

Calcitonin and bipolar disorder: a hypothesis revisited

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Double-blind trials conducted in the early 1980s showed that subcutaneous injections of salmon calcitonin in patients suffering from mania resulted in significant decreases in irritability, euphoria and hyperactivity. Although these results were promising, there were no follow-up studies in this area. A MEDLINE search into the effect of calcitonin on neuronal tissues revealed that calcitonin affects neuronal tissues in a manner similar to that of the currently accepted mood-stabilizing agents — namely by modulating intracellular second messenger signalling mechanisms, stabilizing neuronal membranes and inhibiting neuronal calcium influx. We suggest that these effects of calcitonin on neuronal tissues, combined with earlier clinical research showing its efficacy in treating the acute symptoms of mania, make calcitonin a candidate for further research in the treatment of bipolar disorder.

Des études à double insu réalisées au début des années 80 ont montré que des injections sous-cutanées de calcitonine de saumon chez les patients atteints de manie réduisent considérablement l'irritabilité, l'euphorie et l'hyperactivité. Même si ces résultats étaient prometteurs, on n'a réalisé aucune étude de suivi dans ce domaine. Une recherche dans MEDLINE sur l'effet de la calcitonine sur les tissus neuronaux a révélé qu'elle les affecte un peu comme les thymorégulateurs courants — c'est-à-dire en modulant les mécanismes de signalisation du second messenger intracellulaire, en stabilisant les membranes neuronales et en inhibant l'influx de calcium neuronal. Nous sommes d'avis que, compte tenu de ces effets de la calcitonine sur les tissus neuronaux, conjugués à la recherche clinique antérieure qui en a démontré l'efficacité pour traiter les symptômes aigus de la manie, il est justifié de pousser les recherches sur l'utilisation de la calcitonine pour le traitement des troubles bipolaires.

The only clinical investigation of the use of calcitonin in the treatment of mania was conducted by Carman et al¹ in 1984. Thirty patients suffering from either psychosis or mania participated in a double-blind

placebo-controlled crossover trial. There was a substantial and significant reduction in agitation scores in more than 85% of the patients with mania, from 2 to 30 hours after injections of active salmon calcitonin.

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Medical subject headings: amino acid neurotransmitters; anticonvulsants; bipolar disorder; calcitonin; calcitonin gene-related peptide; calcium channel blockers; central nervous system agents; glutamic acid; receptors, calcitonin; receptors, calcitonin gene-related peptide; lithium; second messenger systems

J Psychiatry Neurosci 1998;23(2):109–17.

Submitted Aug. 9, 1997

Revised Dec. 30, 1997

Accepted Jan. 6, 1998

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The patients with mania who received salmon calcitonin had significantly lower scores on the Global Mania Scale and on the Mania component of the Brief Psychiatric Rating Scale (BPRS) than when they received a placebo. This effect was observed even in patients taking stable dosages of neuroleptics or lithium and thought to have reached maximal improvement. Calcitonin significantly reduced euphoria, irritability and hyperactivity in 26 of the 30 patients with mania. On the Depression component of the BPRS there was a concomitant increase in scores, but no change in scores on the Psychosis component.

To evaluate the hypothesis that exogenously administered calcitonin might correct a deficiency in endogenous calcitonin, cerebrospinal fluid (CSF) samples were drawn and calcitonin levels measured by radioimmunoassay. CSF calcitonin levels were significantly lower in patients with mania than in the control group and in people who were depressed or had recovered from bipolar disorder. Furthermore, the percentage of patients suffering from mania with detectable CSF calcitonin was 11%, whereas the percentage in the control group was 57%. While promising, this research is limited by a number of methodological problems, demonstrates acute effects only, and does not address the question of long-term efficacy. Since 1984 no further research has been conducted in this area.

