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Review

Synaptic changes in the hippocampus of adolescent female rodents associated with resilience to anxiety and suppression of food restriction-evoked hyperactivity in an animal model for anorexia nervosa

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ABSTRACT

Anorexia nervosa is a mental illness that emerges primarily during early adolescence, with mortality rate that is 200 times higher than that of suicide. The illness is characterized by intense fear of gaining weight, heightened anxiety, obstinate food restriction, often accompanied by excessive exercise, in spite of mounting hunger. The illness affects females nine times more often than males, suggesting an endocrine role in its etiology. Its relapse rate exceeds 25%, yet there are no accepted pharmacological treatments to prevent this. Here, I summarize studies from this laboratory that have used adolescent female rodents in activity-based anorexia (ABA), an animal model of anorexia nervosa, with the goal of identifying neurobiological underpinnings of this disease. We put forth a hypothesis that a GABAergic mechanism within the hippocampus is central to regulating an individual's anxiety which, in turn, strongly influences the individual's resilience/vulnerability to ABA. In particular, we propose that ionotropic $GABA_A$ receptors containing the subunits alpha4 and delta, are at play for exerting shunting inhibition upon hippocampal pyramidal neurons that become more excitable during ABA. Since these receptors confer insensitivity to benzodiazepines, this pharmacological profile of ABA fits with lack of report indicating efficacy of benzodiazepines in reducing the anxiety experienced by individuals with anorexia nervosa. The idea that the GABAergic system of the hippocampus regulates resilience/vulnerability to anorexia nervosa complements current opinions about the important roles of the prefrontal cortex, amygdala, striatum, gustatory pathways and feeding centers of the hypothalamus and of the neuromodulators, serotonin and dopamine, in the etiology of the disease.

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Abbreviations: ABA, activity-based anorexia; AN, anorexia nervosa; CON, control; EX, exercise; FR, food restriction; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; LTP, long-term potentiation; MWM, Morris water maze; Rm, membrane resistance; SR, stratum radiatum; SLM, stratum lacunosum-moleculare; THP, 3α,5α[β]-tetrahydroprogesterone; Rs, receptors; Vm, membrane potential

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1. Introduction

By now, it is firmly established that neurons of juvenile sensory neocortex are exquisitely sensitive to an individual's environment, culminating in receptive field properties that closely mirror an individual's sensory experience (Aoki and Erisir, 2012; Bear and Singer, 1986; Hubel and Wiesel, 1970; Rauschecker and Singer, 1979; Wiesel, 1981). However, the final stage of brain development lies beyond the juvenile stage, at the end of adolescence. With this final stage of development comes bursts of creativity and energy that lead many to out-perform their younger siblings and parents (see the Time magazine Nov 9 2015 issue for examples of teen exuberance (2015)), but also the emergence of many mental disorders. The residual growth that continues through adolescence can be the window of opportunity for the environment to exert life-long influences that are more cognitive or emotional than sensory. The advantage of such a window is that it allows for mental capacity to become finely tuned to life's challenges and opportunities, well timed to the stage when an individual prepares to leave the nest and face more unpredictable and complex sensory and social settings. However, the mechanisms enabling experience to sculpt brain function may also be the substrates that contribute to an individual's vulnerability to mental illnesses.

This chapter will report on recent findings pertaining to the neurobiological basis of anorexia nervosa, a mental disorder that emerges most often at early adolescence and especially in females. A number of excellent review articles on the subject of anorexia nervosa (Casper et al., 2008; Compan et al., 2012, 2015; Kaye et al., 2009, 2011) and animal models for anorexia nervosa (Casper et al., 2008; Gutierrez, 2013) already exists, but these do not consider the possible involvement of the hippocampal formation. This chapter is intended to complement the pre-existing reviews by presenting data indicative of additional contributions made by the hippocampus in anxiety regulation and resilience/vulnerability to anorexia nervosa. These ideas are based mostly on data derived from an animal model of anorexia nervosa, called activity-based anorexia (ABA), applied to adolescent female rodents.

2. Anorexia nervosa

2.1. *General description*

Anorexia nervosa is a mental illness characterized by continuously severe, self-imposed starvation and intense anxiety (Kaye et al., 2004), manifested as fear of gaining weight (APA, 2013). The estimate of lifetime prevalence is 1–2% world-wide (Hudson et al., 2007; Smink et al., 2014). About 25% of the individuals with anorexia nervosa suffer from a chronic and relapsing course (Hudson et al., 2007; Steinhausen, 2002). The mortality rate for anorexia nervosa is the highest of all mental disorders (Arcelus et al., 2011). Among females diagnosed with anorexia nervosa (1–2% of the general population, world-wide), the mortality rate is estimated to be 0.56% per year. This rate is more than twice that of the female psychiatric inpatients 10–39 years old, 12 times higher than the annual death rate for females 15–24 years old in the general population, and more than 200 times greater than the suicide rate in the general population (Sullivan, 1995). One longitudinal study indicated that 15.6% of the patients in the study that were diagnosed with anorexia nervosa died from causes related to anorexia nervosa within 21 years (Zipfel

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