Oxytocin redux

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CONSIDERED FOR MANY YEARS to be primarily a circulating hormone contributing to parturition and lactation, over the past three decades oxytocin’s broader spectrum of bioactivity has revealed important roles in the control of anterior pituitary hormone secretion, the stress response, social behaviors, cardiovascular control, fluid and electrolyte homeostasis, and appetite regulation. Most of these observations clearly reflect actions not related to release from the neurohypophysis, but instead release from distinct neuronal populations within the central nervous system (CNS) and perhaps even actions of peptide produced outside of the CNS. No longer overshadowed by the intense focus on vasopressin, oxytocin’s anorexigenic and autonomic effects, together with the emerging evidence of its actions on energy expenditure and social cognition, have taken center stage, and the peptide has become recognized to be an important homeostatic regulatory factor.

Soon after its original characterization by Vigneaud and colleagues (14) in 1953, the smooth muscle actions of oxytocin were recognized to be critical for efficient parturition and milk let down (12, 35). Even before its characterization, physiologists had recognized that extracts of posterior pituitary glands stimulated uterine contractions (12). With the realization that distinct receptors for vasopressin and oxytocin existed, and yet some promiscuicity in terms of ligand specificity could be demonstrated, much work in the middle of the 20th century was directed at identifying the unique actions of oxytocin and vasopressin. It came as no surprise that overlapping activities were observed considering the common evolutionary ancestries of not only the two peptides themselves but also their cognate receptors (18).

The classical view of neurohypophysial oxytocin release was challenged when nascent immunohistochemical approaches began to demonstrate broad projections of oxytocin-positive cell fibers throughout the CNS (9), and autoradiographic techniques revealed the presence of oxytocin binding sites in hypothalamic and extrahypothalamic sites (20, 53), many not seemingly related to the conventional physiological actions of the circulating hormone (Fig. 1). Indeed oxytocin-positive fibers are not only present in the internal layer of the rat median eminence but also in the external layer where they intermingle with the fenestrated capillary endothelial cells of the developing hypophysial-portal vasculature (50), suggesting a true neuroendocrine action of the nonapetide in the anterior pituitary gland. Indeed, Gibbs (17) demonstrated the presence of oxytocin in rat hypophysyal portal plasma in levels more than 10 times higher than those in the peripheral circulation (17). By that time oxytocin had been demonstrated to stimulate prolactin secretion at the level of the lactotroph itself (26), an action that was subsequently shown to be physiologically relevant (51). Surprisingly, oxytocin also exerted hypothalamic actions to inhibit prolactin secretion, suggesting a negative feedback mechanism balancing appropriate hormone secretion under selective physiological states (49). An even bigger surprise was the revelation that oxytocin interacted with hypothalamic circuits controlling gonadotropin secretion. Those studies were the first to employ plant lectin-based cytotoxin approaches to determine the physiological relevance of the pharmacological action of a neuropeptide in hypothalamic function (50).

The ricin-oxytocin cytotoxin targeting methodology was also applied to the study of oxytocin’s central action to inhibit salt appetite (3, 4). Those authors not only demonstrated the physiological relevance of the CNS actions of oxytocin in osmotically driven salt appetite but also presented evidence for a sodium receptor mechanism independent of the osmotic mechanisms regulating salt appetite (4). Subsequent studies by Morris and colleagues (44) employing oxytocin gene-knockout mice further evidenced a physiologically relevant role for oxytocin in salt appetite. Where oxytocin acts in CNS to express these actions remains unknown; however, Verbalis and colleagues (39) did speculate that these actions of oxytocin might reflect a broader action of the peptide to inhibit solute ingestion.

The realization that oxytocin-positive neurons (9, 34, 52, 54, 55) innervated CNS sites known to be important in cardiovascular function suggested autonomic actions. Indeed the broad distribution of oxytocin receptor mRNA expression throughout the CNS, but specifically in brain stem sites important to cardiovascular and respiratory control, supported that hypothesis (61). Although controversial in the beginning (15, 42), oxytocin has been demonstrated to activate the autonomic system when administered into the cerebroventricles (41) or directly into the rostral ventrolateral medulla (27). Oxytocin gene knockout mice were reported to display mild hypotension (30, 44). Oxytocin-positive neurons have been observed to colocalize with sympathetic preganglionic neurons in the thoracic spinal cord (57), and the peptide has been demonstrated to activate these neurons in vitro (13). Local application of oxytocin increased heart rate in anesthetized rats, and the ability of PVN stimulation to increase heart rate was blocked by oxytocin antagonists administered into the same area of spinal cord (64). More recently, the ability of oxytocin antagonist pretreatment in the lateral ventricle to abrogate the actions of CRH and nesfatin-1 to elevate mean arterial pressure when administered also into the lateral ventricle suggested that oxytocin not only acts directly to activate sympathetic outflow but also interacts with a variety of other neural circuits influencing autonomic function (66). The interaction of oxytocin with CRH and stress circuitry (11, 54, 66) may underlie some of the prosocial actions of oxytocin (63, 67) as well as the appetitive actions of the peptide (37).

