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SCIENTIFIC REVIEWS

Opioid Control of Renal Excretion of Water and Sodium

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Summary : *The kidneys act to regulate total body water and sodium via numerous neural and humoral mechanisms, including pathways that involve the renal sympathetic nerves, antidiuretic hormone, atrial natriuretic factor, and the renin-angiotensin-aldosterone system. In addition to these pathways, evidence indicates that opioid peptide systems participate in regulation of the renal excretory function by modulating neural and/or humoral pathways within the kidneys, periphery or central nervous system. Briefly, this premise stems from the following findings: a) central, peripheral, and intrarenal administration of native and synthetic opioid agonists produces changes in the renal excretion of water and sodium, b) endogenous central opioid mechanisms participate in the cardiovascular and renal responses produced by psychoemotional (air jet stress) and dietary (sodium deficiency) stress, and c) endogenous opioid systems contribute to the deranged renal excretory responses observed in the pathology of cirrhosis with ascites.*

The actions of opioids are mediated by 3 types of opioid receptors named mu, kappa and delta. Administration of selective opioid agonists can produce diuresis/antidiuresis and natriuresis/antinatriuresis depending on the type of opioid receptors activated. To completely understand how opioid systems influence kidney function, it is important to understand how each opioid system acts individually or in concert to alter renal function. In that regard, considerable research has been performed to elucidate the role of mu, kappa, delta and the recently discovered opioid receptor-like 1(ORL-1) receptors in renal excretory function.

The purpose of this article is to provide a brief review of the particular renal responses produced by opioids and the mechanism(s) by which these compounds affect renal function.

Key Words: *opioids, kidney, diuresis, natriuresis, ADH, renal sympathetic nerves*

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Su ve Sodyumun Böbreklerden Atılımının Opioid Kontrolü

Özet : *Vücudun su ve sodyum dengesinin böbrekler tarafından düzenlenmesinde pek çok nöronal ve hormonal faktörler (renal sempatik sinirler, antidüretik hormon, atriyal natriüretik faktör, renin-anjiyotensin-aldosteron sistemi gibi) rol oynarlar. Bunlara ilave olarak, opioid sistemlerin de renal fonksiyonun regülasyonunda rol oynadığı şu bulgulara dayanılarak önerilmektedir: a). doğal veya sentetik opioid agonistlerin direkt santral, periferik veya intrarenal olarak uygulanmalarının renal su ve sodyum atımında değişikliğe neden olması, b). endojen santral opioid mekanizmaların farklı stress modellerinde oluşan renal fonksiyon değişikliklerinde rol oynaması, c). vücudun sıvı dengesinin bozulduğu patolojilerde gözlenen renal atım bozukluklarında endojen opioid sistem fonksiyonu değişikliklerin rol oynaması.*

Opiodlerin etkileri mu, kappa ve delta olarak adlandırılan başlıca 3 tip opioid reseptörü aracılığı ile oluşur. Opioidlerin renal fonksiyon regulasyonuna etkilerinin incelendiği pek çok çalışmada, selektif opioid reseptör agonistlerinin uygulamasının,etkilediği reseptöre bağlı olarak diürez/antidiürez ve natriürez/antinatriürez oluşturduğu gösterilmiştir. Opioid sistemlerin böbrek fonksiyonunu nasıl etkilediğinin anlaşılmasında her bir opioid reseptör alttipinin renal su ve sodyum atılımına etkilerinin anlaşılması önem taşımaktadir. Bu kapsamda, mu, kappa, delta ve yeni tanımlanan ORL-1 reseptörlerinin renal fonksiyona etkilerini tanımlamaya yönelik pek çok çalışma yapılmıştır. Bu makalenin amacı, çeşitli opioidlerin renal su ve sodyum atımına etkileri ve etki mekanizmalarının anlaşılmasına yönelik çalışmaların değerlendirilmesidir.