We are aware of a patient with refractory bipolar disorder who experienced a marked reduction in the frequency and severity of her manic and depressive episodes when she began taking calcitonin to treat osteoporosis. A MEDLINE search was conducted for articles that examined the relation between calcitonin and bipolar disorder. The results of this search suggested that calcitonin may play a role in the pathogenesis and treatment of bipolar disorder. In this article we will review the effects of calcitonin on central neurotransmitters and on the second messenger systems that are thought to be relevant in the treatment of bipolar disorder. These effects will be compared with the hypothesized mechanisms of action of the known mood stabilizers.

Calcitonin hormones

Calcitonin is a 32-amino-acid polypeptide hormone. It is secreted primarily by the parafollicular, or C-cells, of the thyroid gland, which are of neural crest origin.

These cells migrate to other locations during embryonal development to become secondary sites of calcitonin production; as a result, detectable levels of calcitonin are present even after a total thyroidectomy. In humans these sites include the lungs, adrenal glands, thymus, gastrointestinal tract and the central nervous system (CNS).²

The calcitonin gene, recently mapped to the 11p15.1-15.2 region of chromosome 11,³ exists as 2 copies, the *CALCA* gene and the *CALCB* gene. The primary RNA transcript of the *CALCA* gene undergoes tissue-specific splicing, resulting in the production of either the 32 AA calcitonin or the 37 AA calcitonin-gene-related-peptide (CGRP- α). In the thyroid gland the principal product is calcitonin, but in the CNS and peripheral nervous system (PNS) the primary product is CGRP. The *CALCB* gene encodes CGRP- β and is primarily expressed in the CNS. Calcitonin is known to inhibit bone reabsorption by osteoclasts and to increase renal excretion of calcium. CGRP is a potent vasodilator and may be one of the principal regulators of splanchnic and cerebral blood flow.

It has been hypothesized that in phylogenetic evolution calcitonin was a neurotransmitter that assumed the additional function of a classic endocrine hormone in more complex organisms, as has been demonstrated for thyrotropin-releasing hormone (TRH). Given the neuroectodermal origin of calcitonin-producing cells and the broad distribution of calcitonin-binding sites in the CNS, it is reasonable to assume that calcitonin directly affects neuronal tissues, either as a regulator of neuronal calcium distribution, a modulator of neuronal response or a neurotransmitter.

CNS distribution of calcitonin/CGRP

While calcitonin is the primary gene product produced in the thyroid, and CGRP in the CNS/PNS, both calcitonin and CGRP receptors are widespread in the CNS. There appear to be receptor subsets specific to calcitonin, others that are specific to CGRP, and still others that can bind either calcitonin or CGRP.⁴ Calcitonin-binding sites are most highly concentrated in the hypothalamus, circumventricular organs, preoptic nucleus, nucleus accumbens, amygdaloid nucleus, dorsal raphe nucleus, zona incerta and anterior pituitary. CGRP-binding sites are more widespread; they are found in high densities in re-

gions of the brain related to the olfactory, visual and auditory systems, in the thalamus and cerebellum, in the nucleus accumbens, in the amygdaloid nucleus (with highest concentrations in the central amygdaloid nucleus), in the striatum and in the pituitary gland.⁵⁻⁸

Sites with receptors showing a high affinity for both calcitonin and CGRP include the area postrema, the organosum vasculosum of the lamina terminalis, the stria terminalis, the ventral striatum, the nucleus accumbens, the central nucleus of the amygdaloid, and the wings of the dorsal raphe nucleus.⁴ The ability of CGRP to mimic the effects of centrally administered calcitonin^{4,9-12} supports the hypothesis that there is a high degree of cross-reactivity between calcitonin and CGRP in the CNS.

