

## On the Effect of Aromatherapy with Citrus Fragrance in the Therapy of Major Depressive Disorder

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### Abstract

The effect of aromatherapy on the human central nervous system is a controversial issue in medical sciences. Here we present a hypothesis relating citrus fragrance aromatherapy with brain glucose homeostasis in Major Depressive Disorder. How to conciliate the correlation between depression and resistance to insulin with the fact that glucose transport to neurons is not made directly by insulin? We briefly discuss the mechanism of dynamical glucose balance in the brain, which includes lactate transport from astrocytes to neuronal mitochondria supporting ATP (and then cAMP) production. We hypothesize that odors like vanillin and citrus fragrances fool the brain's glucose level sensors, reducing the subjective feeling of "low energy". This hypothesis can help to explain the surprisingly positive results found in the treatment of depression with aromatherapy.

**Keywords:** Depression; Glucose; Lactate; Brain Homeostasis; Reward System; Aromatherapy

### Introduction

We summarize a hypothesis about the etiology of Major Depressive Disorder (MDD) and relate it to aromatherapy, in search for a better understanding of results obtained by the latter. MDD is possibly related to low glucose metabolism in the brain, leading to a diffuse reduction of cortical activity [1]. Aromatherapy may be effective for the treatment of MDD, but existing results are not conclusive and possible underlying mechanisms are not well established. In this paper, we attempt to move one step forward in this line of research, by making a hypothesis that has practical implication for psychotherapy. We restrict our hypothesis to vanillin and citrus fragrances because encouraging experimental results have been found with lemon odors [2,3] and vanillin [4] using the rat model of MDD.

MDD is compatible with the occurrence of insulin resistance and hyperglycemia, as reported by Lawlor et al. [5] and Timonen et al. [6]. In the depressed diabetes type 2 person, the deficit in neuronal energy metabolism is believed to be caused by a deficit in insulin glucose transport to the brain. In the non-diabetic depressed person, the glucose transport made by insulin is intact, but there are other steps in the transport of energy from the blood-brain barrier to the neuron that may be defective.

First, there is transport of glucose from the capillary vases to astrocytes, where it is used, released, or stored as glycogen. Transport across the endothelial cell composing the blood-brain barrier is made by protein Pgp (P-glycoprotein) [7].

Second, the transport of glucose and its metabolites to neurons is made by glucose transporters (GLUT-1; [7]). Inside neurons glucose reaches the mitochondria, where ATP is produced and becomes available to neuronal metabolism. Norepinephrine and serotonin systems are involved in the control of brain glucose delivery, transport, and uptake. Low levels of glucose in the brain can be caused by down-

regulation of these systems. Failure of glucose uptake initially leads to glycolysis, the breakdown of the stored mode of glucose. Serotonin reuptake inhibitors can impact on the symptoms of depression, although they do not act directly on the primary causes (putatively, those that determine low ATP production in neurons).

Third, lactate transport from astrocytes to neurons [8] is controlled by glutamatergic systems. Glutamate, besides prompting lactate, also inhibits glucose transport to neurons [9]. Among glucose metabolites, lactate plays a primary role as either direct or indirect (gluconeogenesis) energy source. Experts have debated the role of the "lactate shuttle" to sustain neuronal activity [10,11]. We hypothesize that under stress conditions neurons are more likely to depend on lactate; if the brain is under prolonged stress and both glucose and lactate transport are defective, MDD begins.

As a consequence of MDD, there may be a dysfunction of the dopaminergic reward system, and then an increase in glucose consumption as an attempt to compensate. Some of these factors participate in recurrent circuits with brain areas that process affective and cognitive conscious experiences. Therefore, energy transport processes could, in principle, be under the influence of conscious affective and cognitive states that can be influenced by aromatherapy.