Anahtar kelimeler: *opioid, renal, diürez, natriürez, ADH, renal sempatik sinirler*

1. INTRODUCTION

Opium, the dried exudate of the juice of the poppy *Papaver somniferum,* is one of the oldest drugs known to humans. It has been used for thousands of years for relieving pain and diarrhea and also for its mood changing effects. In the beginning of the 19th century, morphine was isolated from opium and

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shown to be the principle alkaloid responsible for this extract's medicinal and non-medicinal effects. Despite morphine's long history, the breakthrough in understanding the actions of morphine and other opioid compounds (e.g. codeine) did not begin until the identification of opioid receptors and endogenous opioid peptides[1,2,3,4]. With the development of selective opioid agonists and antagonists, it has become clear that each subtype of opioid receptor is differentially distributed in the central nervous system (CNS) and periphery[5,6], and exerts unique pharmacological properties[7]. The opioid systems have been implicated in mediating a broad range of behavioral and functional responses such as reinforcement and reward, neuroendocrine modulation, neurotransmitter release, and the regulation of gastrointestinal, cardiovascular and immune functions[8].

In addition to the physiological processes mentioned above, opioids participate in the regulation of renal function[9]. Under different conditions, exogenous and endogenous opioids have been shown to produce marked changes in the renal excretion of water and sodium via multiple neural and hormonal mechanisms[9-12]. Opioids evoke changes in urine output and urinary sodium excretion by modulating neural and/or humoral pathways within the kidneys, periphery or central nervous system[13,14]. To completely understand how opioid systems influence kidney function, it is important to understand how each opioid system acts individually or in concert to alter renal function. In that regard, considerable research has been performed to elucidate the role of mu, kappa, delta and recently discovered opioid receptor-like 1 (ORL-1) receptors in renal excretory function. The purpose of this article is to provide a brief review of the effects and mechanism of action of various opioids on the regulation of renal excretion of water and sodium.

2. EFFECTS OF OPIOID SYSTEMS ON RENAL EXCRETORY FUNCTION

One of the important functions of the kidneys is to maintain body fluid and electrolyte balance despite wide variations in the daily intake of water and sodium[15,16,17]. In addition, the kidneys play a pivotal role in the regulation of arterial blood pressure by regulating body fluid volume and sodium content[17,18]. As a consequence of the kidneys' homeostatic role, the tissues and cells of the body are able to carry out their normal functions in a relatively constant environment.

The kidneys act to regulate total body water and sodium via numerous neural and humoral mechanisms, including pathways that involve the renal sympathetic nerves, antidiuretic hormone (ADH), atrial natriuretic factor (ANF), and the renin-angiotensin-aldosterone system [16,19-21]. In addition to these pathways, evidence indicates that opioid peptide systems may participate in regulating the renal excretory function[8,9]. Briefly, this premise stems from the following findings: a) central, peripheral, and intrarenal administration of native and synthetic opioid agonists produces changes in the renal excretion of water and sodium[9], b) endogenous central opioid mechanisms participate in the cardiovascular and renal responses produced by psychoemotional (air jet stress) and dietary (sodium deficiency) stress[22,23], and c) endogenous opioid systems contribute to the deranged renal excretory responses observed in the pathology of cirrhosis with ascites[24-26]. The particular renal responses produced by opioids and the mechanism(s) by which these compounds affect renal function will be discussed next.

2.1 EFFECTS OF MU OPIOID SYSTEMS ON RENAL EXCRETION OF WATER AND SODIUM

Morphine, a prototype mu opioid agonist, produces an antidiuretic effect in humans and other species [27,28]. In anesthetized dogs, morphine was suggested to decrease urine output by stimulating the secretion of ADH[29]. However, under different experimental conditions, the administration of a mu opioid agonist has been shown to produce an increase in urine output. For instance, peripheral or central administration of mu opioid agonists (e.g. morphine, levarphanol and methadone) produce antidiuresis in rats hydrated with an oral water-load[28,30-32]. In

contrast, in conscious rats that are normally hydrated, peripheral or central administration of a mu opioid agonist (e.g. morphine, dermorphin) produces a marked diuretic response[11,14,30,33,34]. Despite the variable effects on urine output, central or peripheral administration of mu opioid agonists consistently decrease urinary sodium excretion (i.e. produce antinatriuresis)[23,33,35].