The calcitonin and CGRP receptors belong to the G-protein-coupled family of receptors. Specifically, they are members of the receptor subfamily, which includes parathyroid hormone, corticotropin-releasing hormone, growth hormone releasing hormone (GHRH), vasoactive intestinal polypeptide, glucagon and secretin. The calcitonin receptor is coupled to the phospholipase C and adenylate cyclase second messenger systems.^{13,14} It is capable of modulating phosphatidylinositol (PI) hydrolysis and can bind to both Gi and Gs proteins, thereby decreasing or increasing the activity of adenylate cyclase and the intracellular levels of cyclic adenosine monophosphate (cAMP).¹⁵

Neuronal effects of calcitonin and its relevance to the treatment of mania

The pathogenesis of bipolar disorder is unknown. The causes of the disease are probably highly heterogeneous. What is known has largely been deduced by studying the biological markers in patients with bipolar disorder, and by extrapolating from the presumed mechanisms of actions of the currently accepted mood-stabilizing drugs. With respect to biological markers, it has been noted that the platelets and lymphocytes of patients with bipolar disorder have higher levels of intracellular calcium than those of healthy people, and that these levels normalize after treatment.¹⁶ Both lithium and carbamazepine have been noted to reduce [Ca²⁺]_i in patients with bipolar affective disorder, but not in healthy people.^{16,17} In response to 5-hydroxytryptamine (5-HT, serotonin) stimulation, patients with bipolar disorder were

noted to have higher intracellular calcium levels than people in a control group.¹⁶ These observations have led to speculation that the pathogenesis of bipolar disorder may lie in a disturbance of intracellular calcium dynamics. Interest has thus focused on the functioning of cellular systems that regulate intracellular calcium levels, in particular the functioning of the G-protein-coupled PI and calcium-ion second messenger systems. It has been hypothesized that, in patients with bipolar disorder, G-proteins or the PI systems are hyperactive or hyper-responsive, resulting in elevated levels of intracellular calcium.¹⁸ Effective mood stabilizers appear to dampen excessive intracellular signalling by inhibiting calcium mobilization, diminishing generation of PI second messengers, inhibiting protein kinases, directly inhibiting G-protein/receptor coupling, or dampening neuronal excitability.¹⁸⁻²⁰

It has not been proven whether an abnormality of intracellular calcium homeostasis is pathogenically relevant to bipolar disorder. Modulation of neuronal calcium levels and influx has, however, been hypothesized to be a clinically useful marker of therapeutic efficacy. Lithium, as previously noted, reduces [Ca²⁺]_i in the cells of patients with bipolar affective disorder. This is presumed to be a result of the ability of lithium to either suppress the activity of the inositol 1,4,5-triphosphate (IP₃) second messenger system or to decouple calcium flux regulating G-proteins from their receptors.¹⁷ Similarly, the antiepileptics have been noted to modulate glutamate-induced Ca²⁺ influx or inhibit glutamate release. Perhaps the most direct evidence has been the efficacy of the calcium-channel blockers in the treatment of bipolar disorder.

Calcitonin, lithium and second messenger systems

Despite recent advances in the treatment of patients with bipolar disorder, lithium probably remains the most widely used mood-stabilizing agent. However, the precise mechanism of action of lithium remains unclear. Attention has focused on the ability of lithium to inhibit myo-inositol monophosphatase activity and thereby modulate receptor activated, phosphoinositide or protein kinase C mediated signal transduction.^{21,22}

The inositol phosphate / IP₃ system

Inositol phosphates play a major role in receptor-

mediated signal transduction. Membrane PI hydrolysis is stimulated by the activation of muscarinic (M1, M3, M5), α -adrenergic and serotonergic (5-HT₂) receptor subtypes, as well as by histamine, TRH and glutamate receptor activation. Phosphatidylinositol 4,5-bisphosphate (PIP₂) hydrolysis by phospholipase C in turn generates the intracellular second messengers IP₃ and diacylglycerol (DAG). DAG activates protein kinase C (PKC), which phosphorylates intracellular enzymes and proteins, altering their activity. IP₃ facilitates the release of calcium from intracellular stores. This increase in intracellular calcium results in a positive feedback-induced release of additional calcium, further activation of PKC, and activation of cellular processes.

