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Peptides and Psychiatry

Since the 1970s, much has been learned about the role of peptides in the central nervous system (neuropeptides) and behavior. Originally thought to be rare and relatively unimportant compared to the classical neurotransmitters, they are now known to be nearly ubiquitous and extremely important in brain function. Like the 'classical' small molecule neurotransmitters, neuropeptides function as chemical mediators of neuron to neuron communication. However, unlike such classical neurotransmitters, the neuropeptides have often been evolutionarily conserved to act both as local transmitter modulators and as endocrine hormones, thus mediating complex patterns of integrated behavior.

The role of neuropeptides in facilitating complex aspects of behavior makes them ideal candidates in understanding the neurobiological bases of psychiatric disorders. Whereas the classical neurotransmitter systems are involved in the neuronal circuitry mediating all behavior and pathology, the neuropeptide systems appear anatomically distributed, but functionally more limited. Thus these systems may allow an understanding of the physiology and pathophysiology of behavioral repertoires along with the ability to treat psychiatric disorders with more specific treatment modalities. This article will briefly review neuropeptide biology and function in general. Several specific examples of neuropeptides with known behavioral significance are discussed, allowing some generalizations to be made connecting physiological behavior to pathologic disease states.

1. Neuropeptide Biology

Like the classical small neurotransmitters, neuropeptides also function as chemical mediators of neuron to neuron communication via presynaptic release onto postsynaptic receptors. Some neuropeptides serve their function primarily within the central nervous system (CNS), e.g., galanin and enkephalin. However,

other neuropeptides serve as both neurotransmitters and endocrine hormones via pituitary release to act on peripheral sites, e.g., oxytocin and vasopressin. Other neuropeptides serve as local neuromodulators within the brain but also as hormone-releasing factors in the hypothalamus–pituitary system, e.g., corticotropin-releasing factor and thyrotropin-releasing hormone. Finally, some neuropeptides appear to have distinct and separate roles in CNS and periphery, e.g., neurotensin and cholecystokinin.

1.1 Neuropeptide Production

The classical neurotransmitters (i.e., glutamate, GABA, dopamine, serotonin, norepinephrine, and acetylcholine) are formed from small molecule precursors in the cytoplasm, often stored at the terminals where the neurotransmitter is packaged into vesicle pools. Control of pool size is a function of enzyme concentration and precursor availability. In contrast, peptides are the direct products of mRNA translation, essentially small protein products. Most neuropeptides are between 2 and 40 amino acids in length. They are initially formed as larger precursor proteins (pre-hormones) by translation of mRNA into polypeptides that are then cleaved into various active smaller peptides. Within the cell body, vesicles of neuropeptides are packaged in the Golgi apparatus and then transported to the distal regions (axons and dendrites) of the neuron where they are released with neuronal activity. Control of neuropeptide availability is therefore largely a direct function of gene transcription and translation. Thus, change of neuropeptide expression occurs as a function of multiple hormonal and other modulatory influences on neuronal function.

1.2 Neuropeptide Release and Inactivation

Discovered as early as 1940 by the Scharrers, a husband and wife team, peptides are located in secretory granules (vesicles) at the neuronal terminal. Depolarization of the neuronal membrane leads to calcium influx locally, resulting in vesicle fusion with the membrane and release of peptide into the extracellular space. After release from presynaptic nerve terminals, the peptides diffuse across the synaptic cleft, binding to high affinity receptors on the postsynaptic membrane.

Termination of neuropeptide activity occurs when peptidase enzymes cleave the peptides into smaller fragments, disrupting their biologic activity. This is in contrast to small neurotransmitters that are removed from the synaptic cleft primarily by reuptake into the presynaptic terminal, with only modest breakdown by metabolic enzymes in the extracellular space. These

differences in inactivation generally lead to substantially longer periods of activity by the neuropeptides. Numerous peptidases have now been identified from endopeptidases to carboxypeptidases with differential specificities and different solubility vs. membrane-bound characteristics. These may differ among the different neuropeptide systems.

