

Neurobiological Bases of Individual Differences in Emotional and Stress Responsiveness

High Responders–Low Responders Model

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Emotion, as defined by psychologists, is a strong and complex feeling state that is consciously perceived, like anger, fear, happiness, or love. Although we do not have direct animal models of emotions, we have the tools to study in animals some of the variables that represent components of these human traits, including emotional responsiveness and stress reactivity.

Our understanding of the neurobiological bases of emotional responsiveness derives from 2 major classes of work. The first class represents studies interested in brain sites and associated molecules that respond to fear and anxiety. The other class explores the brain circuits that regulate physiological responses to stress. These 2 classes of work do not contradict each other. In contrast, they coalesce into a coherent body of information of great importance to understanding emotion.

We believe that animal differences in emotional reactivity involve some of the same neuronal circuitry that is relevant in humans. This circuitry includes the paraventricular nucleus of the hypothalamus (PVN), monoaminergic nuclei in the midbrain, amygdala, prefrontal cortex, hippocampus, and other limbic and limbic-associated areas.¹ This circuitry determines how an individual perceives a stress and copes with it. It is a disruption of this circuitry that is responsible for why some individuals develop anxiety and major depressive disorders. In this article, we describe what is known about this emotional circuitry among animals that differ in emotional reactivity and stress responsiveness.

LIMBIC-HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The limbic-hypothalamic-pituitary-adrenal (LHPA) axis, along with other sys-

tems, orchestrates an organism's response to environmental stimuli. The LHPA axis operates via the rapid synthesis of glucocorticoids, which are released into the peripheral circulation and impinge on numerous target organs, including the brain. Glucocorticoids work through a combination of genomic and nongenomic mechanisms. They are nongenomically effective within minutes, and their genomic effects last long after the stressful event has terminated. The brain elements of the LHPA axis are critical to defining a stressor and determining how much response it deserves and how long the response ought to last. Stress-induced neuronal events converge to neurons of the PVN. These neurons synthesize, store, and secrete corticotropin-releasing hormone (CRH). On release into the portal blood, CRH interacts with its receptors on the corticotrophs of the anterior pituitary to secrete pro-opiomelanocortin and liberates in the general circulation one of its active peptides, the adrenocorticotropic hormone. This hormone interacts with its own receptors on the adrenal gland to synthesize and release glucocorticoids. Two receptors in the brain mediate the effects of glucocorticoids: glucocorticoid receptors and mineralocorticoid receptors.

Inputs to the PVN include activation pathways that lead to the initiation of the stress response and termination pathways that lead to its cessation. The monoaminergic ascending pathways play a major role in stress activation; intrahy-

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pothalamic pathways modulate the PVN locally. The extended amygdala and the bed nucleus of the stria terminalis are critical in evaluating the emotional nature of the stressor; the hippocampus and prefrontal cortex are implicated in stress termination via glucocorticoid receptors, neurotransmitters, and neuromodulators.

DIFFERING EMOTIONAL REACTIVITY IN RATS

In rats, an animal model of individual differences in emotional reactivity has been developed. When outbred rats are exposed to a novel environment, some rats exhibit high locomotor response (HR), while others exhibit low rates of locomotor activity (LR).² Stress-induced locomotion in a novel environment predicts subsequent behavioral responses of these animals to drugs of abuse.² Therefore, HR rats exhibit higher rates of amphetamine- and cocaine-induced locomotor activity and will self-administer these drugs more than LR rats.^{2,3} In addition, HR rats seek novel and varied environments when given a choice between these environments and environments to which the rats have become habituated.⁴ Furthermore, compared with LR rats, HR rats show less anxiety-like behavior in tests such as the light-dark box and the elevated plus maze.⁵ The light-dark test of anxiety is based on the rats' fear of a bright environment. The elevated plus maze test of anxiety is based on the rats' fear of open and elevated surfaces. In both conditions, HR rats are more apt to explore the bright environment and visit the open elevated arms of the maze compared with LR rats.⁵ Interestingly, the HR rats, while appearing less anxious in novel situations, release high levels of the stress hormone, corticosterone, into their blood streams.^{4,5} It is conceivable that the increased magnitude of stress-induced plasma glucocorticoid secretion in the HR animals plays a role in determining individual differences in expression of novelty-seeking behavior, with HR animals finding the increased glucocorticoids rewarding. Indeed, Pizazza et al⁶ have shown that HR rats