Several mechanisms have been proposed to explain the variable effects that morphine and other mu opioid agonists have on the renal excretion of water. Marchand[30] suggested that the differences in morphine's effect on urine output (i.e. diuresis or antidiuresis) depend on the prior hydration status of the animal studied. Thus, morphine and other mu opioid agonists produce antidiuresis in water-loaded animals via stimulating ADH release[28,30,36]. On the other hand, in normally hydrated or water-restricted rats, mu opioid agonists are suggested to produce diuresis via suppressing ADH secretion[34,37,38].

Despite these findings, the role of ADH in mediating the renal responses to mu opioids has been questioned. In this regard, other research investigations have shown that: 1) morphine produced diuresis in Brattleboro rats, a genetic strain of rodents that lack ADH[39] and 2) administration of morphine to rats does not produce the same pattern of change in urinary electrolyte excretion as does administration of ADH[31,35] . Therefore, mechanisms other than stimulation of ADH release have been suggested to contribute to the antidiuretic effects of mu opioid agonists such as change in renal blood flow (RBF) and/or glomerular filtration rate (GFR). A study by Kapusta and Dzialowski[12] showed that intracerebroventricular (i.c.v.) administration of dermorphin, a selective mu opioid receptor agonist, produced a diuretic and antinatriuretic effect in conscious rats. The diuretic, but not the antinatriuretic, response was abolished by intravenous (i.v.) infusion of ADH, suggesting that the diuretic effect of central mu opioids involved changes in circulating levels of ADH. In addition to the water balance of the animal studied, factors such as the method of urine collection (i.e. bladder cannulation or spontaneous voiding) and variations in experimental protocols (duration of urine sampling) may contribute to the variability of mu opioids on urine output. In regard to differences in experimental methods, it should be noted that morphine inhibits the micturition reflex and can cause urinary retention[27] (i.e. antidiuresis). Therefore, in certain studies in which urine samples were collected via a bladder cannula, this inhibitory effect of morphine on bladder contractility may have been prevented, and a mu-opioid-induced diuretic response revealed.

A number of investigations have reported that mu opioid agonists can increase the plasma levels of ANF[40-43] . Enhanced release of ANF has been suggested to contribute to the diuretic effects of morphine and other mu opioid agonists[11,14] . In conscious, normally hydrated rats, i.c.v. administration of morphine produced a significant increase in urine output which was accompanied by an increase in plasma ANF. These responses occurred without significant changes in systemic hemodynamics[11] . In addition, in the same study, pretreatment of animals with ANF-antibody prevented the morphine-induced diuresis, verifying the role of ANF in this renal response. In other studies, these investigators established that mu opioids act peripherally to promote the release of ANF. This premise was supported by the finding that i.v. administration of TAPP, (a highly selective mu-opioid receptor agonist that lacks the ability to cross the blood-brain barrier), also produced a marked increase in plasma ANF and urine output in conscious rats[14].

Despite the variable effects of mu opioids on the renal excretion of water, morphine and other mu opioid agonists consistently produce a decrease in urinary sodium excretion (i.e. antinatriuresis). Initially, it was proposed that the decrease in urinary electrolyte excretion resulted from a reduction in blood pressure and GFR[28,31]. However, morphine and other mu opioid agonists have been shown to produce a marked decrease in urinary sodium excretion without changing GFR or systemic hemodyna-

