Pharmacology, Biochemistry and Behavior 97 (2011) 700–707

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Mini-review

Tobacco dependence, the insular cortex and the hypocretin connection

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ARTICLE INFO

Available online 9 September 2010

Keywords:
Nicotine
Tobacco smoking
Addiction
Hypocretin (orexin)
Insula
Ventral tegmental area

ABSTRACT

Tobacco use is a major cause of disease and premature death in the United States. Nicotine is considered the key component of tobacco responsible for addiction in human smokers. Accumulating evidence supports an important role for the hypocretin (orexin) neuropeptide system in regulating the reinforcing properties of most major drugs of abuse, including nicotine. Here, data showing that nicotine activates hypocretin-producing neurons in the lateral hypothalamus, and that disruption of hypocretin transmission decreases nicotine self-administration behavior in rats will be reviewed. Recent findings suggesting that plasma hypocretin levels may be related to the magnitude of cigarette craving in abstinent smokers will be discussed. Finally, the data suggesting that hypocretin transmission in the insular cortex may play an important role in regulating nicotine self-administration behavior in rats will be reviewed. This latter finding may provide mechanistic insight into the apparent disruption of tobacco addiction reported in human smokers with stroke-associated damage to the insular cortex.

1. Introduction

Cigarette smoking is one of the largest causes of preventable death and disease in developed countries. Tobacco-related disease is responsible for approximately 440,000 deaths and $160 billion in health-related costs in the United States annually (Centers for Disease Control and Prevention, 2007). Despite the well-known negative health consequences associated with the tobacco smoking habit, only about 10% of smokers who attempt to quit annually without the help of smoking cessation agents remain abstinent after 1 year (Knight et al., 2009). Nicotine is considered the major reinforcing component of tobacco responsible for addiction in human smokers (Stolerman and Jarvis, 1995). Nicotine amplifies reward signals in the brain similar to other major drugs of abuse (Rice and Cragg, 2004), and this action likely accounts for its intrinsic rewarding properties and its ability to increase sensitivity to rewarding non-drug environmental stimuli (Kenny, 2007). Obtaining the stimulatory effects of nicotine on brain reward circuitries likely plays a central role in motivating tobacco consumption and contributes to the persistence of the habit (Donny et al., 2003 and Kenny, 2007).

To date, most investigations into the neurobiological mechanisms of nicotine reinforcement have focused on the role of the mesoaccumbens dopamine system, which comprises dopamine-containing neurons that arise in the ventral tegmental area (VTA) and project to the nucleus accumbens (NAcc); see Fig. 1. Indeed considerable evidence now supports a key role for mesoaccumbens dopamine transmission in nicotine reinforcement (Corrigall et al., 1994 and 1992 and David et al., 2006 and Fu et al., 2000 and Grillner and Svensson, 2000 and Ikemoto et al., 2006 and Kenny et al., 2009 and Laviolette and van der Kooy, 2003 and Mansvelder and McGehee, 2000 and Maskos et al., 2005). However, emerging data suggests that neurotransmitters other than dopamine and brain regions outside the mesoaccumbens axis may also play important roles in the motivational properties of nicotine. In particular, much interest has focused recently on the hypocretin (orexin) neuropeptide system in regulating the motivational properties of various drugs of abuse. Recent data from our laboratory and others suggest that hypocretin transmission is involved in nicotine reinforcement (Hollander et al., 2008 and Lesage et al., 2010). The finding that tobacco addiction can be disrupted in human stroke patients with damage to the insular cortex further emphasizes the importance of non-mesoaccumbens brain regions in tobacco smoking (Naqvi et al., 2007). Here, the role for hypocretin transmission in drug reward, with an emphasis on nicotine, is reviewed. In addition, brain regions within which hypocretin transmission may regulate nicotine reward processes are considered.

