available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Neuronal pathways linking substance P to drug addiction and stress

*K.G. Commons**

Department of Anesthesiology, Perioperative, and Pain Medicine, Children's Hospital Boston; Department of Anaesthesia, Harvard Medical School, 300 Longwood Ave., Enders 1206, Boston, MA, USA

ARTICLE INFO

Article history:
Accepted 5 November 2009
Available online 11 November 2009

Keywords:
Substance P
Neurokinin 1
Nucleus accumbens
Serotonin
Stress

ABSTRACT

Accumulating evidence suggests that the neuropeptide substance P (SP) and its principal receptor neurokinin 1 (NK1) play a specific role in the behavioral response to opioids and stress that may help to initiate and maintain addictive behavior. In animal models, the NK1 receptor is required for opioids to produce their rewarding and motivational effects. SP neurotransmission is also implicated in the behavioral response to stress and in the process of drug sensitization, potentially contributing to vulnerability to addiction or relapse. However, SP neurotransmission only plays a minor role in opioid-mediated antinociception and the development of opioid tolerance. Moreover, the effects of SP on addiction-related behavior are selective for opioids and evidence supporting a role in the response to cocaine or psychostimulants is less compelling. This review will summarize the effects of SP neurotransmission on opioid-dependent behaviors and correlate them with potential contributing neural pathways. Specifically, SP neurotransmission within components of the basal forebrain particularly the nucleus accumbens and ventral pallidum as well as actions within the ascending serotonin system will be emphasized. In addition, cellular- or network-level interactions between opioids and SP signaling that may underlie the specificity of their relationship will be reviewed.

© 2009 Elsevier B.V. All rights reserved.

Substance P (SP) is a member of the tackykinin family of neuropeptides. It is one of the most abundant neuropeptides in the brain and one of the earliest to be purified and sequenced (reviewed by (Hokfelt et al., 2001; Nicoll et al., 1980). It was named SP because it was the active component of a purified preparation (Von Euler and Gaddum, 1931), although later the P of SP became tightly linked with the peptides suspected role in the sensation of pain. However, the association of SP with pain appears to be largely a misstatement of what has emerged as a multifaceted role in modulating behavior at many points across the neuroaxis (Hill, 2000).

SP is thought to primarily act at the neurokinin 1 (NK1) receptor. However, there are three peptide and three receptor members of the tackykinin family and potential for cross-talk between them. SP and a second tackykinin, neurokinin A are both encoded by the preprotackykinin A gene. The third tackykinin, neurokinin B is encoded by a separate gene preprotackykinin B. These three peptides act on three receptor subtypes, neurokinin (NK) 1, 2, and 3. The preferential, although perhaps not exclusive receptor for SP is NK1, for neuokinin A, NK2, and for neurokinin B, NK3 (Regoli et al., 1994). As a neuropeptide, SP coexists with other fast neurotransmitters within axons including gluta-

* Fax: +1 617 730 0967.
E-mail address: Kathryn.Commons@Childrens.Harvard.edu.

0006-8993/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2009.11.014

mate, GABA, serotonin and acetylcholine depending on its location in the brain.

The importance of NK1 signaling to addiction-related behaviors was emphasized by studies using mice lacking functional NK1 receptors. That is, opioids no longer appear rewarding in NK1 knockout mice, at least as indicated in two behavioral paradigms, the conditioned place preference test and drug self-administration behavior (De Felipe et al., 1998a; Murtra et al., 2000; Ripley et al., 2002). In the conditioned place preference test, rodents develop a preference for a chamber previously paired with drug administration. The amount of time spent within the drug-paired chamber in preference to an alternative chamber is thought to reflect a prior reward. The propensity to self-administer drugs is also thought to depend on the rewarding effects of the drugs. These tests also involve motivation, such that they are thought to invoke both neural circuits that mediate reward and the motivation to seek that reward.

The loss of rewarding value of opioids in NK1 knockout mice was consistent with prior studies and further supported by subsequent ones. For example, it had been previously shown that NK1 receptor activation by itself is able to produce conditioned place preference (Hasenohrl et al., 1992; Hasenohrl et al., 1998a; Hasenohrl et al., 1998b; Nikolaus et al., 1999). The effects of SP on major neurotransmitter systems involved in addiction-related behaviors including dopamine, serotonin, norepinephrine, and acetylcholine had also been known (reviewed by Goodman, 2008). In addition, more recent studies have shown that lesion of cells bearing NK1 receptors in the amygdala mimics the results in the NK1 knockout mice (Gadd et al., 2003) and administration of NK1 receptor antagonists to normal mice attenuates their response to opioids on the conditioned place preference test (Jasmin et al., 2006). Thus a variety of approaches have converged to support a role for NK1 signaling in opioid addiction-related behaviors.