mics[10,33]. Continued research in this area has demonstrated that mu opioid agonists produce a decrease in urinary sodium excretion via complex mechanisms that involve central, adrenal and direct renal actions[13,34] . It has been suggested that mu opioids may cause antinatriuresis by a pathway that involves the renal sympathetic nerves. Renal sympathetic nerves play an important role as a neural link between the CNS and the kidney[44]. All functional units of the kidneys (tubular and vascular) are densely innervated with renal sympathetic nerves. Graded electrical stimulation of the renal nerves causes frequency dependent increases in renin secretion, renal tubular sodium and water reabsorption, and decreases in RBF and GFR, thus causing a marked decrease in urinary sodium and water excretion. The role of the renal nerves in producing mu-opioid induced antinatriuresis has been studied by Kapusta et al.[34]. In their studies, central administration of dermorphin, a highly selective mu opioid receptor agonist, produced a marked diuresis and a concurrent reduction in urinary sodium excretion and increased renal sympathetic nerve activity over the course of the antinatriuresis. This latter finding suggests that central dermorphin may have mediated an antinatriuretic response by increasing sympathetic outflow to the kidneys. However, additional mechanisms other than the renal nerves also appear to participate in mediating mu-opioid induced antinatriuresis since bilateral renal denervation did not completely abolish this renal response. In regard to other mechanisms, it has been speculated that alterations in the secretion of hormonal substances from the pituitary or adrenal gland might be involved in mediating central mu opioid-induced changes in urinary sodium excretion[34].

2.1 EFFECTS OF KAPPA OPIOID SYSTEMS ON RENAL EXCRETION OF WATER AND SODIUM

It is well established that central and/or peripheral administration of various kappa opioid receptor agonists (e.g. U-50,488H, spiradoline [U-62,066E], ethylketocyclazocine [EKC], bremazocine) produces characteristic diuresis in a number of species including rats, mice, dogs, and humans[45-52]. The prior hydration status of the animal has been suggested to play an important role in the renal excretory responses produced by mu opioids[30]. Similarly, Leander et al.[53] conducted experiments to examine how different hydration conditions may effect the ability of kappa opioid agonists to affect urine output. These studies reported that all kappa opioid receptor agonists studied (bremazocine, EKC, U-50,488H) produced a diuretic response under different hydration conditions (water loading, euhydration, dehydration). Thus, increased urine output has been suggested as a simple in vivo test for studying the actions of compounds on kappa opioid receptors[47,48]. The diuretic response produced after central or peripheral administration of the kappa opioid receptor agonist appears to involve an action of the drug to inhibit the release of ADH from the pituitary. In conscious rats, subcutaneous (s.c.) injection of EKC, a kappa opioid receptor agonist, produced a dose-dependent increase in urine output[54]. In these studies, the plasma levels of ADH were significantly reduced at a time when urine flow was increased. It has been shown that kappa opioid agonists that cross the blood-brain barrier are potent diuretics. In contrast, kappa opioid analogs with limited ability to penetrate the brain have little efficacy as diuretics[51]. It has been suggested that kappa agonists produce diuresis by a mechanism that involves central kappa opioid receptors protected by the blood-brain barrier (i.e. sites other than those accessible from the peripheral circulation)[51]. Administration of a kappa agonist (e.g. EKC), or a water load (e.g. gavage) to an animal produces diuresis. However, while each manipulation reduces plasma ADH to equivalent levels, EKC produces a greater magnitude increase in urine output[54]. It has been suggested that a portion of the diuresis may be mediated by the actions of kappa opioids to inhibit the effects of ADH in the kidneys. Slizgi and Ludens[54] demonstrated that EKC produced a dose-dependent inhibition of vasopressin-stimulated water flow across the toad bladder, a model of the late renal distal tubule and collecting duct. This suggests that the diuretic activity of EKC may have resulted from blockade of the renal actions of ADH. This mechanism appears to be possible since kappa opioid receptors have been

identified in rat kidneys[54]. Despite these findings, however, kappa opioids have not been shown to alter ADH-mediated water transport in the mammalian collecting duct. Important to this latter observation, it should be noted that kappa opioids, with limited ability to cross the blood-brain barrier, are only weak diuretics. Thus, inhibition of ADH secretion by the central action of kappa opioids is thought to play a predominant role in mediating kappa-opioid induced diuresis. By either pathway, attenuation of the actions of ADH at the level of kidneys or CNS results in enhanced excretion of water and diuresis. An action of kappa opioids to suppress the renal action or CNS release of ADH is supported by studies which have observed that the diuretic response produced by these compounds is abolished by administration of the vasopressin analogue, desmopressin[55]. Moreover, kappa agonist administration does not elicit a diuresis in Brattleboro rats that are genetically deficient in ADH[56,57] .

