipolar patients, since they have normal platelet calcium mobilization profiles in studies that grouped them separately from bipolar and manic patients (22, 23, 33).

A very important point, for most of these studies, peak amplitude has been the only measure reported. By contrast, Okamoto et al. (31) has dissected the calcium response curve to show that untreated bipolar disorder manic patients not only had an enhanced serotonin stimulated calcium peak amplitude, but also an enhanced plateau phase and increased half time. This is similar to inhibition of protein kinase C, according to the work of Kagaya et al. (19), but different from ^{452}His/^{452}Tyr and ^{452}His/^{452}His serotonin-2A receptor variants, where peak amplitude and half-time do not co-vary (15). This dissection may give some insight into possible mechanisms since the shape of the calcium curve is dependent on different pathways. Therefore, it is recommended for future studies that peak height, slope and duration of the declining phase of the curve be measured. Calcium influx and desensitization mechanisms have different contributions to the shape of the curve as outlined previously.

It should be also mentioned that technical considerations are important when measuring receptor-induced calcium mobilization in human platelets. Kusumi and coworkers (40) have shown that serotonin-stimulated $[Ca^{2+}]_i$ declines with time after blood drawing, indicating the importance of measuring calcium as soon as possible after the blood sample is taken. However, the time of sampling, gender, recent meal or exercise did not significantly affect this measurement.

To summarize, enhanced platelet calcium response to serotonin has been observed in depression (bipolar, bipolar I, major, melancholic) and mania, which would suggest that this biochemical measure is not state-dependent. A serotonin-2A receptor-specific abnormality can be eliminated from consideration because enhanced neutrophil response to chemotactic peptide (formyl-methionyl-leucylphenylalanine) and enhanced platelet thrombin response are also observed in some studies. Since the same abnormality is seen in both medicated and unmedicated patients, it is unlikely to be a response to the medication status of the individuals studied. Of interest is the observation that serotonin but not norepinephrine-stimulated calcium mobilization is abnormal in platelets of depressed individuals (27). Given the observation that there is supposed to be synergism between these two calcium responses in platelets (16), one may be able to use this finding to dissect out the nature of the biochemical abnormality. For example, if synergism was present in control platelets but not platelets from affective disorder patients, then second messenger mechanisms may be responsible and should be subjects for further examination.

Five out of seventeen investigations have suggested that baseline intracellular calcium levels may be elevated in

Table 1. Evidence for disturbed intracellular calcium ion homeostasis in affective disorders and comparison groups

Disorder	Tissue	Results	Reference
bipolar, unmedicated	platelet	Enhanced thrombin and platelet-activating factor stimulated $[Ca^{2+}]_i$; elevated baseline $[Ca^{2+}]_i$ (mania).	22
bipolar, unmedicated	platelet	Enhanced $[Ca^{2+}]_i$ baseline and after thrombin.	23
depression, unmedicated	platelet	Enhanced 5-HT-stimulated PI hydrolysis.	24
depression, unmedicated	platelet	Enhanced 5-HT-stimulated $[Ca^{2+}]_i$ but normal thrombin-stimulated $[Ca^{2+}]_i$; normal baseline.	25
bipolar, unmedicated	platelet	Enhanced thrombin-stimulated $[Ca^{2+}]_i$; normal baseline.	26
depression, unmedicated	platelet	Enhanced 5-HT-stimulated $[Ca^{2+}]_i$ but normal norepinephrine-stimulated $[Ca^{2+}]_i$; normal baseline.	27
depression, on medication	platelet	Enhanced 5-HT-stimulated $[Ca^{2+}]_i$ but normal thrombin; normal baseline.	28
bipolar, melancholic unmedicated	platelet	Enhanced 5-HT-stimulated $[Ca^{2+}]_i$; normal baseline.	29
mania, bipolar depression	platelet, lymphocyte	Enhanced $[Ca^{2+}]_i$.	30
mania	platelet	Enhanced 5-HT-stimulated $[Ca^{2+}]_i$.	31
depression	platelet, lymphocyte	Enhanced platelet 5-HT-stimulated $[Ca^{2+}]_i$; reduced lymphocyte $[Ca^{2+}]_i$ to phytohemagglutin.	32
unipolar, bipolar	platelet	Normal response to serotonin, thrombin, platelet activating factor; elevated serotonin-stimulated $[Ca^{2+}]_i$ in lithium treated group; normal baseline.	33
bipolar manic, schizophrenia, alcoholic withdrawn, on medication	platelet	Normal resting and thrombin-stimulated $[Ca^{2+}]_i$ in bipolar manic on haloperidol, and drug free schizophrenics; elevated thrombin response in alcoholic withdrawn.	34
bipolar manic, depression	platelet	Enhanced 5-HT-stimulated $[Ca^{2+}]_i$.	35
depression	neutrophil	Enhanced $[Ca^{2+}]_i$ to chemotactic peptide (formyl-methionyl-leucylphenylalanine).	36
bipolar, major depression	platelet	Enhanced 5-HT-stimulated $[Ca^{2+}]_i$.	37
depression, schizophrenia, substance abuse, on medication	platelet	Enhanced 5-HT-stimulated and baseline $[Ca^{2+}]_i$; in depression only.	38
bipolar I	B lymphoblast	Enhanced basal $[Ca^{2+}]_i$.	39