1.1. Hypocretin neuropeptides

Hypocretin-1 and -2 are 33- and 28-amino acid residue peptides, respectively, derived from the common 131-amino acid prepro-hypocretin precursor peptide. Prepro-hypocretin was first identified by directional tag polymerase chain reaction (PCR) subtractive hybridization as one of a number of mRNA transcripts that are selectively expressed in the hypothalamus (Gautvik et al., 1996). Subsequently, de Lecea et al. (1998) demonstrated that prepro-

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doi:10.1016/j.pbb.2010.08.015

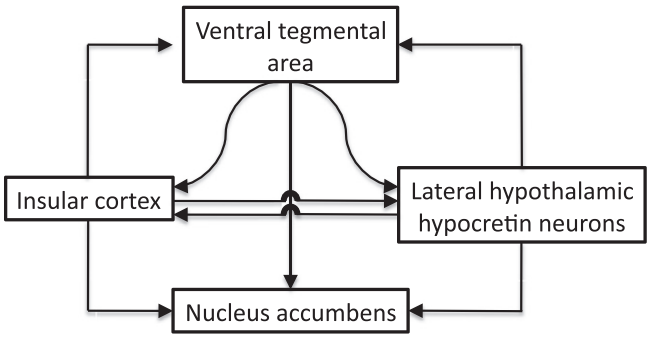

Fig. 1. Schematic representation of addiction-relevant brain regions regulated by hypothalamic hypocretin (Hcrt) neurons. Hypocretin neurons arise in the lateral hypothalamus and perifornical area and project to the ventral tegmental area (VTA), nucleus accumbens (NAcc) and the insula. Dopamine-containing neurons arise in the VTA and project to the NAcc, insula and to hypothalamic Hcrt neurons. GABAergic projects arise in the NAcc and project to the VTA and insula, but not directly to hypothalamic Hcrt neurons.

hypocretin was expressed almost exclusively in a few thousand neuronal cell bodies in posterior and lateral hypothalamic (LH) areas, and that this precursor encoded the hypocretin-1 (Hcrt-1) and hypocretin-2 (Hcrt-2) peptides. The name *hypocretin* reflects the fact that these peptides are synthesized in the *hypothalamus* and are similar to the incretin class of hormones and in particular *secretin* (de Lecea et al., 1998). Almost simultaneously, Sakurai et al. (1998) identified the same precursor and cleaved peptide products in the posterior and LH, and termed these peptides the orexins. The orexins were identified during high-throughput screening of the ability of rat brain extracts to activate orphan G-protein coupled receptors (GPCRs). Brain extracts activated an orphan GPCR originally termed HFGAN72, de-orphanized as the orexin-1 (OX_1) receptor and synonymous with the Hcrt-1 receptor. When brain extracts were purified the active component was identified as orexin-A peptide (Sakurai et al., 1998), synonymous with Hcrt-1 peptide. Subsequently, a second orexin receptor (OX_2; Hcrt-2 receptor) was identified through bioinformatic, full-length cloning and sequencing analyses, which can be activated similarly by Hcrt-1 and Hcrt-2 peptides (Sakurai et al., 1998). Sakurai et al., 1998 also showed that periods of negative energy balance increased prepro-hypocretin expression in hypothalamus (Sakurai et al., 1998). Furthermore, intracerebroventricular (ICV) administration of Hcrt-1 or Hcrt-2 peptide stimulated feeding in non-fasted rats (Sakurai et al., 1998). It was therefore proposed that hypocretins may regulate feeding behaviors and the name *orexin* was coined based upon these observations; deriving from *orexis,* the Greek word for appetite (Sakurai et al., 1998).