self-administer corticosterone more readily than LR rats. However, while HR rats may appear less anxious, they are sensitive to changes in their environmental conditions. For example, it has been shown that a week of social isolation makes HR rats behave like LR rats in an anxiety test.⁵ In another example, it was possible to inhibit HR rats' cocaine self-administration following chronic social defeat.³ It is therefore simplistic to categorize HR rats as less anxious and LR rats as more anxious, or HR rats as drug seekers and LR rats as non-drug seekers. Behavior depends on the environmental conditions, the stressor severity, and the animal's coping mechanisms.

NEUROBIOLOGICAL CORRELATES OF HR-LR PHENOTYPIC DIFFERENCES

Much of the work on the neurobiological correlates of HR and LR behavioral phenotypes has focused on the propensity to self-administer drugs of abuse and on the differential dopamine responsiveness following psychostimulants. Some basal HR-LR differences in gene expression and protein levels have been described, but they were reported in the nigrostriatal or accumbens systems.⁷ Hooks et al⁸ have shown decreased D₂ receptors and increased D₁ receptor binding in the nucleus accumbens of HR compared with LR rats. In our laboratory, we were able to confirm the D₂ difference between HR and LR rats (**Figure 1**).

The D₂ difference between HR and LR rats may be relevant to drug addiction in humans. Indeed, in a study by Volkow et al,⁹ patients with low D₂ levels (like HR rats) exhibited pleasure when they took methylphenidate hydrochloride. In contrast, patients with high D₂ levels (like LR rats) found methylphenidate unpleasant. Therefore, differential activity in the D₂ receptors appears to be involved in determining individual differences in the vulnerability to addiction.

So far, the role of this differential dopaminergic activity in HR and LR rats, especially in the nucleus accumbens, has not been fully explored in terms of its implication in

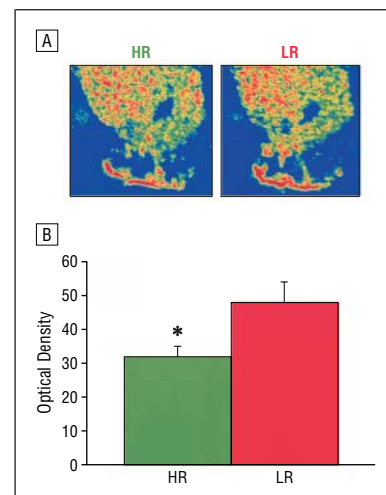


Figure 1. A, Basal dopamine D₂ messenger RNA (mRNA) in nucleus accumbens core and shell of rats with high locomotor response (HR) and low locomotor response (LR): color-enhanced photomicrograph from x-ray films exposed for 4 days after in situ hybridization with antisense complementary RNA probes against rat dopamine D₂ receptor mRNA. Compared with LR rats (n=5), HR rats (n=5) exhibit significantly lower D₂ mRNA expression in the shell area of the nucleus accumbens. There were no differences between HR and LR rats in D₂ mRNA expression in the core area of the nucleus accumbens, caudate putamen, or ventral tegmental area-substantia nigra (data not shown). B, Optical density measurements were analyzed with a 2-way analysis of variance. The between-subject factor was HR-LR, and the within-subject factor was the brain area analyzed. Analysis of variance was followed by post hoc Fisher exact test. The level of significance was set up at 5%. Asterisk indicates $P < .05$.