Considering these observations, the most likely interpretation of the effect of the NK1 knockout on opioid-related behaviors is that the administration of opioids elicits an endogenous SP release that activates NK1 receptors. NK1 signaling may then play a permissive role, or possibly enhance the effects of opioids. Supporting this notion, there has been a report showing that administration of morphine increases extracellular SP, at least in the periaqueductal gray (Rosen et al., 2004).

1. Motivation and reward pathways

Relevant NK1 signaling may occur within several brain areas associated with reward. These include a cadre of structures in the ventral forebrain sometimes referred to as the extended amygdala composed of the bed nucleus of the stria terminalis (BNST), amygdala, nucleus accumbens (posterior shell), and major efferent targets of the extended amygdala particularly the ventral pallidum, lateral hypothalamus, and cortex (De Vries and Shippenberg, 2002; Heimer and Alheid, 1991; Koob, 1999; McBride et al., 1999; Panagis et al., 1995; Shippenberg and Elmer, 1998). Key control of these areas is exerted by the mesolimbic dopamine system, the primary component of incentive, or motivational processes (Koob, 2009; Spanagel and Weiss, 1999). This system is composed of neurons that contain dopamine located in the ventral tegmental area (VTA) that send their axons to the nucleus accumbens. Disruption of the mesolimbic pathway significantly impairs motivation to seek any positive reward be it food, sex, or drugs (Berridge, 2004; Fibiger et al., 1986; Hnasko et al., 2005). These groups of structures together are tightly interconnected functionally, as well as anatomically.

An important SP–NK1 interaction relevant for reward and motivational state may occur in the shell region of the nucleus accumbens (Fig. 1). Morphine activates neurons in the nucleus accumbens and promotes the appearance of certain gene products, such as Fos B in this area. Morphine's activation of Fos B in the nucleus accumbens is substantially decreased in NK1 knockout mice (Murtra et al., 2000). Within the nucleus accumbens SP is present in the local axon collaterals of medium spiny projection neurons (Lee et al., 1997; Napier et al., 1995). SP-containing axons form synapses with aspiny neurons in this area that contain the NK1 receptor, many of which are cholinergic (Martone et al., 1992; Pickel et al., 1976). Activating NK1 receptors drives cholinergic neurons (Bell et al., 1998), which subsequently leads to increased activation of spiny projection neurons within the nucleus (Galarraga et al., 1999). Large cholinergic cells in the nucleus accumbens are active in response to a cue signaling a reward and thus have been suspected to play a role in associative learning (Elliott et al., 1986; Graybiel et al., 1994).

The ventral pallidum is also implicated as an important site for SP signaling. The ventral pallidum has received increasing attention as the "final common pathway" for reward and motivational processes (Smith et al., 2009) and SP precursors are expressed in many neurons in the nucleus accumbens that project to the ventral pallidum (Lu et al., 1998; Napier et al., 1995). Indeed, the SP-containing axons massively innervate the ventral pallidum (Fig. 2) (Groenewegen and Russchen, 1984; Marksteiner et al., 1992) and at least in part terminate on ventral pallidum cholinergic neurons potentially bearing NK1 receptors (Zaborszky and Cullinan, 1992). SP injected directly into this area induces place preference behavior (Hasenohrl et al., 1992; Hasenohrl et al., 1998a; Hasenohrl et al., 1998b; Nikolaus et al., 1999).

In the nucleus accumbens, ventral pallidum, and associated areas, NK1 receptors are prominently located on cholinergic neurons (Kaneko et al., 1993; Parent et al., 1995; Pickel et al., 1976). These cholinergic neurons also contain the third vesicular glutamate transporter, VGLUT3 (Commons and Serock, 2009; Fremeau et al., 2002; Gras et al., 2002; Schafer et al., 2002), and may participate in a selective projection pathway to the basolateral amygdala (Nickerson Poulin et al., 2006). The importance of the basolateral amygdala is in its involvement in learning that has an emotional component. For example learning paradigms including inhibitory avoidance, Pavlovian fear conditioning, food and amphetamine place preference, and stimulus–drug reinforcement associations all utilize circuits within the basolateral amygdala (McGaugh, 2004; Power et al., 2003). Moreover, acetylcholine

Download English Version:

https://daneshyari.com/en/article/4327384

Download Persian Version:

https://daneshyari.com/article/4327384

Daneshyari.com