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BRAIN RESEARCH

Research Report

Drug-induced and genetic alterations in stress-responsive systems: Implications for specific addictive diseases

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ABSTRACT

From the earliest work in our laboratory, we hypothesized, and with studies conducted in both clinical research and animal models, we have shown that drugs of abuse, administered or self-administered, on a chronic basis, profoundly alter stress-responsive systems. Alterations of expression of specific genes involved in stress responsivity, with increases or decreases in mRNA levels, receptor, and neuropeptide levels, and resultant changes in hormone levels, have been documented to occur after chronic intermittent exposure to heroin, morphine, other opiates, cocaine, other stimulants, and alcohol in animal models and in human molecular genetics. The best studied of the stress-responsive systems in humans and mammalian species in general is undoubtedly the HPA axis. In addition, there are stress-responsive systems in other parts in the brain itself, and some of these include components of the HPA axis, such as CRF and CRF receptors, along with POMC gene and gene products. Several other stress-responsive systems are known to influence the HPA axis, such as the vasopressin–vasopressin receptor system. Orexin–hypocretin, acting at its receptors, may effect changes which suggest that it should be properly categorized as a stress-responsive system. However, less is known about the interactions and connectivity of some of these different neuropeptide and receptor systems, and in particular, about the possible connectivity of fast-acting (e.g., glutamate and GABA) and slow-acting (including dopamine, serotonin, and norepinephrine) neurotransmitters with each of these stress-responsive components and the resultant impact, especially in the setting of chronic exposure to drugs of abuse. Several of these stress-responsive systems and components, primarily based on our laboratory-based and human molecular genetics research of addictive diseases, will be briefly discussed in this review.

1. Introduction

The hypothalamic–pituitary–adrenal (HPA) axis is undoubtedly the best studied stress-responsive system, initially with studies in rodent models and subsequently in humans and non-human primates. Although there are several differences, both in components of this axis and then the regulation of each of the components across species, there are also many similarities (see Fig. 1). In this axis, corticotropin-releasing factor (CRF) processed from the CRF gene in the hypothalamus travels to the anterior pituitary where it acts upon CRF-R_1 receptors to bring about the production and release of the gene

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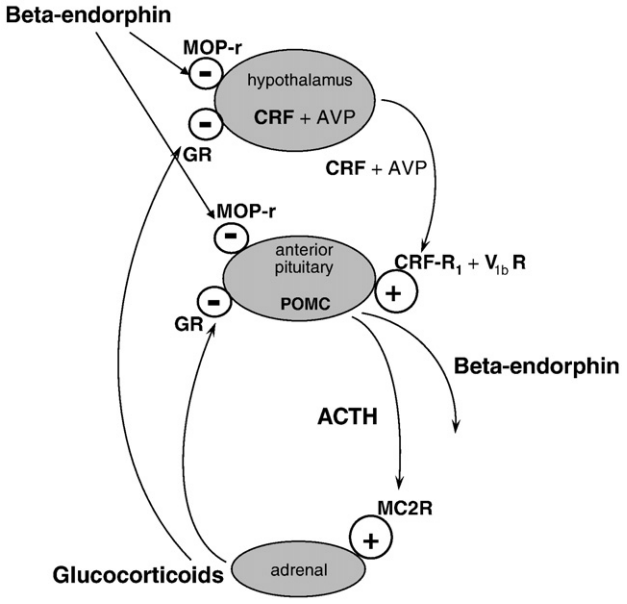

Fig. 1 – Hypothalamic–pituitary–adrenal axis. Stress causes increased mRNA synthesis and release of hypothalamic CRF and AVP into the portal circulation, which acts on CRF-R_1 receptors and V_{1b} receptor in the anterior pituitary, respectively. This induces synthesis of POMC mRNA and peptide in the corticotrope of the anterior pituitary and release into the circulation of beta-endorphin and ACTH, which are derived from processing of POMC. ACTH acts on ACTH receptor (MC2R) in the adrenal cortex and induces release of the stress hormone cortisol (in humans and guinea pigs) or corticosterone (in rats and mice), which are primary mediators of the stress response. Cortisol or corticosterone exerts negative feedback regulation at both the hypothalamus and the pituitary to inhibit the synthesis of POMC and release of ACTH and beta-endorphin via glucocorticoid receptors (GR). In addition to this classical circadian negative feedback regulation by glucocorticoids, the endogenous opioid system, especially the mu-opioid receptors (MOP-r), tonically inhibits this axis.

