Depression, Brain Glucose Metabolism and Consciousness

Maria Alice Ornellas Pereira*, Alfredo Pereira Jr. and Gene Johnson*****

*UNESP (São Paulo State University), Adjunct Professor, Dept. Enfermagem, Faculdade de Medicina, 18618-000, Botucatu – SP – Brasil, malice@fmb.unesp.br
**UNESP (São Paulo State University), Adjunct Professor, Instituto de Biociências, 18618-000, Botucatu – SP – Brasil, apj@ibb.unesp.br
*** Brain-Behavioral Scientist, gjohnson3rd@earthlink.net

Abstract A correlation between depression and resistance to insulin was recently discovered. How to conciliate this finding with the fact that glucose transport to neurons is not made directly by insulin? We present an explanatory hypothesis based on a mechanism of dynamical glucose balance in the brain that includes lactate transport from astrocytes to neuronal mitochondria supporting ATP (and then cAMP) production. The depressed brain has defective ATP production, possibly leading in several cases to excessive glucose consumption without increasing neuronal ATP levels. This hypothesis can help to explain the surprisingly positive results found in the treatment of depression with aromatherapy. Some odors like citrus fragrances possibly fool the brain's glucose level sensors, reducing the subjective feeling of "low energy". Could a conscious process trigger a reaction against the underlying causes of depression?

Key-Words Depression, Glucose, Insulin, Lactate, Brain Homeostasis, Aromatherapy.

Introduction

This paper contains the sketch of an ongoing theoretical study. We summarize a guiding hypothesis about the etiology of Major Depression (MD) and relate it to available data, in search for a better understanding of depression and its relations with consciousness.

MD is strongly correlated with low glucose metabolism in the brain, leading to a diffuse reduction of cortical activity (see Nikolaus et al., 2000). How is it compatible with the occurrence of insulin resistance and hyperglycemia reported by Lawlor et al. (2003) and Timonen et al. (2005)?

In the *depressed diabetic* person, the deficit in neuronal energy metabolism is probably caused by a deficit in insulin glucose transport to the brain. In the *non-diabetic depressed* person, the glucose transport made by insulin is well functioning, 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 the transport of glucose from the capillary vases to astrocytes, where it is used, released, or stored as glycogen. The transport across the endothelial cell composing the blood-brain barrier is made by protein Pgp (P-glycoprotein; see Abbott et al., 2006).

Second, the transport of glucose and its metabolites to neurons is made by glucose transporters (GLUT-1; Abbott et al., 2006). In the interior of the neuron, the 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 downregulation 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 (those that determine low ATP production in neurons).

Third, there is lactate transport from astrocytes to neurons (see Pellerin and Magistretti, 2004) controlled by glutamatergic systems. Glutamate, besides prompting lactate, also inhibits glucose transport to neurons (see Porras et al., 2004). Among glucose metabolites, lactate plays a primary role

as either direct or indirect (gluconeogenesis) energy source. Currently, there is a debate on the role of the “lactate shuttle” to sustain neuronal activity (Aubert et al., 2005; Dienel and Cruz, 2006; Schurr, 2006)

We hypothetize 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, MD begins. As a consequence of MD, there is 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 influenced by conscious affective and cognitive states.

Homeostatic Control of Brain Energy Metabolism

The model of brain energy metabolism proposed by Peters et al. (2005) 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 setpoint, of the LHPA system. This setpoint 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 the case of depression, 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 inhibition of glucose uptake in muscular and adipose tissues. According to Song and Routh (2005), 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", i.e., 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), causing hyperglycemia. The hyperglycemia would then cause the observed insulin resistance, possibly *combined with low ATP levels* in cortical neurons.

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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 depends on conscious processing that creates the sensation of "low energy", eliciting feeding behaviors. We suggest a close relationship between the activity of glucosensing neurons and the generation of conscious experiences of "low energy" typical of the depressed person. Glucosensing neurons, according to this suggestion, would 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 (Lemon, 2004), e.g. by using citrus fragrances (Komori et al., 1995a; 1995b). We suggest that these odors 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 MD.

As the glucosensing 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 Major Depression is the subjective report of "a feeling of total emptiness". Perhaps this feeling is related to failure of both the sensory selection and the sensory sustain

functions of the frontal cortices. Olfactory stimuli are special since they are transmitted directly to the cortex without passing through thalamic circuits. Olfactory mode 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 (see Walling et al., 2004) are likely candidates to be involved in this process.

The power of the chemical senses on humor can be illustrated by a passage from Proust, describing the experience of drinking tea accompained by “petites madeleines”, a little cake flavored with citrus essences (1).

Stimuli that are transmitted via the anterior thalamic nuclei are good candidates to influence humor, since the ventral striatum is part of the associated emotional motor system circuits. The anterior cingulate controls dopaminergic neurons central to the neurophysiology of reward (see Schultz, 2002; Tobler et al., 2005). The altered reward processing typical of Major Depression is mediated by dopamine (see Tremblay et al., 2005).

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 flux with endogenous brain and somatic control systems) would lead to a gradual increase in differential cortical activity and to increases in general motor activity. Restoration of homeostatic control of cerebral metabolism would soon follow.

According to Umhau et al. (2003), 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 the 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 future 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 unfolding of this mental illness, psychosocial rehabilitation methods should be included in the therapy of depression, to induce conscious experiences that feedback on the underlying neurobiological mechanisms. We suggest that this is a wide and important field for the practical application of consciousness research.

(1) The Cookie

> "Many years had elapsed during which nothing of Combray, save what was comprised in the theatre and the drama of my going to bed there, had any existence for me, when one day in winter, on my return home, my mother, seeing that I was cold, offered me some tea, a thing I did not ordinarily take. I declined at first, and then, for no particular

reason, changed my mind. She sent for one of those squat, plump little cakes called "petites madeleines," which look as though they had been moulded in the fluted valve of a scallop shell. And soon, mechanically, dispirited after a dreary day with the prospect of a depressing morrow, I raised to my lips a spoonful of the tea in which I had soaked a morsel of the cake. No sooner had the warm liquid mixed with the crumbs touched my palate than a shudder ran through me and I stopped, intent upon the extraordinary thing that was happening to me. An exquisite pleasure had invaded my senses, something isolated, detached, with no suggestion of its origin. And at once the vicissitudes of life had become indifferent to me, its disasters innocuous, its brevity illusory - this new sensation having had on me the effect which love has of filling me with a precious essence; or rather this essence was not in me it *was* me. I had ceased now to feel mediocre, contingent, mortal". **Proust, M. (1913-27) Remembrance of Things Past**. **Volume 1: Swann's Way: Within a Budding Grove.** Trl. C.K.S. Moncrieff and T. Kilmartin. New York, Vintage: 48-51.

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