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RAPID COMMUNICATION

Chromium treatment of depression

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Abstract

Eight patients with refractory mood disorders received chromium supplements and described dramatic improvements in their symptoms and functioning. In several instances, single-blind trials confirmed specificity of response to chromium. Side-effects were rare and mild, and most commonly included enhanced dreaming and mild psychomotor activation. To our knowledge, this is the first case series describing the response to chromium monotherapy. The putative antidepressant effects of chromium could be accounted for by enhancement of insulin utilization and related increases in tryptophan availability in the central nervous system, and/or by chromium's effects on norepinephrine release.

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Introduction

Chromium is a trace element which appears to affect monoamine neurotransmitter systems (Horacek et al., 1999; Liu and Lin, 1997). Recently, we described a series of patients with refractory dysthymic disorder who responded to chromium potentiation of antidepressant pharmacotherapy (McLeod et al., 1999). We now report the effect of chromium alone in a series of 8 patients with refractory mood disorders. Case summaries for 3 of the patients are presented below; the remaining cases are outlined in Table 1 (case reports are available on request). To our knowledge, this is the first description of chromium monotherapy in the treatment of depression.

Case reports

Case 1

Mr A developed bipolar II disorder with the onset of a major depressive episode in his late 20s. On lithium prophylaxis, his mood stabilized, although he continued to experience periods of irritability. He attributed feelings of being 'slowed down' and a 30-lb weight gain to lithium, and he experienced breakthrough depressions, usually during autumn. Various antidepressants, including amitriptyline and sertraline, provoked unacceptable side-effects.

Within 2 d of commencing a trial with 400 μg/d chromium, the patient reported feeling more relaxed and stable than he ever had since the onset of his bipolar disorder, and his wife noticed a change in his 'attitude'. Soon, the patient decided to discontinue the lithium and continue with chromium alone, he then began to feel more energetic, more stable, and less hungry (and gradually lost 23 lb).

Several months later, he forgot to take his chromium, and within a few days his symptoms returned. In order to 'catch up', he took 800 μg/d and developed diaphoresis each morning and a mild hand tremor. After reducing the dosage to 600 μg/d he again went into complete remission and he has now been symptom-free for 17 months. After more than 1 yr of chromium treatment, he developed uric acid kidney stones. One year after switching to a different chromium preparation, there has been no recurrence of kidney stones.

Case 2

Mr B sought treatment for a major depressive episode of 5 yr duration. He met DSM-IV criteria for bipolar II disorder, with current symptoms of depressed mood, crying spells, hypersomnia, carbohydrate craving with a weight gain of 25 lb in the past year, diminished ability to concentrate, fatigue, and suicidal ideation.

Treatment with sertraline led to improvement in his mood, but he quickly developed unacceptable sexual side-effects. Following a discussion of the limited available information regarding chromium pharmacotherapy, the patient began a treatment trial with 400 μg/d. Shortly

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Table 1. Case summaries

Case	Age	Gender	Diagnosis	Outcome
1	50	M	BP II with seasonal pattern	Response to 600 μg/d; symptom-free for 17+ months; tremor on 800 μg/d
2	38	M	BP II	Response to 600 μg/d
3	47	M	Dysthymic disorder	Response to 400 μg/d*
4	47	M	Depressive disorder not otherwise specified with seasonal pattern	Response to 400 μg/d*; chromium stopped after 4 months; remains in remission after 16 months
5	50	M	Dysthymic disorder	Response to 600 μg/d
6	62	M	Major depressive disorder and adult onset diabetes	Response to 400 μg/d; improvement in stabilization of blood glucose levels
7	43	F	Major depressive disorder	Response to 400 μg/d*
8	50	F	Dysthymic disorder	Response to 500 μg/d

* Participated in a single-blind controlled trial.

after his first dose, he reported experiencing unusually vivid and intense dreams and the beginning of an improvement in his mood. His mood continued to improve, but his carbohydrate craving persisted. After the dose of his chromium was increased to 600 μg/d, his intense craving for food disappeared, and he noticed an unmistakable increase in his energy level, improvement in his concentration and cognition, and normalization in his sleep. By his self-report, his functioning improved from a baseline level of 50 on the GAF scale to 85. Because of intermittent brief dizzy spells, he was examined by a neurologist, who made the diagnosis of orthostatic hypotension. After switching from chromium polynicotinate to chromium picolinate, the dizzy spells have not returned, and he continues to enjoy sustained relief from the symptoms.