5-HT: serotonin, PI: phosphatidylinositol.

platelets or lymphoblasts, but this is not a consistent finding. Taken together, these results suggest a calcium abnormality that is neither receptor- nor cell-specific. Again, this would suggest that a component in the calcium pathway other than the receptor itself may be abnormal. Any theory development should also explain why some but not all receptors exhibit enhanced receptor-mediated calcium mobilization. This consideration would tend to argue against a defect in the calcium pathway components common to all cells and receptors. Another possibility would be calcium pathway components that are not universally present in all cell types. Calcium channels, kinases with uneven distribution are examples of such.

4. Are calcium mobilization abnormalities specific for the affective disorders?

Many new biochemical or anatomical findings in psychiatry first drew enthusiasm which later on resulted in disappointment when the abnormality was found to be present in other diseases. We therefore need to determine whether this calcium abnormality is specific for the affective disorders. A survey of the literature shows that a number of medical conditions, besides the affective disorders, indeed have calcium mobilization abnormalities in peripheral blood cells such as platelets. In alcoholism, elevated cytosolic free calcium concentrations have been found in the platelets of hypertensive drinkers, which gave a weak association with alcohol consumption (41). However, when intracellular calcium mobilization was examined in platelets from alcoholic men, there were no differences in either baseline or serotonin-stimulated cal-

cium levels compared to controls (42), suggesting that any difference in the first study was state, not trait, dependent.

In hypertension, intracellular calcium mobilization has been observed to be abnormal, but the results are not always consistent, thereby requiring further evaluation. Valtier et al. (43) have reported that platelets in human essential hypertension are hyper-reactive to thrombin. Lechi et al. (44) observed increased basal and thrombin-induced intracellular calcium mobilization in platelets of patients with essential hypertension. These abnormalities do not appear to be restricted to platelets, since elevated lymphocyte cytosolic calcium has been observed in a subgroup of essential hypertensive subjects (45). Eberhard et al. (46) have found that hypertension does not affect intracellular calcium uptake in human platelets, but since calcium uptake is only one part of the intracellular calcium mobilization response, it is possible that the abnormality lies in another component of this pathway. Interestingly, hypertensive rats also demonstrate increased platelet calcium (47, 48), but according to Ohno et al. (49), increased intracellular calcium is not coinherited with an inferred major gene locus for hypertension in the spontaneously hypertensive rat. Thus, it is possible that calcium is not involved in the etiology of hypertension, but instead often, but not always, co-varies with this parameter. Likewise, it is also possible that hypertension has many causes, with the calcium abnormalities playing a role in a subgroup of these disorders. Konopka et al. (38) who studied serotonin-induced increases in platelet free calcium concentrations, found that the serotonin-calcium response was correlated with diastolic blood pressure. However, this association was not enough to account for the enhanced $[Ca^{2+}]_i$ response seen in their depressed patient group. They have put forward the suggestion that a defect in calcium regulation may predispose patients to both hypertension and depression, in light of literature (50) showing that depression was three times more common in hypertensive patients than those with other medical disorders. Thus, instead of being a sole mechanism for depression, calcium could be seen as a predisposing factor. Alternatively, defects in the norepinephrine pathway have been implicated to be common to depression and hypertension.

Cho and coworkers (51) have reported that platelets of African Americans have increased calcium stores compared to platelets from Caucasian subjects, although Cooper and Rotimi (52) have disputed this. Thus racial factors may be important to consider when choosing the appropriate control group in clinical investigations.

In addition, a number of other factors have been found to affect intracellular calcium. Platelet membrane fluidity and calcium mobilization are affected in uremia (53). Serotonin-induced elevation of intracellular calcium in human platelets is enhanced by total fasting (54). Diabetes mellitus is associated with increased platelet intracellular calcium (55), and hyperlipidemia affects lymphocyte calcium as well (56).