fear and anxiety, especially because we know that A10 dopaminergic neurons innervating the limbic system are involved in emotion, motivation, and memory formation.¹⁰⁻¹² We also have data showing that HR and LR rats differ in terms of expression of their serotonin (5-HT) receptors 5-HT_{1a} in the hippocampus (**Figure 2**) and 5-HT_{2a} in the cingulate cortex (M.K., unpublished data, 2001). In humans, there exists an extensive literature on the role of 5-HT in anxiety and depression, and it is particularly relevant because of the proposed role of serotonin in the pathophysiological conditions of depression and suicide. More compelling is the evidence of the role of serotonin in the therapeutic actions of antidepressants and the alteration in 5-HT_{1a} and 5-HT_{2a} in suicidal patients and in patients treated with antidepressants.¹³ Animal studies reinforce the impor-

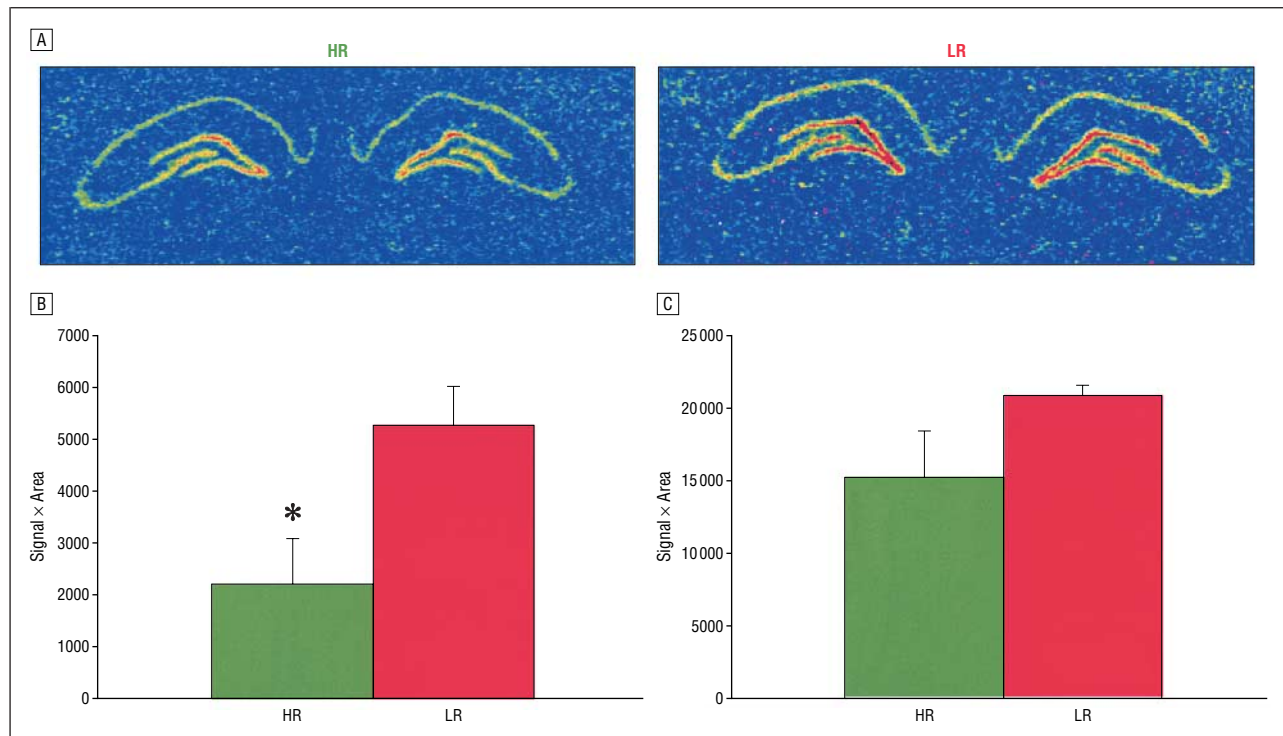


Figure 2. A, Basal serotonin (5-HT) receptor 5-HT1a messenger RNA (mRNA) expression in the hippocampus of rats with high locomotor response (HR) and low locomotor response (LR): color-enhanced photomicrograph from x-ray films exposed for 5 days after in situ hybridization with antisense complementary RNA probes against rat 5-HT1a mRNA. Compared with LR rats (n=5), HR rats (n=5) exhibit significantly lower 5-HT1a mRNA expression in the CA1 area of the hippocampus. There was no significant difference between HR and LR rats in 5-HT1a mRNA expression in the dentate gyrus (DG). B, Individual differences in 5-HT1a in CA1. C, Individual differences in 5-HT1a in DG. Optical density measurements were analyzed with a 2-way analysis of variance. The between-subject factor was HR-LR, and the within-subject factor was the brain area analyzed. Analysis of variance was followed by post hoc Fisher exact test. The level of significance was set up at 5%. Asterisk indicates $P < .05$.

tant role of these receptors in anxiety behaviors. Indeed, while 5-HT1a knockout mice exhibit a substantial increase in anxiety,¹⁴ 5-HT1b knockout mice exhibit decreased anxiety.¹⁵ The knockout findings are concordant with other studies. For example, administration of 5-HT1a agonists into the hippocampus or dorsal raphe decreases anxiety-like behavior in some animal models, an effect blocked by 5-HT1a antagonists.¹⁶ Our results on 5-HT1a and 5-HT2a are therefore promising and may relate to the differential emotional states of HR and LR rats.