Case 3

Mr C suffered from dysthymic disorder, as well as intermittent panic attacks and rage outbursts, since early adulthood. In his early 30s, he entered psychoanalysis, which helped him 'control the damage' that resulted from the rage outbursts, but did not alleviate his mood disorder. His family physician prescribed antidepressants, but because of cognitive side-effects, the patient refused to consider additional antidepressant treatments.

As an alternative, Mr C agreed to a supervised trial of chromium. The first night after commencing with 400 μg/d he experienced strikingly vivid dreams, and over the next several days there was a dramatic improvement in his mood and behaviour. He became much less withdrawn, and enjoyed interactions with colleagues at work to a greater extent than at any time during the previous decades.

After 7 wk of sustained improvement, the patient consented to a trial of single-blind substitution of other ingredients, in order to rule out a placebo effect. After taking vitamin B12 tablets that were almost identical in appearance to the chromium picolinate for 1 wk, he reported that he was 'hungry, tired, had no interest in sex, and was worrying about everything'. The second week of the trial he received oyster shell calcium, and at the end of that week he described feeling sad, anxious, fatigued, hopeless, and hungry, with a substantial sleep disturbance. During the third week of the trial, after receiving a preparation of chromium polynicotinate that was different in appearance from the prior formulation, he reported an immediate response, with remission of all of his symptoms. This dramatic improvement has now lasted 16 months.

Discussion

Our 8 patients experienced striking clinical responses to chromium monotherapy for chronic, refractory mood disorders, which had been present for years, and had failed to respond to multiple clinical interventions. All of the patients experienced clinical remissions, which enabled them to return to more productive levels of functioning without any significant depressive symptoms. The patients were not a homogeneous group (see Table 1), and included individuals with bipolar II disorder (case nos. 1 and 2), dysthymic disorder (case nos. 3, 5, 8), major depression (case nos. 6, 7), and 'minor' depression (i.e. depressive disorder not otherwise specified, case no. 4), with seasonal pattern in a few instances (case nos. 1, 4). There were some common features, however. Most of the patients described carbohydrate craving, even in the absence of a seasonal pattern, and increased appetite. In

this context, it is interesting to note that chromium has well-described effects on carbohydrate metabolism, and increases the efficiency of insulin utilization (Anderson et al., 1997). In fact, case no. 6 experienced improvement in his adult onset diabetes while on chromium. Thus, the dramatic impact of chromium in normalizing appetite in these patients may be linked to this particular biological effect, which in turn may offer a clue to the mechanism of action for chromium's putative antidepressant activity.

There appears to be a relationship between peripheral insulin sensitivity and central serotonergic activity. Depressed patients show poor utilization of glucose in glucose tolerance tests (Wright et al., 1976), and a decreased hypoglycaemic response to insulin (Casper et al., 1977; Wright et al., 1976). Recently, Horacek et al. (1999) demonstrated a relationship between sensitivity to insulin and central serotonergic activity in healthy volunteers, using the hyperinsulinaemic–euglycaemic clamp technique and d-fenfluramine challenge. Chromium's powerful effect in increasing insulin sensitivity could then enhance insulin-mediated increases in tryptophan availability and transport across the blood–brain barrier (Fukagawa et al., 1986; Jamnicky et al., 1991) and consequent serotonin synthesis (Fernstrom, 1976). Such a mechanism could account for the very rapid changes observed in these patients when chromium therapy was discontinued and initiated, since tryptophan depletion and replenishment can stimulate very rapid changes in mood and other symptoms in depressed patients. Alternatively, chromium's effects in these patients could be mediated via its enhancement of norepinephrine release (Liu and Lin, 1997).