1.2. Physiological roles of the hypocretins

As noted above, hypocretins appear to play a role in feeding behavior (Sakurai et al., 1998). Indeed, the Hcrt-1 receptor antagonist SB-334867 decreases food consumption in rats (White et al., 2005), perhaps by enhancing satiety state (Ishii et al., 2004, 2005a,b and Rodgers et al., 2001). Isolated hypocretin neurons are inhibited by glucose and leptin, which usually signal satiety, and stimulated by ghrelin, which usually motivates feeding (Yamanaka et al., 2003). However, hypocretin-induced modulation of feeding behaviors is modest when compared with other feeding-related neuropeptides such as neuropeptide Y (NPY) (Ida et al., 1999). Some studies have found modest or no role whatsoever for hypocretins in feeding behaviors (Fujiki et al., 2001 and Swart et al., 2001 and Yamanaka et al., 1999 and Yoshida et al., 2001). Transgenic mice in which prepro-hypocretin was genetically ablated failed to respond to fasting with the increased wakefulness and activity levels typically observed in wildtype mice (Yamanaka et al., 2003). Furthermore, Funato et al. (2009) found that overexpression of prepro-hypocretin conferred resistance to diet-induced obesity and insulin resistance in mice. These effects were related to increased energy expenditure and reduced caloric intake, and were mediated through the Hcrt-2 receptor (Funato et al., 2009). It has therefore been proposed that hypocretins may not modulate states of satiety and energy balance *per se*, but instead may provide a link between energy balance and arousal state. In this manner hypocretins can promote the increased wakefulness and activity usually associated with periods of reduced food availability (Sutcliffe and de Lecea, 2002 and Yamanaka et al., 2003), or compensatory increases in activity in response to a high-fat diet to facilitate the maintenance of energy homeostasis (Funato et al., 2009). There is now convincing evidence that hypocretins indeed modulate states of arousal and wakefulness (Adamantidis et al., 2007). For example, dogs with null mutation in the Hcrt-2 receptor gene or prepro-hypocretin deficient mice display a behavioral state very reminiscent of human narcolepsy (Chemelli et al., 1999 and Lin et al., 1999). Other behavioral and physiological roles in which the hypocretins have been implicated include glycolysis (Sikder and Kodadek, 2007), gastric acid secretion (Takahashi et al., 1999), respiratory drive (Young et al., 2005), sexual behavior (Muschamp et al., 2007), depressive disorders (Brundin et al., 2007, Ito et al., 2008 and Lutter et al., 2008) and anxiety/panic states (Johnson et al., 2009).

1.3. Hypocretins in drug reward: opiates

There are dense reciprocal innervations between hypocretin neurons in the hypothalamus and areas of the brain involved in drug addiction, including the prefrontal cortex (PFC), nucleus accumbens (NAcc), central nucleus of the amygdala (CeA), bed nucleus of the stria terminalis (BNST) and ventral tegmental area (VTA) (Baldo et al., 2003 and Nambu et al., 1999 and Peyron et al., 1998 and Yoshida et al., 2006). It is perhaps not surprising then that hypocretins have been implicated in the behavioral and physiological actions of drugs of abuse; for recent reviews see Aston-Jones et al. (2009), Borgland et al. (2009b), Boutrel and de Lecea (2008) and DiLeone et al. (2003). Aston-Jones et al. (2009) were the first to implicate the hypocretins, and in particular the Hcrt-1 receptor, in drug reward (Harris et al., 2005). In their study it was shown that exposure to environmental cues in a place conditioning procedure that were repeatedly paired with morphine or other reinforcers robustly activated hypocretin-positive LH neurons in rats, as measured by Fos immunostaining (Harris et al., 2005). Lesions of hypocretin-enriched areas of the LH blocked a conditioned place preference for morphine (Harris et al., 2007). Conversely, chemical activation of LH hypocretin neurons, achieved by infusing the NPY-Y_4 receptor agonist rat pancreatic polypeptide (rPP) directly into the LH (Harris et al., 2005), reinstated a previously extinguished preference for a morphine-associated environment, an effect blocked by the Hcrt-1 receptor antagonist SB-334867 (Harris et al., 2005). Genetic deletion of the prepro-hypocretin gene attenuates the conditioned rewarding and hyperlocomotive effects of morphine in mice, as measured in place conditioning procedures (Narita et al., 2006 and Sharf et al., 2010a). At the neuroanatomical level, microinfusion of Hcrt-1 or Hcrt-2 peptides into the VTA increased levels of dopamine and its major metabolites in the shell region of the NAcc (Narita et al., 2006), suggesting that hypocretin transmission in VTA may play a role in drug-seeking behavior. Interestingly, intra-VTA administration of Hcrt-1 also increased dopamine release in the prefrontal cortex, but not the core region of NAcc (Vittoz and Berridge, 2006 and Vittoz et al., 2008). More directly, infusion of Hcrt-1 peptide directly into the VTA reinstated an extinguished morphine-conditioned place preference in rats (Harris et al., 2005). Finally, it is important to point out that hypocretin transmission has also been implicated in aspects of the aversive opiate withdrawal syndrome (Georgescu et al., 2003 and

Sharf et al., 2008), and could therefore control opiate intake through negative reinforcement processes (Kenny et al., 2006).