Hyperactivity of the HPA axis is a well-documented phenomenon in major depression. This dysregulation is manifested by cortisol hypersecretion, failure to suppress cortisol secretion after dexamethasone administration, exaggerated adrenal responses to endocrine challenges, and blunted adrenocorticotropic hormone responses to CRH administration.¹⁷ The HR-LR differences in expression of genes related to the stress circuitry have been explored, and decreased CRH expres-

sion in the central nucleus of the amygdala of HR rats compared with LR rats was reported.⁵ This finding is consistent with their phenotype of decreased anxiety behaviors. Indeed, when injected into the amygdala, CRH antagonists reduce fear-related responses,¹⁸ and lesions of the central nucleus of the amygdala disrupt CRH-potentiated conditioned fear responses.¹⁹ This evidence supports the idea that CRH in the central nucleus of the amygdala produces anxiogenic effects. The amygdala plays a major role in emotional responses to aversive stimuli.²⁰ Low levels of CRH in the central nucleus of the amygdala in HR rats might represent one of the factors that allow them to engage in novelty-seeking behavior.

Another critical component of the differences in anxiety-related behaviors between HR and LR rats is the finding that hippocampal expression of glucocorticoid receptors was significantly decreased in HR rats (M.K., Piervencenzo Piazza, MD, PhD, Michel Le Moal, MD, PhD, and Stefania Maccari, PhD, un-

published data, 1996). This decrease in glucocorticoid receptors expression is responsible for the decreased anxiety that is apparent in HR rats when exploring an anxiogenic environment. This was studied in an experiment that revealed that a glucocorticoid receptor antagonist could lead LR rats to behave indistinguishably from HR rats in terms of their response pattern in an anxiety test and their locomotor response to novelty.⁵ Along with the differential corticosterone responses of HR and LR rats when exposed to novel environments described herein, these studies support the notion that glucocorticoids and their receptors may represent a critical switching mechanism in the way stressful events modulate emotional behavior, at rest and following stress.

CONCLUSIONS

Many questions arise about the cause of these individual differences: is it genetic, is it maternal behavior, and will a certain initial tendency that

was genetic or developmental alter behavior in such a way as to further bias the gene expression, enhancing the individual differences? Regardless of the cause, such a behavioral and neuronal phenotype may serve as a substrate for alterations of emotional reactivity.

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