Calcitonin has been observed to inhibit hydrolysis of inositol phosphate in neuronal, pituitary and osteoblastic tissues.²³⁻²⁶ This in turn inhibits the release of calcium from intracellular stores and inhibits the influx of extracellular calcium.²⁷ The ability of calcitonin to inhibit TRH-stimulated inositol phosphate production in anterior pituitary cells is well established.^{23,25} Of particular interest with respect to a possible role in the treatment of bipolar disorder is the apparent ability of peripherally administered eel calcitonin to inhibit norepinephrine- and serotonin-stimulated inositol phospholipid hydrolysis in diffuse regions of the hippocampus and cerebral cortex.²⁴ The effect is specific to the adrenergic and serotonergic systems, as carbamylcholine-induced and basal IP₃ levels were unchanged. This suggests that, unlike lithium, calcitonin does not exert its effect by generally inhibiting phosphoinositidase. The administration of calcitonin did not affect prazosin binding, suggesting that calcitonin exerts its effect by decreasing coupling between α -adrenergic receptor sites and phosphoinositidase, rather than by decreasing the number or affinity of adrenergic receptors. Calcitonin also appeared to enhance signal transduction at β -adrenergic receptors, as reflected in the potentiation of β -adrenergic stimulated cAMP accumulation. Both calcitonin and ketanserin, a specific 5-HT₂ receptor antagonist, reduced serotonin-induced IP₃ hydrolysis in the hippocampus and cerebral cortex. Calcitonin does not have any specific antagonistic properties at 5-HT₂ receptors, suggesting that it may act by inducing a down-regulation of 5-HT₂ receptors.²⁴ This may be the result of a long-term increase in serotonin levels.²⁸⁻³²

The inhibition of inositol phospholipid hydrolysis

by calcitonin is of interest in the treatment of bipolar disorder, since this is also the hypothesized mechanism of action of lithium. Lithium, at therapeutic concentrations, is an inhibitor of the enzyme inositol monophosphatase, which plays a role in the recycling of inositol phosphates. Studies have shown that lithium inhibits norepinephrine-stimulated inositol phospholipid hydrolysis,²¹ an effect also exhibited by peripheral calcitonin administration.²⁴

The cyclic AMP system

It is generally accepted that calcitonin increases levels of cAMP by interacting with Gs-coupled receptors, which activate adenylate cyclase. Studies have shown that peripheral calcitonin administration increases serum levels of cAMP and also potentiates the increase in cAMP observed after β -adrenergic receptor activation.²⁴ In contrast, a study has shown that calcitonin administration reduces levels of cAMP in selected areas of the brain in rats, although these results have not been replicated.³³

With respect to the treatment of patients with bipolar disorder, the effect of currently available mood stabilizers on cAMP is not clear. While some studies report decreased basal and epinephrine-induced cAMP levels after lithium administration,³⁴ others have shown tissue- and region-selective increases in basal cAMP levels with blunted β -adrenoceptor-stimulated cAMP responses.³⁵ This increase in basal cAMP levels is thought to result from decreased receptor coupling to inhibitory G-proteins (Gi), which removes a tonic inhibition on cAMP levels.³⁶ Long-term lithium treatment has been shown to result in an increase in both basal and post-receptor-stimulated adenylate cyclase activity in platelets,³⁶ which is thought to be most compatible with the attenuation of Gi functioning. Whether calcitonin and lithium affect cAMP levels in similar and clinically relevant ways in patients with bipolar disorder is unknown. What is known is that they both exert an effect on G-protein-coupled adenylate cyclase activity and alter intracellular levels of cAMP.