1.3 Neuropeptide Receptors

Neuropeptide receptors are generally of the G-protein coupled class of seven transmembrane receptors. Peptides released into the synaptic cleft activate these receptors via high-affinity binding and mediate internal signaling events via the cytoplasmic G-protein coupled effector. Activation of these receptors activates and inhibits a variety of second messenger systems and can result in cell firing, modulation of membrane threshold, phosphorylation and dephosphorylation events, and alteration of gene expression. These changes can thus have direct effects on the target cells or can modulate effects of other neurotransmitters. Furthermore, as in the hypothalamic-pituitary system, activation of hormone-releasing factor receptors causes release of other neuropeptides into the periphery, e.g., thyrotropin-releasing hormone activates release of thyroid-stimulating hormone from the thyrotrophs in the pituitary.

1.4 Colocalization of Neuropeptides and Classical Neurotransmitters

Neuropeptides are often found in neurons that also contain one of the small classic neurotransmitters. However, the neuropeptides and small neurotransmitters often have different dynamics of release and subserved different functions. For example, in some neurons with slow firing, release is limited to small neurotransmitter vesicles. With rapid burst firing and prolonged depolarization, however, the calcium concentration in the presynaptic terminal is significantly elevated, leading to release of neuropeptide vesicles in addition to neurotransmitter. Thus the different dynamics of release along with differential receptor activation allow these colocalized mediators to carry different functional signals in neuronal circuitry.

2. Behavioral and Psychiatric Aspects of Neuropeptides

The impetus for understanding neuropeptide biology since the 1970s has led to great advances in endocrinology and has had a significant impact on psychiatry. It is becoming increasingly evident that many

psychiatric disorders are associated with neuropeptide abnormalities. Alterations in specific neuropeptide-containing neurons have been shown in Alzheimer's disease, Parkinson's disease, Huntington's disease, mood disorders, anxiety disorders, eating disorders, and schizophrenia.

There are over 100 neuropeptides now identified and currently being scrutinized. This rapid expanse of knowledge cannot be summarized here. Therefore, a few examples of neuropeptide systems are discussed below which have known behavioral, physiological, and pathological significance. As with those discussed below, many neuropeptides have multiple roles in somatic sites, the central nervous system, and as hormonal mediators linking them. Understanding the physiologic role of these molecules will likely guide the understanding of pathophysiology and treatment of the psychiatric disorders in which they are involved.

2.1 Corticotropin-releasing Factor—Model of Integrated Stress Response

Corticotropin-releasing factor (CRF) was originally identified in crude form in 1955 and finally structurally identified in 1981 as a 41 amino acid peptide. It is the primary stimulant of adrenocorticotropic hormone (ACTH) release from the anterior pituitary, initiating the hypothalamic-pituitary-adrenal (HPA) peripheral stress response. It clearly also functions as a putative neurotransmitter in the brain coordinating global responses to stressors. In higher organisms, CRF appears to mediate a complex behavioral program integrating the endocrine, immunologic, autonomic, and behavioral responses to stress.

CRF appears to be of crucial importance in many psychiatric disorders. Dysregulation of the HPA axis in major depression has been one of the most consistent findings in biological psychiatry since these abnormalities were first identified. As the field continues to understand the nature vs. nurture debate of psychopathology, the role of the endogenous stress response system in the stress-diathesis model of affective and anxiety disorders becomes paramount.

2.1.1 CRF, the physiologic mediator of stress. There is now abundant evidence that CRF and related peptides are the primary central nervous system (CNS) mediators of stress. Stress, *per se*, is generally defined as extraordinary demand on the organism or alterations in psychological homeostatic processes. Initially, the importance of CRF was thought to be primarily endocrine via activation of ACTH from the pituitary, with subsequent release of cortisol and other glucocorticoids from the adrenal gland. Since the 1980s, however, its role in the brain independent of the

HPA axis has been firmly established. Consistent with its role as a neurotransmitter mediating complex repertoires, CNS administration of CRF mimics many of the behaviors and autonomic responses seen with physiologic stress.