1.4. Hypocretins in drug reward: psychomotor stimulants

In addition to opiates, hypocretin transmission also regulates the neurochemical, motivational and neuroplastic effects of cocaine and amphetamine. Amphetamine treatment or exposure to a cocaine-paired environment increases the activation of hypocretin neurons, as measured by Fos immunoreactivity (Fadel et al., 2002 and Harris et al., 2005 and McPherson et al., 2007 and Quarta et al., 2009). Further, SB-334867 attenuates amphetamine- and cocaine-induced increases in mesoaccumbens dopamine transmission (Espana et al., 2010 and Quarta et al., 2009). Blockade of Hcrt-1 but not Hcrt-2 receptors can attenuate reinstatement of extinguished cocaine-seeking responses induced by cocaine-paired discrete stimuli (Smith et al., 2009) or a cocaine-paired context (Smith et al., 2010) in rats. Boutrel et al. (2005) have shown that ICV infusion of Hcrt-1 peptide reinstated extinguished operant responding for cocaine. Moreover, this effects was abolished by simultaneous blockade of noradrenergic and corticotrophin releasing hormone 1 (CRF-1) receptors (Boutrel et al., 2005). Conversely, SB-334867 attenuated stress-induced reinstatement of extinguished cocaine-seeking behavior (Boutrel et al., 2005). Interactions between Hcrt-1 receptors and brain stress systems may therefore regulate drug-seeking behavior, and there is an accumulating body of evidence in support of such a relationship (Paneda et al., 2005 and Winsky-Sommerer et al., 2005). Indeed, footshock stress activates orexin neurons in the perifornical-dorsomedial hypothalamus (Harris et al., 2005), and behavioral stressors increase Hcrt-1 peptide mRNA levels in the LH (Ida et al., 2000). Hcrt-1 peptide increases circulating corticosterone levels in a dose-dependent manner following ICV administration (Ida et al., 2000), and also increases circulating levels of adrenocorticotropic hormone (ACTH) and central expression of CRF mRNA (Al-Barazanji et al., 2001 and Russell et al., 2001). Hcrt-1 receptors can augment the release of the potent stress hormone secretagogue norepinephrine (Hirota et al., 2001 and Matsumura et al., 2001 and Walling et al., 2004). CRF-containing neurons synapse onto hypocretin-positive cells in the LH, hypocretin neurons express CRF-1 and CRF-2 receptors, and application of CRF directly onto LH slices increases the firing rate of hypocretin neurons (Winsky-Sommerer et al., 2004). Further, the non-selective CRF receptor antagonist α-helical-CRF blocks hypocretin-induced grooming and face-washing behaviors in rats (Ida et al., 2000). Taken together, these data suggest that hypocretin and CRF systems may interact in regulating drug-seeking behaviors. There is evidence, however, that both systems can also act independently of one another. Wang et al. (2009) have shown that intra-VTA injection of Hcrt-1 peptide increases extracellular levels of dopamine and glutamate in the VTA, and reinstates extinguished operant responding for cocaine. These effects were blocked by the Hcrt-1 receptor antagonist SB-408124 but not by α-helical-CRF (Wang et al., 2009). Furthermore, intra-VTA administration of α-helical-CRF blocked footshock-induced increases in extracellular glutamate and reinstatement of cocaine-seeking (Wang et al., 2005), whereas SB-408124 did not (Wang et al., 2009). These data are somewhat at odds with the findings of Boutrel et al. (2005), who reported that brain-wide disruption of noradrenergic and CRF-1 receptor systems abolished hypocretin-stimulated cocaine-seeking. Hence, it is likely that hypocretin and CRF systems interact to regulate cocaine-seeking in various brain regions, but that this interaction does not occur in the VTA.