Calcitonin, anticonvulsants and neuronal stabilization

In the past decade there has been an increasing awareness that anticonvulsants are efficacious in the

treatment of patients with bipolar disorder. While lithium appears to inhibit overactivity by suppressing signal-transduction pathways, it is hypothesized that anticonvulsants reduce the spread of any abnormal or excessive neuronal activity that may be present in patients with mania.³⁷ The exact mechanism of action is unknown, but likely candidates are the ability of anticonvulsants to inhibit rapid neuronal firing by decreasing sodium conductance, to antagonize the neuroexcitatory effects of glutamate, and to inhibit glutamate release. Inhibition of neuronal depolarization would in turn inhibit calcium influx through voltage-gated calcium channels. Interestingly, lithium also appears to inhibit N-methyl-D-aspartate (NMDA)-receptor-stimulated Ca²⁺ influx by inhibiting NMDA receptor-coupled PI systems.

Calcitonin and anticonvulsants share many neuronal actions. Calcitonin inhibits spontaneous neuronal activity in a dose-dependent manner.^{9,38-43} This appears to be due to the induction of a slow outward current associated with a decrease in Na⁺ conductance causing membrane hyperpolarization.⁴¹ This effect is mimicked by applying forskolin, a potent adenylate cyclase activator, and is potentiated by phosphodiesterase inhibitors, suggesting that the effect is mediated by an increase in intracellular cAMP. Sobaniec et al⁴⁴ demonstrated that peripherally administered calcitonin exerts an anticonvulsive effect in rats similar to that exerted by valproic acid.

Calcitonin and glutamate

Glutamate is an excitatory-amino-acid neurotransmitter that stimulates phosphoinositol hydrolysis, IP₃ generation and neuronal calcium influx. The NMDA receptor subtype is primarily involved in the regulation of intracellular free calcium concentrations. In addition to suppressing spontaneous neuronal activity, calcitonin also suppresses glutamate-evoked neuronal activity⁴⁰ and antagonizes glutamate-induced aversive behaviour.⁴⁵⁻⁴⁷ Calcitonin potentiates the inhibition of quinolinic acid by MK-801 and PCP (non-competitive NMDA antagonists), but not by CPP and 7C1K (competitive NMDA antagonists).⁴⁶ This suggests that the calcitonin effect is not mediated by interaction at the NMDA receptor, but might be mediated by the interaction at a calcium ion channel. An alternative hypothesis is that calcitonin antagonizes glutamate (an IP₃/DAG stimulator) by inhibiting the IP₃/DAG sec-

ond messenger system. CGRP is also a potent neuronal stabilizer and suppresser of excitatory-amino acid-induced activity, with the ability to completely abolish the response of Purkinje's cells in the cerebellum to aspartate.⁴² The success of lamotrigine (a glutamate release inhibitor) in the treatment of patients with refractory bipolar disorder⁴⁸ suggests that the antagonism of glutamate-induced calcium influx may be a target for treatment.

Calcitonin, calcium-channel blockers and neuronal calcium flux

Calcium is a ubiquitous intracellular signaller. It can be mobilized not only through the PI system, but also by a variety of stimuli. There are 3 voltage-gated membrane calcium channels, L, N, and T, that allow calcium to enter cells in response to neuronal depolarization. Binding of the calcium-channel blockers to receptors on the calcium channels results in a marked decrease in transmembrane calcium currents.

Increased intracellular calcium levels and enhanced serotonin-induced platelet calcium mobilization have been noted in patients with bipolar disorder.⁴⁷ This has focused attention on derangements of neuronal calcium homeostasis as a possible pathogenic mechanism of bipolar disorder. Trials with calcium-channel blocking agents, such as nimodipine, have shown encouraging results; however, their use is restricted because of adverse side effects. Presumably as a result of the modulation of the IP₃/DAG system, calcitonin inhibits calcium flux into neuronal tissue. In this manner, calcitonin mimics the effect of the calcium-channel blockers. Calcitonin has been shown to inhibit the TRH-stimulated increase in intracellular calcium in anterior pituitary cells^{27,49} and in osteoblast-like cells.²⁶ It has also been shown to inhibit calcium uptake by hypothalamic tissues — this is thought to be the mechanism by which calcitonin activates serotonergic pathways.⁵⁰ Calcitonin increased the effects of co-administered nimodipine on brain amines (increased 5-hydroxyindoleacetic acid [5-HIAA], 5-HIAA/5-HT ratio and 5-HT levels), presumably by inhibiting neuronal calcium influx. Nimodipine and calcitonin had a purely additive effect on brain amines, suggesting a similar mechanism of action.