Neurons expressing and releasing CRF are located in neuroanatomic locations which are thought to be critical for the stress response, including areas of neocortex, limbic system, and midbrain. In the limbic system, the central amygdala and bed nucleus of the *stria terminalis* are regions of the so-called 'extended amygdala' believed to be involved in stress and anxiety. CRF neurons from these regions project to many midbrain and brainstem sites mediating internal stress responses. The *locus coeruleus* and the *raphe nucleus* in the midbrain receive these CRF projections, influencing the activation of norepinephrine and serotonin circuits, respectively. Thus stress activation of the CRF system can disrupt attention and vigilance, concentration and memory, sleep and wakefulness via these transmitter systems, and it is likely involved in their abnormal functioning in mood and anxiety disorders.

There are multiple experimental paradigms further implicating the central CRF system as the prime mediator of the acute and prolonged stress response. Rodents administered CRF directly into the CNS show decreased reproductive behaviors, altered sleep, increased grooming, increased signs of despair, increased neophobia, and altered appetite, all of which mimic the behavioral stress response. Furthermore, rodents raised with early life stress (primarily maternal separation) hypersecrete CRF from the hypothalamus and amygdala, both during the stress and later as adults.

Administration of CRF into the CNS of nonhuman primates elicits many signs of behavioral despair including increased vocalization, decreased exploration, and increased huddling. These effects are reversed by CRF receptor antagonists, as are the behavioral consequences of environmental stress. Consistent with these experiments are early studies of maternal deprivation in young Bonnet macaque monkeys. These experimental animals exhibited sustained behavioral despair with decreased locomotion, decreased exploration, and altered food intake, similar to those animals with centrally administered CRF. These animals persistently exhibited a prolonged activation of the HPA axis with elevated cortisol and ACTH peripherally.

Stress exposure to maternal-infant dyads without separation appears to have similar long-term effects. Young Bonnet macaques raised in naturalistic settings by mothers with an unpredictable food supply showed increased signs of anxiety compared to those with a predictable food supply. These symptoms were accompanied by elevated CSF CRF concentrations. Remarkably, the grown youngsters consistently showed continued signs of anxiety and affective

disturbance after removal from these stressful living constraints, and their CNS CRF and HPA axis activity remained hypersensitive to other stressors later in life.

2.1.2 CRF, the pathologic mediator of depression and anxiety. The preceding paragraphs suggest that the CRF system must play a critical role in the development of stress-related disorders. It is now becoming increasingly clear that depressive and anxiety disorders have significant inheritable and environmental components. The likelihood of an individual to develop an affective disorder is related to genetic vulnerability in addition to his or her biologic capacity to respond to stress. The experiments above suggest that this capacity is somewhat plastic, influenced by extent of early life stress. Multiple lines of evidence have shown that CNS CRF systems are altered in mood and anxiety disorders.

Many studies have reproduced the early findings that CRF CSF concentrations are elevated in depressed individuals compared to healthy comparison subjects, and that the levels resolve with resolution of the depressed state. Dysregulation of the HPA axis also continues to be validated. The CRF stimulation test (depressed patients show a blunted ACTH response) along with the Dexamethasone Suppression Test (depressed patients do not suppress cortisol) as well as the combined Dex/CRF test developed by Holsboer remain very sensitive tests of major depressive disorder. Furthermore, MRI and CT evidence has revealed increased pituitary and adrenal gland size in depression, consistent with hypersecretion of CRF and ACTH, respectively.

The role of CRF in anxiety disorders is also likely critical, though less well established than in depression. In animal models, direct CNS CRF administration is markedly anxiogenic, and conversely CRF receptor antagonists are anxiolytic. In experimental models, alprazolam, a short acting benzodiazepine, leads to decreased *locus coeruleus* CRF concentrations after acute administration, an effect which may mediate its anxiolytic action. Patients with post-traumatic stress disorder (PTSD) also exhibit elevated CRF concentrations in CSF and a blunted ACTH response to CRF challenge. However, they are hypocortisolemic and exhibit supersuppression to dexamethasone, suggesting that they differ from patients with depression.