As noted above, ICV or intra-VTA administration of Hcrt-1 peptide reinstates extinguished cocaine-seeking behaviors. Boutrel et al. (2005) found that ICV infusion of Hcrt-1 peptide did not alter ongoing cocaine-self-administration behavior. Hypocretin transmission may therefore selectively regulate "relapse" like behaviors in abstinent rats, but play no role in the reinforcing effects of the drug that maintain ongoing drug-taking behavior (Aston-Jones et al., 2008 and Smith et al., 2009). Alternatively, it is possible that cocaine consumption activates hypocretin systems to such a degree that further activation through ICV administration of Hcrt-1 has no effects on drug intake. Consistent with this possibility, blockade of Hcrt-1 receptors using SB-334867 decreased cocaine self-administration in rats (Borgland et al., 2009a and Espana et al., 2010). Intra-VTA infusion of SB-334867 also decreased responding for cocaine. Interestingly, the inhibitory effects of SB-334867 on cocaine self-administration behavior were most evident when rats responded for the drug under a progressive ratio (PR) schedule of reinforcement (Borgland et al., 2009a and Espana et al., 2010), whereas SB-334867 had no effects on cocaine intake under a low stringency fixed-ratio 1 (FR1) reinforcement schedule (Espana et al., 2010 and Smith et al., 2009). In unpublished observations from our laboratory we found that SB-334867 dose-dependently decreased cocaine self-administration under a more stringent FR5 schedule of reinforcement (Hollander and Kenny, unpublished observations). Thus, hypocretin transmission may be necessary to maintain drug-taking behavior when the high levels of effort are required to obtain the drug, but not when the drug is readily available. Consistent with this possibility, the inhibitory effects of SB-334867 on consumption of a palatable reinforcer (high-fat chocolate food) were recently shown to be dependent upon the level of effort necessary to obtain the reinforcer (Borgland et al., 2009a).

In addition to regulating the behavioral actions of cocaine and amphetamine, hypocretin transmission also plays an important role in the neuroplasticity induced by these drugs. Hcrt-1 peptide was shown to potentiate NMDA receptor-mediated excitatory post-synaptic currents (EPSCs) in VTA dopamine neurons and to translocate NMDA receptors to the surface of these cells (Borgland et al., 2006), effects blocked by systemic administration of SB-334867 (Borgland et al., 2006). Activation of Hcrt-1 receptors facilitated NMDA receptor-mediated transmission in the VTA through a protein kinase C (PKC) and phospholipase C (PLC) dependent mechanism (Borgland et al., 2006), suggesting that Hcrt-1 receptors couple to Gq-proteins *in vivo*. Hcrt-1 peptide also facilitated cocaine-induced potentiation of excitatory inputs to the VTA (Borgland et al., 2006), highlighting a potential mechanism through which Hcrt-1 receptors may induce persistent alterations in the motivation to consume cocaine. Interestingly, strengthening of presynaptic glutamatergic inputs to the VTA occurs only in rats that respond for high-value reinforcers such as cocaine or high-fat food (Borgland et al., 2009a). More recently, it was shown that the mixed Hcrt-1 and Hcrt-2 receptor antagonist DORA-1 completely blocked the altered gene expression patterns seen in the VTA, dorsal raphe nucleus and ventrolateral preoptic nucleus in amphetamine-sensitized mice (Winrow et al., 2010). In particular, the modified expression patterns of genes associated with synaptic plasticity in amphetamine-treated mice were abolished by DORA-1 (Winrow et al., 2010).

1.5. Hypocretins in drug reward: alcohol

Hypocretin transmission plays an important role in alcohol consumption and alcohol seeking during periods of abstinence (Lawrence, 2009). Reinstatement of extinguished alcohol seeking is associated with activation of hypocretin neurons (Dayas et al., 2008 and Hamlin et al., 2008). Intra-LH infusion of Hcrt-1 peptide stimulates ethanol consumption (Schneider et al., 2007). Moreover, SB-334867 dose-dependently decreases alcohol consumption in rats (Lawrence et al., 2006 and Moorman and Aston-Jones, 2009), and attenuates cue- and yohimbine-induced reinstatement of extinguished alcohol seeking (Lawrence et al., 2006 and Richards et al., 2008). Intriguing data is emerging related to the mechanisms through which hypocretin transmission may regulate ethanol consumption.

Chronic ethanol intake increases levels of circulating triglycerides, which in turn can stimulate hypothalamic hypocretin neurons and promote ethanol intake (Barson et al., 2009). This suggests that hypocretin transmission may regulate the close correlation between alcohol consumption and preference for fatty foods, and that fatty foods may provoke alcohol seeking through stimulation of hypocretin systems. More recently it was shown that ICV administration of neuropeptide S (NPS) activated hypocretin neurons (Niimi, 2006) and that persistent increases in alcohol seeking induced by NPS are related to its stimulatory effects on hypocretin transmission (Cannella et al., 2009).