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Recently, against the backdrop of the numerous, diverse studies on oxytocin’s pharmacological and physiological effects, great interest has developed in its anorexigenic actions (48). Here is where rapid progress is being made not only in studies conducted in laboratory animals (rodents) but also in those in nonhuman primates and humans. Evidence for the anorexigenic action of oxytocin arose from animal studies conducted over 25 yr ago (2, 39), which identified not only the anorexigenic action of oxytocin but also its ability to inhibit gastric motility (16, 47). It should be noted that nausea-producing chemical agents and cholecystokinin, itself a potent anorexigenic agent, stimulate oxytocin release (38, 60). Those initial pharmacological studies were extended by the observations that oxytocin gene deletion resulted in increased sucrose ingestion (1). The oxytocin knockout animals also ingested increased sodium chloride solutions (44). Furthermore, oxytocin receptor-deficient mice developed late-onset obesity (59), as did the oxytocin-deficient animals (10).

Recent insight into the mechanisms underlying the anorexigenic actions of oxytocin has come from studies by Blevins and colleagues (7, 8) in Seattle. They have demonstrated that both central and peripheral administration of oxytocin decreased food intake and body weight in normal rats, leptin receptor-deficient rats, and diet-induced obese animals (19, 31). Furthermore, Blevins and colleagues (6) have presented evidence that peripheral oxytocin administration to male, obese rhesus monkeys reduced food intake and body weight, while increasing energy expenditure and lipolysis. Several potential sites of action of oxytocin in brain have been demonstrated the ventromedial hypothalamic nucleus (36), the arcuate nucleus (28), the ventral tegmental area (32), and the nucleus tractus solitarius (40). Which sites are most important remains to be determined; however, the brain stem action (40) holds promise for one important reason. Rinaman (45) had demonstrated that oxytocin fibers innervate the nucleus tractus solitarius, and Rinamin and Rothe (46), that GLP-1 signaling is necessary for the anorexigenic action of oxytocin. Recently, Grill and colleagues (40) extended that work by demonstrating that a medial nucleus tractus solitarius site of action of oxytocin to augment vagal afferent signal processing follows a nutrient preload, a procedure that also increased oxytocin content in this region.

Endocrine actions

Milk letdown (+)
Parturition (+)

Neuroendocrine actions

PRL (+)
ACTH (+)

Social cognition (+)
Stress response (+)

Affiliative behavior (+)

Appetite regulation
Food (–)
Salt (–)

Autonomic regulation (+)

OT

Fig. 1. In addition to its neuroendocrine actions in the anterior pituitary gland (AP) and endocrine effects when released from the posterior pituitary (PP), oxytocin exerts multiple behavioral actions in brain, some stimulatory (+), while others inhibitory (–) in nature. PRL, prolactin; ACTH, adrenocorticotropin.

The importance of these findings resides in the fact that blood brain-penetrant oxytocin analogs may be developed that can access this area for therapeutic purposes [for an excellent review, see Blevins and Baskin (5)]. Indeed, Blevins and colleagues have demonstrated the ability of peripherally administered oxytocin to significantly reduce food intake (19, 31), raising the possibility that circulating oxytocin may access brain areas important in appetite regulation via sites where the blood brain barrier is “leaky.” However, one cannot rule out the possibility that the anorexigenic effect of those injections resulted from activation of vagal afferents themselves (16, 38, 47, 60, 62). Although it has been estimated that very little circulating oxytocin actually penetrates back into the brain (29), it is possible that there is a link between the central actions of the peptide on energy use and its action on adipocytes to stimulate lipolysis (65).

Do the experimental findings in animals translate to humans? Neumann and Slattery (33) recently reviewed the literature on the effects of oxytocin administration on anxiety-related behaviors in rodents and in that review identified parallels to results emerging from human studies, where correlations between anxiety state and social recognition/fear have been drawn. Furthermore, although the mechanisms certainly have yet to be established, oxytocin administration in humans has resulted in positive emotional outcomes (33, 43). Lawson and colleagues (22, 23) demonstrated an association between elevated postprandial plasma oxytocin levels and the severity of disordered eating in patients with anorexia nervosa. Furthermore, the hyperphagia of Prader-Willi Syndrome has been hypothesized to be a result of decreased oxytocin production in the paraventricular nucleus of those individuals (56). Similarly, the obesity of single-minded 1-gene SIM1 variants is accompanied by oxytocin deficiency (58), and the condition in mice can be reversed by oxytocin treatment (21). These observations set the stage for the very promising studies reported by Lawson and colleagues (24) in which they administered intranasal oxytocin to healthy fasting men. The results of this crossover study demonstrated that intranasal oxytocin reduced caloric intake and increased circulating levels of the anorexigenic hormone cholecystokinin without altering arterial pressure or heart rate. Respiratory quotient was reduced by oxytocin ad-
ministration, suggesting increased fat use and improved insulin sensitivity.

This initial work by Lawson and coworkers (24) certainly will lead to even more intense study of the possible therapeutic value of oxytocin for the treatment of eating disorders. Issues of safety and efficacy under conditions of long-range therapy must be examined, but it is clear that the wealth of literature supports the potential for the development of oxytocin-based analogs for the treatment of obesity and associated comorbidities (5, 6), as well as affective disorders (33). The potential behavioral and cardiovascular consequences resulting from this approach, of course, will have to be carefully scrutinized, as the efficacy of, and the mechanisms underlying, the effects of intranasal oxytocin remain controversial (25, 43).

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