In summary, the effects of CRF administration mimic acute anxiety and chronic depression, CRF₁ receptor antagonists block some of these symptoms in model systems, and patients with depressive and anxiety disorders show alterations of the central and peripheral CRF-HPA system. These data are nicely linked to a growing understanding of the developmental role of stress on the CRF system and its possible *sequellae* later in life. This allows a reformulation of the stress-diathesis model: early untoward life

events associated with development of depression and anxiety in adulthood give rise to long-lasting changes in CRF neurons, thus increasing the individuals' vulnerability to affective and anxiety disorders. See *Depression; Anxiety and Anxiety Disorders*.

2.2 Oxytocin and Vasopressin—Models for Complex Behavioral Regulation

Oxytocin (OT) and vasopressin (AVP) are members of the same nine amino acid class of peptides and have similar behavioral effects. Due to their interactions and similar effect on behavior, they will be considered together here. These peptides are best characterized in terms of organizing a complex behavior, that of social affiliation. This includes reproductive behavior, parental behavior, parent–child bonding, and grooming–sitting together behaviors in nonhuman primates. They are recently evolved and mediate many mammalian-specific reproductive and social behaviors. However, there are profound species differences in receptor expression, which in some cases mediates species-specific sets of behavior.

2.2.1 Oxytocin and vasopressin mediate social interaction.

The best known peripheral effects of OT are facilitation of lactation–milk ejection, and uterine contraction during labor. AVP serves in the periphery primarily to regulate blood pressure and plasma volume. These functions are mediated via the magnocellular neurons projecting from the paraventricular nucleus (PVN) of the hypothalamus to the posterior pituitary where the peptides are released into the general circulation. Central effects are mediated via the PVN projection of parvocellular neurons to areas of the limbic system, neocortex, and autonomic areas of the brainstem. These central effects include modulation of reproductive behavior, parental behavior, infant attachment, and other prosocial effects.

One of the best studied models of affiliation is the formation of pair bonds. Multiple lines of evidence have demonstrated that in several rodent model systems, OT and AVP are critical for these behaviors. The prairie vole has been an excellent model for these studies because these animals are highly affiliative, show strong monogamous behavior, frequent physical contact, nest building, and shared parental care. OT in females and AVP in males appears to be responsible for formation of partner preference. In this species, mating facilitates pair bond formation, and OT and AVP are released centrally with mating. OT antagonists in females and AVP antagonists in males block formation of the partner preference, whereas the respective agonists administered centrally facilitate partner preference in the absence of mating. These results suggest that these peptides are both necessary

and sufficient for this aspect of pair bonding. Furthermore, a closely related species, the montane vole, shares many similar nonsocial behaviors with the prairie vole, but they are generally isolative, are clearly not monogamous, and males show little parental care. The critical difference in species appears to be the regulation of the OT and AVP receptor distribution in the brain. For example, the prairie vole has OT receptors in regions important for reward (*nucleus accumbens* and prefrontal cortex), whereas the montane vole shows primary distribution in the lateral septum, possibly responsible for the peptide's effect on self-grooming, but poor socialization. This is supported by evidence that centrally administered AVP increases affiliative behavior in the monogamous prairie vole, but not the montane vole. Furthermore, transgenic mice expressing the AVP receptor in the prairie vole brain distribution pattern results in a prosocial response to centrally administered AVP.

Parental behavior and infant attachment also appear to be dependent on OT and AVP systems. Parturition is associated with significant shifts in maternal behavior in some species, including relentless nest building, licking, grooming, and protection of the pups. These behaviors are blocked by central administration of OT receptor antagonists. Neonatal voles crave social contact with 'distress calls' vocalized in as early as five-day old pups with maternal separation. Centrally administered OT in eight-day old pups results in significantly reduced distress calls, but no evidence of sedation or other behavioral change, suggesting that OT influences the maternal separation response.

Evidence for other social behaviors mediated by these systems include increased levels of social grooming by centrally administered OT or AVP, and the correlation of decreased plasma OT with increased social stressors in primates. Finally, there is an interesting cognitive response to these peptides. Oxytocin appears to facilitate extinction and attenuates passive avoidance. It is hypothesized that these effects may allow the relinquishing of normal social avoidance to establish critical social bonds.