Finally, in addition to opiates, psychomotor stimulants and alcohol, hypocretin transmission also plays an important role in regulating seeking behaviors for non-drug reinforcers, including high-fat palatable food (Clegg et al., 2002 and Nair et al., 2008 and Zheng et al., 2007), sucrose (Richards et al., 2008 and Thorpe et al., 2005) and copulation (Muschamp et al., 2007). Recent findings using SB-334867, Hcrt knockout mice and RNA interference-mediated knockdown of orexin have shown that hypocretin transmission at Hcrt-1 receptors plays an important role in motivation to respond for food reinforcement, supporting a role for hypocretin transmission in maintaining physiological levels of caloric intake (Sharf et al., 2010b). Overall, these findings highlight the important role for hypocretin transmission in the reinforcing and conditioned rewarding effects of drugs of abuse and non-drug reinforcers, and the motivation to seek drugs during periods of abstinence. In addition, the VTA appears to be an important brain site regulating these actions of hypocretin.

2. Hypocretin transmission regulates the reinforcing effects of nicotine

Emerging evidence suggests that hypocretin transmission also plays a key role in the reinforcing properties of nicotine and may contribute the persistence of the tobacco habit in human smokers. Intravenous nicotine self-administration increased Hcrt-1 receptor expression in the arcuate nucleus of the hypothalamus, but decreased Hcrt-1 receptor expression in the rostral lateral hypothalamus of rats (Corrigall, 2009 and Lesage et al., 2010). Chronic systemic nicotine treatment dose-dependently increased expression levels of Hcrt-1 and Hcrt-2 receptors and prepro-hypocretin in the hypothalamus of rats (Kane et al., 2000). Somewhat paradoxically, in a separate study Kane et al. (2001) found that chronic nicotine treatment decreased the affinity and density of Hcrt-1 peptide binding sites in hypothalamic tissues. Consistent with a stimulatory effect of nicotine on hypocretin transmission, acute nicotine injections increased Fos immunoreactivity selectively in Hcrt-1 peptide-positive hypothalamic neurons (Pasumarthi et al., 2006). Furthermore, nicotine-induced activation of the paraventricular nucleus of the hypothalamus (PVN), also measured by increased Fos immunoreactivity, was abolished in mutant mice in which the gene for prepro-hypocretin was genetically deleted (Plaza-Zabala et al., 2010).

Our laboratory found that SB-334867 dose-dependently decreased intravenous nicotine self-administration behavior in rats tested under FR5 and PR schedules of reinforcement, at doses that did not alter responding for food rewards under the same reinforcement schedules (Hollander et al., 2008). Similarly, Lesage et al. (2010) also found that SB-334867 decreased nicotine self-administration behavior in rats, and have extended these findings by showing that the mixed Hcrt-1/-2 receptor antagonist almorexant also decreased nicotine intake. In common with other drugs of abuse, nicotine amplifies reward signals in the brain (Rice and Cragg, 2004), reflected behaviorally as nicotine-induced lowering of intracranial self-stimulation (ICSS) thresholds in rats (Bauco and Wise, 1994 and Harrison et al., 2002 and Huston-Lyons and Kornetsky, 1992 and Kenny and Markou, 2006). We found that SB-334867 dose-dependently attenuated nicotine-induced lowering of ICSS thresholds in rats (Hollander et al., 2008). Similarly, systemic nicotine administration increased responding for sucrose rewards in rats responding under a PR schedule of reinforcement, and the mixed Hcrt-1/-2 receptor antagonist DORA-1 attenuated this effect (Winrow et al., 2010). Thus, blockade of hypocretin transmission likely decreases nicotine intake by abolishing the stimulatory effects of the drug on brain reward systems. Finally, ICV infusion of Hcrt-1 peptide reinstated extinguished nicotine seeking responses in mice (Plaza-Zabala et al., 2010), suggesting that hypocretin transmission regulates both ongoing nicotine consumption and nicotine seeking during periods of abstinence.

Evidence in human smokers is consistent with a role for hypocretin transmission in maintaining the persistence of the tobacco habit. Circulating levels of Hcrt-1 peptide were similar between smokers and non-smokers (Aksu et al., 2009 and von der Goltz et al., 2009). However, when abstinent smokers were allocated to two groups based on their craving for tobacco (low versus high), a significant negative correlation was detected between plasma Hcrt-1 peptide levels and craving (von der Goltz et al., 2009). Assuming that the source of circulating Hcrt-1 peptide is from the central nervous system and not produced systemically, these findings support the view that hypocretin transmission plays a role in tobacco craving in abstinent smokers.