Despite inhibiting the secretion and/or renal action of ADH, kappa opioids are suggested to evoke diuresis by a pathway independent of this hormone. For instance, studies by Rimoy et al.[58], and Reece et al.59 demonstrated that the selective kappa opioid agonists, spiradoline (U-62066) and CI-977, increased urine output in human subjects without changing plasma ADH. Similarly, the kappa opioid agonist, bremazocine, increased water excretion in rats without altering plasma ADH levels[48,55] . Related to these findings, it has been suggested that the diuretic effect of kappa opioids might be mediated by a substance released from the adrenal glands. This hypothesis stems from the findings that, in rats, bilateral adrenalectomy prevents the kappa opioid-induced diuresis[57,60,61]. In related studies, Wang et al.[62] proposed that kappa agonists increase the release of epinephrine from the adrenal gland, and this catecholamine stimulates alpha-2 receptors in the kidneys to produce diuresis. This premise was based on the observation that the kappa agonist-induced diuretic response was abolished by pretreatment of animals with the alpha-2 receptor antagonist, yohimbine.

Administration of kappa opioids decreases the urinary excretion of sodium and urine osmolality. In conscious rats, i.c.v. administration of U-50,488H (1µg total), a selective kappa opioid agonist, increased urine flow rate and decreased urinary sodium excretion. In these studies, U-50,488H also produced an increase in efferent renal sympathetic nerve activity during the duration of the antinatriuretic response[52] . Prior bilateral renal denervation prevented the decrease in urinary sodium excretion produced by i.c.v. U-50,488H. Therefore, it was concluded that central kappa opioids produce antinatriuresis via an increase in sympathetic outflow to the kidneys. In addition, it should be noted that the antinatriuresis produced by peripheral administration of U-50,488H (and other kappa opioid agonists) may involve simultaneous activation of both renal nerve-dependent (central) and -independent pathways. This is suggested since the antinatriuretic response produced by i.v. infusion of kappa opioids was not abolished by prior bilateral renal denervation[63]. It is possible that the renal nerve-independent pathways involve kappa opioid-induced changes in the secretion of other factors such as renin, aldosterone or catecholamines. Although opioids have been reported to affect the plasma levels of these substances[64,65], it remains to be established whether these alterations trigger the subsequent changes in renal function.

2.3 EFFECTS OF DELTA OPIOID SYSTEMS ON RENAL EXCRETION OF WATER AND SODIUM

The role of delta opioid systems in the regulation of renal function is less well characterized compared with mu or kappa opioids. However, several lines of evidence suggest that delta opioid systems may, in fact, have important influences on the renal handling of water and sodium. First, delta opioid receptors are also widely distributed in CNS regions involved in the regulation of cardiovascular function and fluid and electrolyte balance[5,66-68], and are also located in peripheral tissues such as the kidneys and the adrenal glands[6] . Indirect evidence to support this possibility comes from the observation that central/ peripheral administration of methionine-