In summary, oxytocin and vasopressin have important roles in the initial affiliative and territorial stages of reproductive behaviors that are dependent on gender and species, along with influences on parental, attachment, and group social behavior. These neuropeptides appear to alter the affective processing of social stimuli via regionally specific regulation of neuropeptide receptors.

2.2.2 Possible roles for oxytocin and vasopressin in psychopathology.

The data for these neuropeptides in animal affiliation suggest that they might also be important in human psychopathology in which relationships or social attachments are abnormal. Measures

of CSF OT and AVP concentrations have yielded inconsistent results in patients with schizophrenia or major depressive illness, though only a handful of studies have been performed. However, post mortem studies have suggested significant changes in several pathological processes. Significant increases in the number of hypothalamus AVP and OT cells have been found in post mortem studies of depressed subjects. Post mortem studies also revealed a > 40 percent decrease in OT cells in the Prader–Willi syndrome, a genetic disorder notable for obesity, mental retardation, hyposexuality, and inappropriate behavior. Several studies have consistently found elevated OT concentrations in OCD subjects, along with normal to elevated concentrations of AVP. One possible explanation for a role in OCD would be the relationship between OT and AVP and grooming behavior and their role in extinguishing avoidant behavior.

Most interesting would be the human disorders along the schizoid spectrum to autism, in which limited interpersonal skills and social impairment are paramount. With autism, the onset is clearly developmental prior to three years old, with most families noting decreased social interest in the first months of life. It is clearly genetically transmitted with monozygotic twins having approximately 36–91 percent concordance, compared to < 0.1 percent in the general population. In one study of autistic children, plasma OT was about half that of age-matched controls. Furthermore, autistic children failed to show the normal developmental increase in OT compared to controls. Although many clinical studies remain to be done (no study of CSF samples is yet reported), the preclinical data suggest that the OT and AVP systems are critical for normal social behavior and memory. Studies are also yet to be reported on the schizoid and avoidant spectrum disorders, but given the specificity of the OT and AVP systems, one suspects that there may be some abnormalities. Given the complexity of OT and AVP receptor gene regulation with known polymorphisms in humans, one could hypothesize that some aspects of social temperament are genetically influenced by the precise expression patterns and regulation of these behaviorally relevant peptides and receptors.

2.3 Cholecystokinin and Neurotensin—Models of Complex Neuromodulators

Cholecystokinin (CCK) and neurotensin (NT) are unrelated, evolutionarily conserved peptides of 8 and 13 amino acids, respectively. They are discussed in this section as examples of the large group of peptides that less clearly integrate a specific behavioral repertoire. They are found in numerous tissues and subserve many different roles including local paracrine, endocrine, and neurotransmitter functions. However,

their similarities are intriguing. They share endocrine functions regulating feeding behavior and induction of satiety in the periphery along with neuromodulatory functions interacting with the primary reward and appetitive circuitry in the central nervous system. Furthermore, there is mounting evidence that they each may play significant roles in the pathophysiology of schizophrenia, and in the case of NT in the mechanism of action of antipsychotic drugs.

2.3.1 Cholecystokinin and neurotensin involvement in feeding, autonomic regulation, and nociception. CCK was one of the first of the gastrointestinal hormones discovered and one of the most abundant neuropeptides in the brain. In contrast, NT was initially discovered from bovine hypothalamic extracts and later found to be an important gastrointestinal hormone. In the periphery, CCK and NT are each released by the small intestine shortly after a meal, and remain elevated in the plasma for several hours. They both stimulate pancreatic and biliary secretion along with modulating small and large intestinal motility. Although they do not cross the blood–brain barrier, they have an apparently conserved function in the CNS. They are both thought to have a role in mediating satiety and inhibiting feeding within the CNS.

They share the property of regulating autonomic and nociceptive information from the midbrain to the cortex. CCK and NT released in the midbrain have been shown to directly modulate excitatory visceral transmission through the parabrachial nucleus to the thalamus. Furthermore, both have been shown to exert potent analgesic effects when injected directly into the CNS. Thus they appear to be involved in regulating sensory information representing the internal state of the organism. Modulation of autonomic outflow is evident by their role in regulating vascular tone and thermoregulation.