As noted above, the VTA is an important brain site in which hypocretin transmission regulates the rewarding actions of abused drugs. The role of hypocretin transmission in the VTA in regulating nicotine intake has not yet been assessed. However, data from our laboratory and others suggest that hypocretin transmission in cortical areas of the brain may be involved in the behavioral actions of nicotine. Obtaining the cognitive-enhancing properties of nicotine contained in tobacco smoke is hypothesized to play a role in sustaining tobacco smoking behavior (Evans and Drobes, 2009). Fadel et al. (2005) have shown that Hcrt-1 peptide stimulates basal forebrain cholinergic neurons and thereby triggers the release of acetylcholine into the PFC. Further, nicotine activated Hcrt-1-containing neurons that project to basal forebrain cholinergic neurons (Pasumarthi and Fadel, 2008). Similarly, Lambe et al. (2003) have shown that nicotine stimulates corticothalamic neurons to increase glutamatergic transmission in PFC. It was also found that hypocretin transmission stimulates the same corticothalamic afferents as nicotine (Lambe and Aghajanian, 2003 and Lambe et al., 2005), perhaps through inhibition of hyperpolarization-activated/cyclic nucleotide (HCN)-gated channels (Li et al., 2009). It has therefore been proposed that the stimulatory action of hypocretin transmission on cortical cholinergic and glutamatergic transmission may serve to integrate hypothalamic arousal and forebrain attention systems (Fadel et al., 2005), and could contribute to nicotine-induced increases in attention (Lambe et al., 2003 and Pasumarthi and Fadel, 2008). As discussed below, hypocretin transmission in cortical regions may also regulate nicotine self-administration behavior.

3. The insular cortex and tobacco smoking

As recently discussed as part of this mini-review series (Paulus et al., 2009), the insula is a cortical brain region involved in processing interoceptive information related to emotional and motivational states to facilitate maintenance of physiological homeostasis (Gray and Critchley, 2007). The insula is hypothesized to play a key role in encoding the taste and relative incentive value of food (Balleine and Dickinson, 2000 and Lin et al., 2009 and Small et al., 2001) and other reinforcers (Liotti et al., 2001 and Liu et al., 2007). This brain region may also regulate the experience of conscious urges and cravings, including those for drugs of abuse (Damasio et al., 2000 and Gray and Critchley, 2007 and Naqvi et al., 2007). Indeed, it was recently proposed that the insula may detect disequilibrium between

predicted internal body state and actual body state, and that the magnitude of the message error derived from this insular-dependent computation in drug users may drive drug-seeking behaviors (Paulus et al., 2009). In support of this hypothesis is the recent observation that stroke-associated damage to the insular cortex in human smokers resulted in a profound disruption of tobacco addiction, characterized by spontaneous cessation of the smoking habit and a low urge to smoke thereafter (Naqvi et al., 2007). Conversely, abstinence-induced cigarette craving in smokers is highly correlated with insular activation (Wang et al., 2007). These data support an important role for the insular cortex in drug addiction processes; for recent reviews see (Goldstein et al., 2009 and Naqvi and Bechara, 2009). Indeed, the insula innervates, and is in turn innervated, by many addiction-relevant brain regions including the VTA and NAcc (Bubser et al., 2005 and Christie et al., 1987 and Reynolds and Zahm, 2005) (Fig. 1).