### Homeostatic Control of Brain Energy Metabolism

The model of brain energy metabolism proposed by Peters et al. [12] comprises two mechanisms:

(1) "ATP-sensitive potassium channels measure the ATP concentration in neurons of the neocortex and generate a 'glutamate command' signal. This signal affects the brain ATP concentration by locally (via astrocytes) stimulating glucose uptake across the blood-brain barrier and by systemically (via the LHPA - Limbic-Hypothalamic-Pituitary-Adrenal-system) inhibiting glucose uptake into the muscular and adipose tissue";

(2) "High-affinity mineralocorticoid and low-affinity glucocorticoid receptors determine the state of balance, i.e. the set point, of the LHPA system. This set point can permanently and pathologically be displaced by extreme stress situations... by starvation, exercise, infectious diseases, hormones, drugs, substances of abuse, or chemicals disrupting the endocrine system".

In this model, when the set-point determined by the activity of corticoid receptors is displaced, the brain control of glucose uptake can be defective, then leading to obesity and other problems, which may be related to insulin resistance. In MDD, we hypothesize that the initial cause may be a defect on glucose transport, leading to low ATP levels in neurons. According to the first mechanism above, this situation will trigger a glutamate signal that stimulates glucose uptake across the blood-brain barrier, and the inhibition of glucose uptake in muscular and adipose tissues.

According to Song and Routh [13], the activity of lactate-excited neurons decreases the activity of glucosensing neurons, leading to a decrease in glucose transport. However, these authors report that glucose and lactate "have opposing effects on VMN (ventromedial hypothalamic nucleus) glucose-inhibited neurons": lactate excites glucose-inhibited glucosensing neurons. Therefore, a failure in the activity of lactate-excited neurons would lead to the silencing of glucosensing neurons and then to an increase of glucose levels in the blood, but not reaching the neurons. The hyperglycemia would then cause the observed insulin resistance, possibly combined with low ATP levels in cortical neurons.

### Brain Metabolism and Aromatherapy

The depressed brain possibly has a defective neuronal ATP production caused by defective brain glucose and lactate transport. This situation leads to the silencing of glucosensing neurons, which in turn leads to an excessive glucose levels in the blood without increasing neuronal ATP levels, because of the deficit in brain energy transportation.

The increase in glucose consumption is prompted by the sensation of "low energy", eliciting feeding behaviors. Glucosensing neurons participate in recurrent circuits with brain systems responsible for the generation of such subjective feelings.

This view can help to explain the surprisingly positive results found in the treatment of depression with aromatherapy and essential oils [14], specially by using lemon citrus fragrance [2]. This hypothesis has been corroborated by results obtained with a rat experimental model of MDD [3].

According to Ernst et al. [15], "The amount of rigorous scientific data to support the efficacy of complementary therapies in the treatment of depression is extremely limited". This deficit was not fully balanced in the last decades, although some results with the rat experimental model of MDD suggest a possibly efficacy of aromatherapy in MDD. For instance, in a recent publication Xu et al. [4] claim that "Our results indicated that vanillin could alleviate depressive symptoms in the rat model of chronic depression via the olfactory pathway. Preliminary analysis of the monoamine neurotransmitters revealed that vanillin elevated both serotonin and dopamine levels in brain tissue. These results provide important mechanistic insights into the protective effect of vanillin against chronic depressive disorder via olfactory pathway. This suggests that

vanillin may be a potential pharmacological agent for the treatment of major depressive disorder".

Aromatherapy has also been used in the treatment of postpartum depression [16-19]; palliative care [20], bipolar disorder [21]; anxiety and mild depression [20,22] and traumatic disorders [23], in all these cases sufficient evidence of therapeutic effects is still missing.

Although experimental results are not conclusive, we hypothesize that in aromatherapy there may be a psychosomatic effect by which citrus fragrances fool the brain's glucose level sensors, producing a feeling of "increased energy" that interrupts the over-ingestion of glucose, leading to a decrease in the hyperglycemic process. This conscious experience, in turn, can influence other brain processes involved in the etiology of MDD, in a similar fashion of other cases that involve the "placebo effect".

### Discussion

As the proposed glucosensor fooling does not correct the failure in energy transportation in the brain, the treatment with fragrances may be a placebo that does not affect the causes of depression and therefore does not promote the cure. However, it poses an interesting question: as long as it affects the conscious experiencing of depression, reducing the feeling of "low energy" and lack of disposition for everyday life, could it influence the underlying causes of depression? In other words, could this conscious process generate a psychosomatic effect on the neurobiological imbalances that cause depression?