2.3.2 Cholecystokinin and neurotensin modulation of dopaminergic systems. In addition to the above functions, CCK and NT appear to be integrally involved in modulating the dopaminergic systems within the brain. Although they are co-localized with other neurotransmitters and modulate serotonin, acetylcholine, and other neuropeptides in some areas, there appears to be a consistent role for these peptides in modulating dopamine circuits. Dopamine (DA) is found in three principle pathways: the mesolimbic/mesocortical pathways involved in motivation, reward, and cortical processing; the nigrostriatal pathways involved in mediation of locomotor movements; and the tuberoinfundibular pathways controlling pituitary release of prolactin. The role of CCK

and NT in modulation of the mesolimbic circuitry originating in the ventral tegmental area (VTA) is of particular interest. Within this mesencephalic nucleus, NT and CCK are co-localized in many dopaminergic neurons that project to the *nucleus accumbens*. NT and CCK are also found in cortical neurons, likely modulating the terminal projections of dopaminergic axons.

Both NT and CCK induce an initial increase in firing rate of dopaminergic neurons when released into VTA, along with an increase in DA release in the *nucleus accumbens*. This increased firing appears to be due to inhibition of D2 autoreceptors by decreasing affinity for DA. This change is thought to occur via intracellular transduction mechanisms and allosteric receptor–receptor interactions between the D2 receptor and the CCK and NT receptors. In contrast, at high doses and with chronic treatment, these peptides significantly decrease spontaneous activity of dopaminergic firing via depolarization inactivation. Thus, these neuropeptides have the ability, *in vivo*, of modulating dopaminergic function at the level of the midbrain and in the projection areas.

Whether the varied roles of feeding behavior, autonomic and nociceptive regulation, and dopaminergic modulation are functionally related is unclear. Some have speculated that these peptides were evolutionarily involved in the primary functions of feeding and feeding regulation. The CNS must be able to organize homeostatic mechanisms around this critical behavior including cardiovascular tone and temperature regulation because much of the blood volume goes to the gut postprandially. Relative analgesia postprandially might be crucial for maintaining the primary function of digestion. Finally, as complex behavior evolved, these neuropeptide systems may have served to couple the primary reward of feeding to the central motivation/reward circuitry.

2.3.3 Cholecystokinin, neurotensin, and schizophrenia. The underlying pathology in schizophrenia remains unknown. The empirical observation that all effective antipsychotics were also dopaminergic antagonists contributed to the original DA hypothesis. However, more recent research has failed to find consistent abnormalities within the dopaminergic system, *per se*, in schizophrenic patients. Additionally, evidence for disturbances in the glutamatergic, GABA-ergic, serotonergic, and cholinergic systems have accrued. One way to reconcile the vast data is that the activity of multiple neurotransmitter systems may be altered via a dysregulation of normal activity. Because neuropeptides are known to play an important role in neurotransmitter modulation, these systems have received increasing attention as both possible mediators of the pathophysiology in schizophrenia as well as potential targets for novel therapeutics.

Although several neuropeptide systems may contribute to the abnormal circuitry in schizophrenia, the majority of data point to NT and CCK as being the most likely candidates of the known neuropeptides. Their role as modulators of the dopaminergic system was outlined above. Additionally, both the serotonergic *raphe nuclei* and brainstem cholinergic nuclei are innervated by peptidergic neurons, especially NT. Within the DA system, these neuropeptides mimic the effects of antipsychotic medication in their acute activation of the VTA dopaminergic neurons and in their chronic inactivation of these neurons. Furthermore, treatment with an NT receptor antagonist appears to mimic atypical antipsychotics in that chronic administration leads to decreased VTA firing, with no effect on the nigrostriatal system. This effect is thought to be mediated via feedback onto the VTA from the prefrontal cortex where local injection of the NT antagonist has the same effect. This would also be consistent with newer theories of schizophrenia which invoke disruption of large mesolimbic–cortical activation loops as mediating the pathophysiologic events.