product proopiomelanocortin (POMC). This is further processed in the pituitary to yield several extremely important hormones, including the major stress-responsive hormone in the mammalian species, adrenocorticotropin hormone (ACTH), as well as beta-endorphin, the longest (31 amino acids) and longest-acting (over 30 min in humans) endogenous opioid, and which is both peripherally active, as well as active in the central nervous system. Other very important neuropeptides are processed from the single gene product of POMC. These include alpha-, beta-, and gamma-melanotropin (melanocyte-stimulating hormone or MSH), as well as other neuropeptides. Some of these have been closely linked to appetitive behaviors and, thus, feeding disorders.

The focus of this review article is to be on the role of stress responsivity in the impact of drugs of abuse and the implications of those effects on stress responsivity in the development of and perpetuation of specific addictive diseases.

ACTH acts primarily on the adrenal cortex where it brings about the processing and release of all the enzymes in pathways leading to the production of cortisol in humans, non-human primates and guinea pigs, and also corticosterone in rats and mice. In turn, those glucocorticoids, in addition to acting at diffuse sites of the body to assure overall response to stress, including sugar and fat mobilization and metabolism, also act in a negative feedback mode by decreasing production and release of CRF in the hypothalamus and also act directly in the anterior pituitary, bringing about reduction of processing and release of POMC and its neuropeptides. Studies of many other groups have shown that the glucocorticoids act in the hippocampus, where the functional relationships to stress responsivity are less clearly delineated, but seem to be closely associated with reduction in hippocampal size when there is chronic exposure to excessive levels of glucocorticoids and thus to a decrement in learning and memory (see reviews of McEwen, 1980; McEwen et al., 1992; Kreek, 1996a,b, 1997; Kreek and Koob, 1998; Kreek, 2000; Kreek et al., 2002, 2004, 2009). In addition to the important negative feedback control of the HPA axis by the glucocorticoids, it has been found that mu-opioid receptor activation by beta-endorphin, or possibly one of the mu-opioid receptor-directed enkephalins, apparently tonically inhibits both production of CRF in the hypothalamus and POMC peptides in the anterior pituitary (Kreek, 1973a; Volavka et al., 1980; Kreek et al., 1983a; Kosten et al., 1986a,b; Culpepper-Morgan et al., 1992; Culpepper-Morgan and Kreek, 1997; Schluger et al., 1998; Farren et al., 1999; Rosen et al., 1999). It is not known whether this opioid inhibition of CRF and POMC occurs in other parts of the brain. However, negative inhibition of CRF and POMC by glucocorticoids in other regions of the brain has been studied to a modest extent, and in these other regions of gene expression, there does not seem to be negative feedback modulation by the glucocorticoid system. All of these neuroendocrine systems discussed in these four paragraphs have been extensively reviewed in textbooks of endocrinology and do not necessarily represent the work from our laboratory, although we have included comments from our laboratory, when particularly pertinent, such as our contribution of discovering the opioid control of the human HPA stress-responsive axis, which we will not detail further in this review.

Both CRF and its CRF-R_1 receptor (as well as the CRF-R_2 receptor, which has as its primary ligands the urocortins, which will not be further detailed in this brief review) are located in other parts of the brain beyond the hypothalamus (see Table 1). Regions which are of particular interest to our group, prefrontal cortex and amygdala, are brain regions in which the genes of the CRF and CRF-R_1 are expressed (measurable mRNA levels) (see Table 1). Also, gene expression of POMC has been identified in several brain regions in addition to the anterior pituitary. However, the use of very modern extended-range mass spectrometric analyses to determine the precise processing of the single gene product, POMC, to specific neuropeptides in different brain regions has not been extensively pursued.

Another neuropeptide system, the vasopressin system, was identified years ago but only modestly studied over many years; it is also known to directly impact upon the HPA axis in humans. Both early work and more recent work from our laboratory, and