One striking aspect of the phenomenology of MDD is the subjective report of "a feeling of total emptiness". Perhaps this feeling is related to the failure of sensory processing and attentive functions of the frontal cortices. Olfactory stimuli are special in the sense that they are transmitted directly to the cortex without passing through thalamic circuits. Olfactory anticipatory conditioning might be powerful enough to act as a "tipping point" to trigger an initially modest change in a static depression state, i.e., a "single point of light penetrating the darkness". Conditioned stimuli that release bonding-related neuropeptides as oxytocin and orexin [24] are likely candidates to be involved in this process.

The power of chemical senses on the modulation of humor can be explained by the following processes. Stimuli transmitted via the anterior thalamic nuclei are good candidates to influence humor, since the ventral striatum is part of the associated emotional motor system circuit. The anterior cingulate controls dopaminergic neurons central to the neurophysiology of reward [25,26]. The altered reward processing typical of MDD is mediated by dopamine [27]. Recurrently triggering an olfactory system-cued conditioned reward expectation circuit could initiate a gradual up-regulation of dopamine receptors in the frontal cortex and a parallel increase dopamine metabolic turnover and release in the mesolimbic dopamine reward system of the ventral striatum. Up-regulating this important dopamine system (which coordinates exogenous environment events with endogenous brain and somatic control systems responses) would lead to a gradual increase in differential cortical activity and general motor activity. Restoration of homeostatic control of cerebral metabolism would soon follow.

According to Umhau et al. [28], peripheral blood glucose concentrations are "correlated with the cerebrospinal fluid concentrations of the dopamine metabolite, homovanillic acid and the noradrenaline metabolite, 3-methoxy-4-hydroxyphenylglycol. These

correlations may represent a homeostatic relation between brain neurotransmitter activity and blood glucose". Considering this correlation, it is possible that conscious processing of odors, by influencing the dopaminergic system and the release of neuropeptides, exerts an influence on peripheral blood glucose concentration levels, then acting on the putative causes of depression. This is one among several lines of research that emerge from the above discussion.

### Concluding Remarks

This study leads to important questions to inspire research on depression: Does the onset and continuity of depression depend only on neurobiological unconscious mechanisms? Or does conscious processing have a role in the onset and treatment of depression?

If conscious processing plays an important role in the evolution of this mental disease, psychosocial methods should be included in the therapy of MDD to induce conscious experiences that feedback on the underlying neurobiological mechanisms.