Behavioral studies with centrally administered NT and CCK also mimic effects of typical and atypical antipsychotic medication. They both decrease stimulant-induced locomotion and spontaneous locomotion. They also decrease avoidance, but not escape, responding in a conditioned avoidance paradigm. Perhaps most importantly, they both appear to effect models of sensorimotor gating, which is becoming increasingly accepted as a critical objective symptom of schizophrenia. The hypothesized decreased ability of these patients to screen for appropriate sensory data may lead to ‘involuntary flooding’ of indifferent sensory input. This might lead to cognitive abnormalities, thought disorganization, and the positive symptoms (hallucinations and delusions) which are hallmarks of schizophrenia. Prepulse inhibition (PPI) of the startle reflex (defined by decreased startle to sound if preceded by weaker sound), and latent inhibition (LI) (reduced associative learning if subject is pre-exposed to stimulus), are the two most common measures of sensorimotor gating. In humans, PPI and LI are disrupted in schizophrenic patients, and are normalized in some studies of schizophrenics treated with antipsychotic medication. In animal models, dopaminergic agonists and other psychomimetic compounds disrupt PPI and LI, and these are returned to normal with antipsychotic treatment. NT and to a lesser extent, CCK, also clearly modulate PPI and LI in animal models. These results provide substantial evidence for the role of NT and possibly CCK in the circuits that are affected by antipsychotic medication.

Finally, there is significant evidence of abnormal regulation of CCK and NT in the CNS of schizophrenic patients. Although no consistent changes have been found post mortem with NT levels, NT receptor binding has reproducibly been found to be decreased

in some cerebrocortical regions in schizophrenia. Concentrations of NT in the CSF are reproducibly decreased in nonmedicated schizophrenics. These levels return to normal with effective treatment, and lower NT concentrations have been correlated with more severe psychopathology, particularly negative symptoms. Similar findings of NT abnormalities have not been found in affective disorders, anorexia, or Alzheimer's disease, suggesting some specificity of the findings in schizophrenia. Post mortem CCK levels have been consistently decreased in cerebrocortical and limbic regions of schizophrenic subjects, but CSF CCK changes have not been as reproducible. See *Schizophrenia, Treatment of*.

3. Summary

Since the 1970s, the biology and behavioral roles of many neuropeptides have been elucidated. They have moved from a position of relative unimportance in behavioral neuroscience to pre-eminence. In their roles as neurotransmitter and neuromodulator, paracrine and endocrine hormone, individual neuropeptides may at times subserve different functions in the CNS and periphery. However, many neuropeptides share a conserved function organizing different neural systems with the periphery in behaviors important for co-ordinated activity of the organism.

Corticotropin-releasing factor is essential in the physiologic mediation of stress, and likely critical in the pathophysiology of depression and anxiety. Oxytocin and AVP subserve many social roles from bonding to parental behavior, and they may underly some pathologic processes involving socialization such as autism. Finally, the peptides NT and CCK have similar roles in feeding, autonomic and analgesic regulation, and DA modulation in the brain. Their dysfunction may contribute to the pathophysiology of schizophrenia.

The knowledge of these neuropeptide systems in psychopathology provides wonderful opportunities for future rational therapeutic approaches. CRF₁ receptor antagonists show great promise in preclinical and early clinical trials for the treatment of depression and anxiety. Oxytocin has been found to improve socialization in some experiments of schizophrenic patients and may provide future hope for autistic disorders. Neurotensin and CCK receptor agonists provide important targets for future system-directed treatment options in schizophrenia. In summary, via their role in the organization of behavioral repertoires, neuropeptide systems may ultimately elucidate mechanisms and provide novel treatment options for many psychiatric diseases.

See also: Endocrinology and Psychiatry; Hypothalamic–Pituitary–Adrenal Axis, Psychobiology of; Neurotransmitters; Women and Psychiatry

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Perception and Action

Perceiving without acting is hardly possible: scrutinizing an object visually presupposes directing the eyes at it, which sometimes involves moving the head or even

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