and leucine-enkephalin evoke changes in renal excretory function[69-72]. Since both methionine- and leucine- enkephalin have a high affinity for delta opioid receptors, it is possible that these endogenous opioids mediate their renal responses via a delta opioid receptor pathway. The first direct evidence for the role of delta opioids on renal excretory function comes from our work in which peripheral administration of BW373U68 (BW) caused diuresis and natriuresis in rats[73] . BW is a non-peptide that has been demonstrated to be a selective delta opioid receptor agonist in various in vivo and in vitro studies[74,75]. In conscious rats, i.v. infusion of BW markedly increased urine flow rate and urinary sodium excretion without altering systemic or renal hemodynamics. In these studies, the peripheral administration of SNC-80, a non-peptide delta opioid receptor agonist, also produced a profound diuretic and natriuretic responses[73]. A major finding of this study is the observation that the renal excretory responses produced by BW and SNC were dependent on intact renal nerves. The diuresis and natriuresis produced by i.v. infusion of BW were abolished in rats having undergone chronic bilateral renal denervation, indicating that renal responses produced by peripheral administration of the delta opioid receptor agonist are mediated via a renal nerve-dependent pathway. Although not tested in these studies, BW may cause diuretic and natriuretic response by altering (i.e. decreasing) sympathetic outflow to the kidneys, the release of the neurotransmitter from the nerve terminals, or the postsynaptic renal tubular (or vascular) actions of norepinephrine. Further studies are required to explore the role of these pathways in mediating renal responses produced by BW and other delta opioid ligands.

We have also investigated the role of central delta opioid systems on renal excretory function. In these studies, the selective delta opioid agonists SNC-80 and DPDPE were administered directly to the CNS via an i.c.v. cannula and our preliminary results indicate that central administration of the either drug produced a profound increase in urine output without altering urinary sodium excretion in conscious rats[76]. The inhibition of the responses by pretreatment with naltrindole, the selective delta opioid receptor antagonist, indicates that in fact these responses were mediated by central delta opioid receptors. However, the difference in urinary sodium excretion in response to peripheral or central administration of the selective delta agonists should be further investigated.

It can be concluded that, when activated, opioid systems (mu, kappa, and delta) act collectively to increase urine output. Interestingly, selective mu and kappa opioid agonists produced a significant decrease in urinary sodium excretion, whereas, activation of delta opioid receptors either did not alter the urinary sodium excretion or produced a change in an opposite direction (i.e. natriuresis). It appears that opioid systems can differentially alter the renal excretion of sodium upon activation.

2.4 EFFECTS OF NOCICEPTIN/ORPHANIN FQ ON RENAL EXCRETION OF WATER AND SODIUM

Nociceptin/ Orphanin FQ (N/OFQ) is an endogenous opioid-like peptide that has been isolated from brain tissue[77,78] and shown to be the endogenous ligand of the ORL-1 (opioid receptor-like 1) receptor. ORL-1, in fact, is a new receptor protein that has been identified in mice CNS and human and murine cDNAs have also been characterized[79,80]. N/OFQ, its precursor prepro-N/OFQ and ORL-1 are distributed throughout the CNS regions known to be involved in the regulation of autonomic and cardiovascular function, fluid and electrolyte balance such as the paraventricular and supraoptic nucleus of the hypothalamus, the central amygdala, the nucleus of the solitary tract, and in pre-vertebral and para-vertebral ganglia[79-81]. In addition to the presence of ORL-1 transcripts in CNS, ORL-1 receptors are also located in peripheral organs such as the spleen, intestine, vas deferens and kidneys[82,83].

N/OFQ was shown to be involved in nociception, producing nociceptive or antinociceptive actions depending on the experimental conditions. Subsequent research demonstrated that, similar to classical

opioid systems, N/OFQ evokes marked changes in other biological systems including cardiovascular and renal functions[84]. Initially, we have demonstrated that intravenous infusion of N/OFQ produced a profound increase in urine flow rate and a decrease in urinary sodium excretion in conscious Sprague-Dawley rats[85]. In further studies, central administration of N/OFQ into conscious animals produced a concurrent diuresis and antinatriuresis[85]. Previous investigations on opioid systems demonstrated that ORL-1 receptor and its endogenous ligand, N/OFQ have a sequence homology most similar to that of the kappa opioid receptor and dynorphin, respectively[78-80] , thus suggesting that these systems may evoke changes in renal excretory function via common pathways. Since the renal responses produced by central administration of N/OFQ were not blocked by pretreatment with the kappa opioid receptor antagonist, nor-binaltorphimine, it was suggested that nociceptin produced a selective water diuresis via a central nervous system mechanism independent of kappa-opioid receptors. Together, these were the first observations suggesting that endogenous N/OFQ may be a novel peptide involved in the central control of water balance and electrolyte concentration[85].