Thus, enhanced intracellular calcium mobilization is not restricted to the affective disorders. This limits its diagnostic utility in the sense that intracellular calcium mobilization changes are not predictive of affective illness. On the other hand, calcium measurements do give insights into possible biochemical pathway aberrations that may be shared with other disorders. Since a number of biochemical components may lead to enhanced intracellular calcium mobilization, dissection of the component responsible for the aberrant response is important. For example, factors that may contribute to aberrant serotonin receptor-induced calcium mobilization include: serotonin-2A receptor genotype and density; coupling components such a guanine nucleotide regulatory proteins, which link the serotonin-2A receptor to IP_3 signal generation; IP_3 receptor densities; calcium store levels; calcium channels involved in influx of calcium ions; and desensitization mechanisms.

5. Do antidepressants affect intracellular calcium mobilization?

Given the largely reproducible observations that bipolar affective disorder patients have elevated serotonin-induced platelet calcium mobilization, the question arises as to whether antidepressant treatment contributes to or ameliorates this calcium response. As previously discussed, elevated serotonin-stimulated intracellular calcium is observed in both medicated and unmedicated patients. This is consistent with the hypothesis of trait dependence of the elevated calcium response. Whether antidepressants can alter intracellular calcium, is a question addressed in several studies. We have included both platelet and non-platelet studies in this discussion because both are important for evaluation of antidepressant-induced changes. Platelets, which lack a nucleus, do not have transcriptional mechanisms and so may give results different from glioma or neuronal cells. They are important however, because they aid interpretation of human clinical data, which are obtained predominantly from platelets. Glioma and neuronal cells on the other hand, possess transcriptional regulation, which most likely results in regulatory changes more closely approximating those in brain.

Antidepressants have been found to have a number of effects on intracellular calcium. They have been found to block depolarization or voltage-dependent Ca^{2+} influx, suppress intracellular Ca^{2+} oscillations (57, 58), bind to dihydropyridine-sensitive L-type Ca^{2+} channels (59) and promote Ca^{2+} release from IP_3-sensitive calcium stores

(60). Thus, more than one site of action is apparent. Clomipramine (antidepressant) and verapamil (Ca^{2+} channel blocker with antidepressant properties), in their therapeutic concentrations, inhibit Ca^{2+} influx, resulting in an inhibition of the sustained "plateau" phase which occurs after the Ca^{2+} peak, for serotonin-stimulated Ca^{2+} mobilization in C6 rat glioma cells (61). In the case of some antidepressants such as mianserin and amoxapine, inhibition of serotonin receptor-mediated calcium mobilization can be correlated to the affinity of these compounds for the receptor itself (62). While this study involves serotonin-2C receptors and not serotonin-2A receptors, it is a reminder that antidepressants may bind to the receptor itself. At higher concentrations, most psychotropic drugs begin to affect multiple systems or targets. Specific serotonin uptake inhibitors for example, have been tested for modulation of intracellular calcium in platelets (63). The general finding is that micromolar concentrations of antidepressants are required to produce these effects and the effects reported in other studies (64–66). In this concentration range, sertraline, fluoxetine and paroxetine are calmodulin antagonists and have similar calcium mobilization effects when compared to traditional calmodulin antagonists such as W-7 and calmidazolium (63, 67). This includes both elevation of baseline $[Ca^{2+}]_i$ levels as well as enhancement of thrombin-stimulated intracellular calcium mobilization. It should be noted that thrombin-stimulated calcium mobilization tended to be enhanced at lower concentrations of antidepressants than were effective in elevating baseline $[Ca^{2+}]_i$ levels (63). This difference in the dose-response relationship may imply more than one mechanism of action for these antidepressant effects. However, the effect of the calmodulin antagonist W-7 was similar to that of the antidepressants in this study, suggesting that calmodulin antagonism alone is sufficient to account for the changes in platelet calcium (63). The effective concentrations of antidepressants for these calcium effects are higher than the generally accepted therapeutic concentrations in the nanomolar range. Thus, these effects may be more relevant for toxic side effects than therapeutic action.