Uncontrolled case reports of a putative new treatment raise the question of placebo effect. The remarkably rapid onset of clinical response, and the rapid relapse when chromium treatment was interrupted, is not characteristic of established antidepressants or mood stabilizing agents, and is suggestive of a placebo response (although it could also be explained on the basis of very rapid changes in tryptophan availability as described above). However, several aspects of these cases do not support a placebo response. Each of the patients had a chronic mood disorder, and most had failed to respond to prior treatment trials. In three instances (case nos. 3, 4, 7), single-blind trials were employed, and confirmed specificity of the chromium response. The almost uniform, spontaneous description of vivid dreaming after the onset of chromium treatment suggests that chromium exerts central nervous effects. Finally, the sustained remission in previously refractory patients is not typical of a placebo response.

Chromium dietary supplements are considered to be safe, especially in oral formulations within the dosage range for these patients (Duncan, 1999). However, it should be noted that one of the patients (case no. 1) experienced an adverse event while taking a chromium preparation (the development of uric acid renal stones), although a cause-and-effect relationship was not clearly established [see Duncan (1999), for a review of the safety of chromium use and renal disease]. Several patients described mild psychomotor activation while taking chromium, including tremor and a 'caffeine-like effect', and most experienced vivid dreaming. Three patients experienced an unpleasant flushing sensation and orthostatic hypotension while taking chromium polynicotinate but not chromium picolinate.

This preliminary report raises some important questions: (1) 'Is chromium in fact an effective and safe antidepressant?' (2) 'Like lithium, does it possess mood stabilizing properties, as well as antidepressant effects?' (3) 'What is the optimal dose range, and is there a relationship between plasma levels and therapeutic and/or side-effects?' Based on the dramatic and sustained responses that these patients experienced, we believe that further study, including prospective, double-blind controlled trials, is clearly warranted.

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References

Anderson RA, Cheng N, Bryden NA (1997). Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. *Diabetes 46*, 1786–1791.

Casper RC, Davis JM, Pandy G (1977). Neuroendocrine and amine studies in affective illness. *Psychoneuroendocrinology 2*, 105–113.

Duncan MG (1999). The effects of nutritional supplements on the treatment of depression, diabetes, and hypercholesterolemia in the renal patient. *Journal of Renal Nutrition 9*, 58–62.

Fernstrom JD (1976). The effect of nutritional factors on brain amino acid levels and monoamine synthesis. *Federation Proceedings 35*, 1151–1156.

Fukagawa NK, Minaker KL, Young VR (1986). Insulin dose dependent reductions in plasma amino-acids in man. *American Journal of Physiology 250*, E13–E17.

Horacek J, Kuzmiakova M, Hoschl C, Andel M, Bahbonh R (1999). The relationship between central serotonergic activity and insulin sensitivity in healthy volunteers. *Psychoneuroendocrinology 24*, 785–797.

Jamnicky B, Sliepcevic M, Hadzia M, Juretic D, Broric O (1991). Tryptophan content in serum and brain of fasting insulin-treated diabetic rats. *Acta Diabetologica Latina 28*, 11–18.

Liu PS, Lin MK (1997). Biphasic effects of chromium compounds on catecholamine secretion from bovine adrenal medullary cells. *Toxicology 117*, 45–53.

McLeod MN, Gaynes BN, Golden RN (1999). Chromium potentiation of antidepressant pharmacotherapy for dysthymic disorder in 5 patients. *Journal of Clinical Psychiatry 60*, 237–240.

Wright JH, Jascisin JJ, Radin NA (1976). Glucose metabolism in unipolar depression. *British Journal of Psychiatry 132*, 386–393.