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Letter to the Editor

Is Hunger a Driver of the Cognitive Development?

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Sir

In their recent paper, Elman *et al*, 2006 nicely summarized the possible associations between food intake and reward mechanisms in patients with schizophrenia. They hypothesized that schizophrenic patients may have a predilection for excessive consumption of fast food-type nutrition owing to functionally impaired neural substrate comprising homeostatic and reward mechanisms.

In our view, recent neuroendocrine findings in basic research can also help us to understand these complex mechanisms better. Diano *et al*, 2006 have found evidence that a hormone produced in the stomach directly stimulates the higher brain functions of spatial learning and memory development. The study showed that the hormone ghrelin, previously associated with growth hormone release and appetite, has a direct, rapid, and powerful influence on the hippocampus, a higher brain region critical for learning and memory: peripheral ghrelin can enter the hippocampus and bind to local neurons promoting alterations in connections between nerve cells in mice and rats. Ghrelin is synthesized principally in the stomach—the first hormone found to stimulate appetite and food intake in humans, a peptide that has a role in the regulation of feeding behavior. Ghrelin also provides a peripheral signal to the hypothalamus to stimulate food intake and adiposity.

This important finding can have a large impact on how we see the development of cognitive processes, especially in the light of the treatment efforts of such disabling conditions like schizophrenia. Atypical antipsychotics are widely used in the treatment of schizophrenia (Lieberman *et al*, 2005). Considerable evidence suggests that atypical antipsychotic-associated weight gain seems positively correlated with clinical and cognitive improvement of schizophrenic patients (Ascher-Svanum *et al*, 2005). During treatment with olanzapine, weight gain may be observed, frequently with an increase in appetite, but it is not clear whether or not this increase fully explains the weight gain. Antipsychotic-related weight gain is consistent across geographies, although the extent is variable (Sussman, 2001). On the other hand, some studies found correlation between ghrelin levels and atypical antipsychotic treatment: for example, the concentration of circulating ghrelin is significantly increased during olanzapine treatment (Murashita *et al*, 2005). Assessment of the relationship between atypical antipsychotic use, weight gain, and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population.

Can it be possible that the positive correlation between treatment-related weight gain and cognitive improvement is a result of the increased ghrelin production? It is possible that those antipsychotics, where treatment-emergent weight gain is observed, may have more impact on cognitive improvements of the patients as well.

Polimeni and Reiss (2003) and Karagianis (2003) have commented about how schizophrenia fits with the theory of evolution. Natural selection suggests that traits are preserved and perpetuated if they offer some survival advantage. The paranoia associated with schizophrenia can actually be seen as an advantage in a hostile environment. If this weight gain–cognition relationship hypothesis is valid, it can also be explained by the evolution theory of natural selection. Simply put, those individuals who had enough food around did not need to be clever enough to seek more nutritive territories. Those who were hungry and were clever enough to survive despite this might pass on their cognitive advantages to their descendents. Furthermore, those who had to fight for food everyday had probably less effective sleep at night, which is also linked to higher ghrelin levels (Copinschi, 2005). In this aspect, besides driving other advantages, hunger was probably a driver of the evolution of the cognitive processes, and ghrelin may have been the mediator.

Of course, we do not state here that overweight people are somehow smarter, because it is not the case and it is easy to explain: hunger is just increasing ghrelin level, which may boost the brain power, and the urge to find food also creates more competitive skills. However, obesity is controlled by many other factors, for example, physical activity level,

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which was probably also higher among early humans than in modern society. The bottom line is the reward system of the food and the energized brain, which could result in better cognitive development in an individual or even in a species developmental level.

More research is needed to clarify this exciting link between energy expenditure regulation and cognition, and lessons may be drawn from other fields, such as genetics and system theory. Considering these issues through proactive, multidisciplinary dialogue could result in more understandable approach for the big picture of human development.

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