Data from our laboratory and others suggests that hypocretin transmission in cortical areas of the brain may play an important role in drug reward. Temporary inactivation of the insular cortex in rats, achieved through intra-insula infusion of the local anesthetic lidocaine, reversibly blocked amphetamine seeking behavior in rats (Contreras et al., 2007). Interestingly, amphetamine seeking behavior in rats was associated with simultaneous increases in Fos immunoreactivity in both insular cells and hypocretin-containing cells in the LH (Contreras et al., 2007). This may represent the simultaneous activation of two independent neurobiological substrates that are involved in drug seeking in an unrelated manner. Alternatively, it is possible that this temporally coincident activation of the insula and LH hypocretin neurons may represent a direct link between these two brain sites. Consistent with hypothesis and previous reports (Date et al., 1999 and Peyron et al., 1998), we found dense innervation of Hcrt-1 peptide-containing neurons throughout the insular cortex of rats. In addition, we also detected the expression of Hcrt-1 receptors on cells in this brain region. More importantly, direct administration of SB-334867 into the insula, but not into the somatosensory cortex, dose-dependently decreased nicotine self-administration but not responding for food rewards in rats. These data suggest that insular hypocretin transmission regulates the reinforcing effects of nicotine. Considering the reciprocal innervation between the insular cortex, hypothalamic hypocreint neurons and the mesoaccumbal dopamine system (Alberto et al., 2006 and Bubser et al., 2005 and Uramura et al., 2001 and Yoshida et al., 2006) (Fig. 1), it is possible that insular hypocretin transmission may regulate nicotine intake by coordinating the responsiveness of the NAcc and/or VTA to nicotine and nicotine-paired environmental stimuli. Overall, these findings suggest that decreased tobacco consumption in human smokers with stroke-induced insular damage may arise at least in part from disruption of hypocretin transmission in this brain region.

There are a number of mechanisms through which hypocretin transmission in the insular cortex may impact nicotine intake in rats and the tobacco habit in human smokers. Experimentally induced stroke in rats increases plasma norepinephrine, epinephrine and dopamine when the area of brain damage includes the insular cortex (Smith et al., 1986), suggesting that the insula exerts a tonic inhibitory influence on the sympathoadrenal system. Cigarette smoking is known to activate the sympathetic nervous system (Narkiewicz et al., 1998). Thus, activity of the insular cortex may influence tobacco consumption through modulation of the autonomic nervous system and the impact of tobacco on this system. Interestingly, the insular cortex has one of the highest levels of extra-striatal dopamine transmission in the brain (Jones et al., 1986). Furthermore, dopamine transmission in this brain site regulates cocaine self-administration behavior (Di Pietro et al., 2008) and reinstatement of extinguished cocaine or sucrose seeking in rats (Di Pietro et al., 2006 and Hamlin et al., 2006). Thus, it is an interesting possibility that insular hypocretin transmission may regulate nicotine self-administration in rats and tobacco smoking behavior in humans through modulation of dopamine transmission in this brain site, similar to its proposed role in the VTA (Borgland et al., 2006 and Harris et al., 2005).

4. Conclusions

The data reviewed above provide strong evidence for a critical role for hypocretin transmission in regulating the reinforcing properties of nicotine, and suggest that Hcrt-1 receptors may be important targets for the development of novel therapeutics to aid smoking cessation efforts. Hypocretin transmission in the mesoaccumbens axis is involved in drug reward, but hypocretin transmission in cortical areas may also be important. In particular, the finding that disruption of hypocretin transmission at Hcrt-1 receptors in the insular cortex decreases nicotine intake in rats suggests that destruction of insular hypocretin transmission in smokers who suffer damage to this brain region may explain the profound disruption of tobacco addiction observed in these individuals.

Many important issues concerning the role of hypocretin transmission in addiction remain to be solved. Future areas of investigation will include identifying the precise neurocircuitries through hypocretinergic transmission influences drug-seeking behavior. Although impressive advances have been made in understanding the signaling cascades activated in response to Hcrt receptor stimulation (Borgland et al., 2006), much work still needs to done in order to refine our understanding of the intracellular signaling events through which hypocretinergic transmission regulates drug-seeking behavior. Also, the long-term effects of drug consumption on hypocretinergic transmission and the role of such plasticity in the development of compulsive drug-taking behaviors is still relatively unclear. Finally, the precise role for Hcrt-2 receptors in regulating drug-taking behavior is still unclear and progress in this regard will likely necessitate assessment of drug self-administration behavior in mice with genetic manipulations in one or both of the Hcrt receptors and the availability of highly selective Hcrt-2 ligands.

In summary, hypocretinergic transmission plays a key role in regulating drug-seeking behaviors and the development of safe and effective ligands at Hcrt-1 and Hcrt-2 receptors may have considerable clinical utility for the treatment of substance abuse disorders.

Acknowledgments

The author is grateful to the National Institute on Drug Abuse for their support (DA020686). This is manuscript 20546 from The Scripps Research Institute.

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