The mechanisms by which N/OFQ alters renal excretion of water and sodium are not still well understood but it appears that a number of pathways might be important in mediating these responses including renal nerves, vasopressin and oxytocin. As mentioned in previous sections, both the vascular and tubular segments of the kidneys are densely innervated with renal sympathetic nerves and the changes in renal nerve activity significantly alters the specific functions of the kidneys i.e. GFR, RBF, renal blood flow, and tubular handling of water and sodium[44]. The increased activity of renal sympathetic nerves increases sodium and water reabsorption thus causing marked decrease in urinary sodium and water excretion. It has been shown that central administration of N/OFQ evoked a significant decrease in renal sympathetic nerve activity in parallel to antinatriuretic and diuretic responses. However, renal nerves do not appear to mediate the renal effects of this peptide because: a). changes in efferent renal nerve activity should produce reciprocal alterations in urinary sodium excretion, thus, such decrease in renal nerve activity is not in accord with a mechanism of antinatriuretic action, b). in animals that have undergone chronic bilateral renal denervation, renal responses to the central administration of the peptide were not altered85. Therefore, these results indicate that despite the decrease in renal nerve activity, renal sympathetic nerves are not involved in antinatriuretic effects of N/OFQ.

The other mechanisms that have been suggested to be involved in the renal responses of N/OFQ include the ADH and oxytocin. Anatomical studies have demonstrated that the ORL-1 receptor mRNA and the precursor N/OFQ mRNA are expressed in several nuclei of the hypothalamus[86,87]. Therefore, the renal effects of N/OFQ may be caused by its effect on the secretion of ADH and/or oxytocin. However, the role of hypothalamic ORL-1 receptors in renal responses to N/OFQ should be further investigated.

In regard to future therapeutic importance, the non-peptide analogues of nociceptin may offer the first clinically useful therapeutic tools for the management of hyponatremia and water-retaining diseases (such as patients with the syndrome of inappropriate secretion of antiduretic hormone, congestive heart failure, cirrhosis with ascites, or in the adult respiratory distress syndrome) since they cause diuresis and concurrent antinatriuresis. While kappa-agonists (e.g. enadoline, spiradoline) have the potential to be effective as water diuretics because of their diuretic and antinatriuretic effects, the CNS side effects (e.g. dysphoria) limit their clinical use in humans.

3. CONCLUSION

As discussed in previous sections, administration of opioid receptor agonists is capable of producing changes in the renal excretion of water and sodium. The particular renal excretory response (e.g. diuresis or antidiuresis) appears to depend, at least in part, on the type of opioid receptor activated. However,

an important question that remains to be answered is whether endogenous opioids participate in the physiological regulation of renal function and maintenance of daily sodium and/or water balance. This possibility might be investigated by determining the changes in renal excretory function produced by the administration of an opioid receptor antagonist. If endogenous opioid systems have a tonic influence on the renal handling of water and/or sodium, then opioid antagonist administration would be expected to produce a change in renal excretory function. Using this approach, however, controversial results regarding the effects of endogenous opioid systems on renal function have been observed, and in general opioid systems appear to remain quiescent and have no influence on renal function until activated by a particular condition or stimulus (e.g. dietary sodium restriction, stress)[22,23,63].

In conclusion, to elucidate how opioid systems affect kidney function, it is important to understand how each opioid system acts individually, or in concert, to modify the renal excretion of water and sodium. The knowledge of how opioid systems participate in the renal handling of water and sodium under physiologic or pathologic conditions will help the development of better therapeutics for clinical use.

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