Calcitonin and the amine neurotransmitters

Peripherally administered calcitonin has many ob-

servable effects on CNS levels of brain neurotransmitters. As previously noted, calcitonin increases brain 5-HT and 5-HIAA levels,²⁸⁻³² particularly in the hypothalamus and hippocampus. The precise role of the disturbances in serotonergic tone in the pathogenesis of bipolar disorder is unknown; however, serotonin is known to dampen or inhibit a number of functions subserved by other neurotransmitters. Some studies have observed lower CSF levels of 5-HIAA in patients with mania and in patients with bipolar disorder who are depressed; these levels persist after recovery.⁵¹ Recent postmortem studies have also indicated reduced 5-HT turnover and reduced 5-HIAA levels in the brains of patients with bipolar disorder.⁵² The permissive theory of bipolar disorder holds that both the manic and depressed phases of bipolar disorder are characterized by low central 5-HT function, and thus defective serotonergic dampening of other neurotransmitter systems (especially norepinephrine and dopamine). Serotonin is thought to serve as a "neurochemical brake" on certain innate behaviour, and the loss of serotonergic tone is thought to result in a loss of control over impulsiveness or aggression or both.⁵³ Calcitonin may have a role in treating bipolar disorder by enhancing serotonergic tone and increasing the serotonergic modulation of other neurotransmitter systems. Calcitonin is unlikely to affect all serotonergic neurons in a similar way. It appears to antagonize phosphoinositide hydrolysis at 5-HT₂ post-synaptic receptors and facilitate cAMP increases at 5-HT_{1A} receptors.⁴⁵

Mania has been thought to be a state of increased dopaminergic drive. Calcitonin has been hypothesized to decrease dopamine levels in the substantia nigra and striatum, which explains the ability of calcitonin to potentiate haloperidol-induced catalepsy and depress amphetamine-induced locomotor activity.⁵⁴⁻⁵⁶ L-dopa and amphetamines are both capable of inducing manic/hypomanic states, especially in susceptible patients with bipolar disorder. Amphetamine behavioural responses, such as increased locomotion, aggression and enhanced startle response, can be reversed with long-term treatment with lithium and neuroleptics.⁵¹ The ability of calcitonin to reduce amphetamine-induced locomotor activity may provide an animal model for the effectiveness of calcitonin in the treatment of mania.

As previously noted, calcitonin inhibits α 1-adrenergic induced IP₃ hydrolysis and potentiates β -adrener-

gic cAMP accumulation. Mania is thought to be a condition of α -adrenergic overactivity,⁵¹ and recent postmortem studies have indicated that patients with bipolar disorder have enhanced levels of norepinephrine.⁵² This is consistent with the hypothesized decreased calcitonergic tone in patients with mania, as is the observed decreased binding at β -adrenergic receptors in the lymphoblastoid cells in some families with bipolar disorder.⁵⁷

Interestingly, recent studies have postulated a link between elevated CSF CGRP levels and depression.⁵⁸ The behavioural and neuroendocrine effects of calcitonin/CGRP mimic those found in the human depressive syndrome (anorexia, locomotor retardation, sleep disturbance, decreased levels of GH/TSH/PRL, and increased levels of adrenocorticotrophic hormone [ACTH] and cortisol). The clinical efficacy of tricyclic antidepressants, which are capable of antagonizing the behavioural effects of calcitonin,⁵⁹ appears to be related to their ability to down-regulate postsynaptic β -adrenergic receptors or decrease the β -adrenergic stimulation of cAMP⁵¹ while increasing synaptic levels of norepinephrine and possibly serotonin. Thus, it could be hypothesized that one of the mechanisms by which tricyclics may be effective in the treatment of depression is by modulating calcitonin/CGRP induced β -adrenergic potentiation, and α -adrenergic and serotonergic inhibition. Calcitonin release in the thyroid gland is under β -adrenergic control. If CNS calcitonin is similarly under β -adrenergic control, then the alleviation of some of the behavioural manifestations of depression by tricyclics may be secondary to decreased CNS calcitonin/CGRP release.