While these studies have generally focused on acute drug effects, it is possible that chronic antidepressant administration may produce secondary effects on calcium mobilization. This requires further examination, especially since chronic not acute antidepressant treatment is therapeutically relevant. There is a fair amount of data suggesting that antidepressants can induce receptor responsiveness changes over time. Both enhanced and decreased serotonin-2 receptor function have been reported after chronic administration of specific serotonin reuptake inhibitor-type antidepressants (68, 69). Citalopram, for example, inhibits desensitization of serotonin-2A receptor mediated calcium mobilization in glioma cells, at concentrations that do not affect calcium mobilization by themselves (70). The reuptake inhibiting properties of citalopram did not appear to be relevant for this effect, rather the authors suggested a calmodulin-dependent mechanism. Additionally, calcium channel blockade with nifedipine alone produced no changes, but modulated antidepressant-induced down-regulation of the beta-adrenergic system (71). Shimizu et al. (72) did not find changes in Ca^{2+} mobilization in fronto-cortical neurons after chronic exposure to desipramine and mianserin. Thus, there may remain other properties of antidepressants, not fully worked out, which are likely to be important for receptor signaling modulation. In the case of lithium, which has been used for treatment of manic and depressive episodes, no effects on serotonin- or thrombin-induced platelet calcium mobilization were observed after chronic administration (73). This may not reflect changes in other cells if transcriptional changes are required, since platelets lack a nucleus. Yamaji et al. (74) for example, have reported that chronic treatment with antidepressants or lithium can inhibit serotonin stimulated intracellular mobilization in C6 rat glioma cells. Verapamil, a calcium channel blocker had similar effects, which is interesting considering that some calcium channel blockers are considered to have antidepressant potential (75, 76). C6 glioma cells, unlike platelets, have transcriptional mechanisms which may contribute to the different results observed by Yamaji et al. (74) and Kusumi et al. (73). Effects of antidepressant compounds on gene expression and their consequences on the Ca^{2+} signaling pathway may be the next important area of study.

6. Conclusions

In summary, we have shown that depression appears to be associated with elevated platelet serotonin-stimulated intracellular calcium mobilization. Whether baseline calcium and non-serotonin-stimulated calcium mobilization are also aberrant is not as clear-cut in the literature. However, it is felt that this issue should be cleared up in the next decade given the relative ease of the calcium techniques available to the clinician researcher. This additional information is important since it establishes the specificity of the calcium abnormality, which in turn, gives clues about underlying mechanisms. Specificity of calcium abnormalities for the serotonin-stimulated response would imply a serotonin-related mechanism. This could range from endocrine-abnormalities which modulate serotonin receptor function to genetic polymorphism in the receptor protein. A more generalized calcium abnormality could involve calcium channel or

second messenger issues.

Whether abnormalities in calcium mobilization are responsible for the etiology of the disorder, is not clear. Certainly, calcium channel blockers such as verapamil have been suggested to have antidepressant properties (77). However, verapamil has been reported to competitively inhibit serotonin reuptake and imipramine binding, which in themselves are properties of many antidepressants that are not calcium channel blockers (78, 79). Thus, the antidepressant potential of verapamil is not proof that calcium channel blockade is therapeutically relevant. Interestingly, verapamil was not effective as an antidepressant in patients resistant to tricyclic antidepressants (80). Since tricyclic antidepressants are thought to function via blockade of neurotransmitter reuptake, this would be consistent with verapamil's therapeutic value via its serotonin reuptake inhibitory properties. Therefore, it would make sense that a resistance to tricyclics would mean a resistance to verapamil as well. To prove that calcium channel blockade may alleviate symptoms of depression, clinical trials are necessary with calcium channel blockers that do not also block serotonin uptake.

Also, as we have tried to point out, other disorders, especially hypertension, are characterized by calcium abnormalities that look very similar to those reported for the affective disorders. Perhaps calcium should be seen as a predisposing factor rather than a cause. A trait rather than state dependence is suggested by the current literature.

Interestingly, antidepressant drugs do affect intracellular calcium mobilization and baseline calcium levels. This occurs at two levels. One is via inhibition of calcium influx. This is a property shared with verapamil, which inhibits serotonin-receptor mediated calcium influx (81). The second involves enhanced release from intracellular calcium stores. These two sites of action appear to give opposite results. When calcium influx is inhibited, the receptor-mediated calcium response is also inhibited. On the other hand, enhanced release from intracellular stores has the potential to elevate baseline calcium levels, and may enhance the receptor-mediated calcium response initially, but not chronically if stores are not adequately replenished. The dosages required are higher than the therapeutic dose range however. Whether chronic administration of the lower therapeutically relevant concentrations of antidepressants also affects intracellular calcium is an area in need of further study.

Many investigators are searching for fast antidepressant drugs. It is interesting to ask whether calcium-modifying drugs have potential as faster acting antidepressants, either alone or in combination with traditional antidepressant treatments. To take verapamil as an example, administration of this drug together with an SSRI antidepressant may enhance the later's inhibition of reuptake if their mechanism of actions are synergistic. Alternatively, the inhibition of calcium influx provided by the calcium channel blocker may alter neuronal functioning in response to receptor stimulation. DePetrillo and coworkers (82) have found that chronic administration of verapamil decreases protein kinase C activity in human lymphocytes. A combination of antidepressant and calcium channel blocker may produce similar effects more rapidly after chronic administration compared to administration of either compound alone.

Although the nature of the therapeutic changes provided by antidepressants still elude us, with more specific antidepressants and a clearer understanding of what they do, advances in therapeutics for the affective disorders should be forthcoming.

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