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### References

1. Nikolaus S, Larisch R, Beu M, Vosberg H, Müller-Gärtner HW (2000) Diffuse cortical reduction of neuronal activity in unipolar major depression: a retrospective analysis of 337 patients and 321 controls. *Nucl Med Commun* 21: 1119-1125.
2. Komori T, Fujiwara R, Tanida M, Nomura J, Yokoyama MM (1995) Effects of citrus fragrance on immune function and depressive states. *Neuroimmunomodulation* 2: 174-180.
3. Komori T, Fujiwara R, Tanida M, Nomura J (1995) Potential antidepressant effects of lemon odor in rats. *Eur Neuropsychopharmacol* 5: 477-480.
4. Xu J, Xu H, Liu Y, He H, Li G (2015) Vanillin-induced amelioration of depression-like behaviors in rats by modulating monoamine neurotransmitters in the brain. *Psychiatry Res* 225: 509-514.
5. Lawlor DA, Smith GD, Ebrahim S; British Women's Heart and Health Study (2003) Association of insulin resistance with depression: cross sectional findings from the British Women's Heart and Health Study. *BMJ* 327: 1383-1384.
6. Timonen M, Laakso M, Jokelainen J, Rajala U, Meyer-Rochow VB, et al. (2005) Insulin resistance and depression: cross sectional study. *BMJ* 330: 17-18.
7. Abbott NJ, Rönnbäck L, Hansson E (2006) Astrocyte-endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci* 7: 41-53.
8. Pellerin L, Magistretti PJ (2004) Neuroenergetics: calling upon astrocytes to satisfy hungry neurons. *Neuroscientist* 10: 53-62.
9. Porras OH, Loaiza A, Barros LF (2004) Glutamate mediates acute glucose transport inhibition in hippocampal neurons. *J Neurosci* 24: 9669-9673.
10. Aubert A, Costalat R, Magistretti PJ, Pellerin L (2005) Brain lactate kinetics: Modeling evidence for neuronal lactate uptake upon activation. *Proc Natl Acad Sci U S A* 102: 16448-16453.
11. Schurr A (2006) Lactate: the ultimate cerebral oxidative energy substrate? *J Cereb Blood Flow Metab* 26: 142-152.
12. Peters A, Schweiger U, Pellerin L, Hubold C, Oltmanns KM, et al. (2004) The selfish brain: competition for energy resources. *Neurosci Biobehav Rev* 28: 143-180.
13. Song Z, Routh VH (2005) Differential effects of glucose and lactate on glucosensing neurons in the ventromedial hypothalamic nucleus. *Diabetes* 54: 15-22.
14. Lemon K (2004) An Assessment of Treating Depression and Anxiety with Aromatherapy. *International Journal of Aromatherapy* 14: 63-69.
15. Ernst E, Rand JI, Stevinson C (1998) Complementary therapies for depression: an overview. *Arch Gen Psychiatry* 55: 1026-1032.
16. Mantle F (2002) The role of alternative medicine in treating postnatal depression. *Complement Ther Nurs Midwifery* 8: 197-203.
17. Weier KM, Beal MW (2004) Complementary therapies as adjuncts in the treatment of postpartum depression. *J Midwifery Womens Health* 49: 96-104.
18. Imura M, Misao H, Ushijima H (2006) The psychological effects of aromatherapy-massage in healthy postpartum mothers. *J Midwifery Womens Health* 51: e21-27.
19. Conrad P, Adams C (2012) The effects of clinical aromatherapy for anxiety and depression in the high risk postpartum woman - a pilot study. *Complement Ther Clin Pract* 18: 164-168.
20. Soden K, Vincent K, Craske S, Lucas C, Ashley S (2004) A randomized controlled trial of aromatherapy massage in a hospice setting. *Palliat Med* 18: 87-92.
21. Andrescu C, Mulsant BH, Emanuel JE (2008) Complementary and alternative medicine in the treatment of bipolar disorder--a review of the evidence. *J Affect Disord* 110: 16-26.
22. Okamoto A, Kuriyama H, Watanabe S, Aihara Y, Tadai T, et al. (2005) The effect of aromatherapy massage on mild depression: a pilot study. *Psychiatry Clin Neurosci* 59: 363.
23. Longacre M, Silver-Highfield E, Lama P, Grodin M (2012) Complementary and alternative medicine in the treatment of refugees and survivors of torture: a review and proposal for action. *Torture* 22: 38-57.
24. Walling SG, Nutt DJ, Lalies MD, Harley CW (2004) Orexin-A infusion in the locus ceruleus triggers norepinephrine (NE) release and NE-induced long-term potentiation in the dentate gyrus. *J Neurosci* 24: 7421-7426.
25. Schultz W (2002) Getting formal with dopamine and reward. *Neuron* 36: 241-263.
26. Tobler PN, Fiorillo CD, Schultz W (2005) Adaptive coding of reward value by dopamine neurons. *Science* 307: 1642-1645.
27. Tremblay LK, Naranjo CA, Graham SJ, Herrmann N, Mayberg HS, et al. (2005) Functional Neuroanatomical Substrates of Altered Reward Processing in Major Depressive Disorder Revealed by a Dopaminergic Probe. *Arch. Gen. Psychiatry* 62: 1228- 1236.
28. Umhau JC, Petrusis SG, Diaz R, Rawlings R, George DT (2003) Blood glucose is correlated with cerebrospinal fluid neurotransmitter metabolites. *Neuroendocrinology* 78: 339-343.