Discussion

Despite very encouraging results from double-blind placebo-controlled trials,¹ there have been no further studies examining the efficacy of calcitonin to treat mania. In part, this may be due to the continuing and unresolved debate about whether peripherally administered calcitonin has access to the CNS. Some authors have suggested that calcitonin achieves a wide CNS distribution after peripheral administration,^{1,6,60} but the evidence is inconclusive and other studies appear to contradict this result.^{61,62} Clinical studies have demonstrated effects at the level of the CNS and adjacent structures after the peripheral administration of calcitonin. Behavioural effects include anorexia,^{1,50,57} the in-

hibition of locomotor activity,^{1,54} depressed mood¹ and analgesia.^{60,63-65} Neuroendocrine effects include decreased levels of growth hormone (GH) and decreased GH response to GH-RH,⁶⁶⁻⁶⁸ decreased levels of thyroid stimulating hormone (TSH) and decreased TSH response to TRH,⁶⁷⁻⁷⁰ elevated serum levels of ACTH, β -endorphin and cortisol,^{63,64,66,71} and elevated CNS serotonin levels.²⁸⁻³² One cannot, however, rule out the possibility that the central actions of peripherally administered calcitonin listed above represent the effects of calcitonin binding to accessible CNS sites in the circumventricular organs⁷² and the pituitary.

On the other hand, studies have shown that peripherally administered calcitonin can have widespread neuronal effects, such as increased latency of brain stem auditory evoked potentials⁷³ and general anti-convulsant properties, which would support the use of calcitonin to treat CNS disorders. Furthermore, Carman et al¹ have shown that, in monkeys, salmon calcitonin enters CSF from 2 to 30 hours after subcutaneous administration, with peak levels between 12 and 18 hours. This time course matches closely the observed behavioural effects of peripherally administered salmon calcitonin, suggesting that these behavioural effects represent the direct effects of calcitonin in the CNS.

Although there has been no further work since the initial trials by Carman et al¹ on the efficacy of calcitonin in patients with mania, a substantial body of evidence has accumulated over the past few years on the neuronal effects of calcitonin, which are as follows:

- it inhibits inositol phospholipid hydrolysis and IP₃ generation;
- it inhibits DAG/PKC mediated protein phosphorylation;
- it alters G-protein-coupled cAMP activity;
- it inhibits NMDA-induced calcium influx;
- it stabilizes neuronal activity and may have anti-seizure activity;
- it antagonizes dopaminergic activity; and
- it facilitates serotonergic activity.

These effects are shared by the currently accepted mood-stabilizing medications such as lithium, divalproex sodium and carbamazepine. The foregoing suggests that calcitonin warrants further study as a potential mood-stabilizing agent.

It is interesting to speculate whether a derangement of calcitonin regulation may be involved in the pathogenesis of bipolar disorder. Carman et al¹ reported

lower CSF levels of calcitonin in patients with mania than in people in a control group or in patients with schizophrenia. The calcitonin gene has recently been mapped to the 11p15.1-15.2 region on the short arm of chromosome 11, in the region of the *HRAS* oncogene and the tryptophan hydroxylase gene. This is also the putative site of the bipolar gene identified by Egeland et al⁷⁴ in Amish families. Hence, a primary genetic defect involving the calcitonin gene or its promoter sequences may play a role in the pathogenesis of bipolar disorder in some families.

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