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News and reviews

Role of hemokinin-1 in health and disease

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ABSTRACT

Hemokinin-1 (HK-1), the newest tachykinin encoded by the Tac4 gene was discovered in 2000. Its name differs from that of the other members of this peptide family due to its first demonstration in B lymphocytes. Since tachykinins are classically found in the nervous system, the significant expression of HK-1 in blood cells is a unique feature of this peptide. Due to its widespread distribution in the whole body, HK-1 is involved in different physiological and pathophysiological functions involving pain inflammation modulation, immune regulation, respiratory and endocrine functions, as well as tumor genesis. Furthermore, despite the great structural and immunological similarities to substance P (SP), the functions of HK-1 are often different or the opposite. They both have the highest affinity to the tachykinin NK1 receptor, but HK-1 is likely to have a distinct binding site and signalling pathways. Moreover, several actions of HK-1 different from SP have been suggested to be mediated via a presently not identified own receptor/target molecule. Therefore, it is very important to explore its effects at different levels and compare its characteristics with SP to get a deeper insight in the different cellular mechanisms.
Since HK-1 has recently been in the focus of intensive research, in the present review we summarize the few clinical data and experimental results regarding HK-1 expression and function in different model systems obtained throughout the 16 years of its history. Synthesizing these findings help to understand the complexity of HK-1 actions and determine its biomarker values and/or drug development potentials.

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Abbreviations: HK-1, Hemokinin-1; EKA/B/C/D, Endokinin A/B/C/D; SP, Substance P; Tac1/2/3, Preprotachykinin 1/2/3 gene; NK1/2/3, Tachykinin NK1/2/3 receptor.

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1. Introduction

The tachykinin family is one of the most intensively investigated group of neuropeptides. Until 2000 the family had been composed of 3 peptides, substance P (SP), neurokinin A (NKA) derived from the preprotachykinin A/Tac1 gene and neurokinin B (NKB) encoded by the preprotachykinin B/Tac3 gene. In 2000, the newest member of the family, hemokinin-1 (HK-1) encoded by the preprotachykinin C/Tac4 gene was discovered. Its name differs from that of the other tachykinins due to its first demonstration in B lymphocytes (Zhang et al., 2000). Since tachykinins are classically found in the nervous system, the significant expression of HK-1 in blood cells is a unique feature of this peptide. It also contributed to the adaptation of the receptor nomenclature, the neurokinin or "SP-receptor" name was not appropriate anymore and therefore was changed to tachykinin NK1 receptor (Patacchini et al., 2004). Later, the Tac4-encoded neuropeptides were identified in tissues of several strains, including humans (Kurtz et al., 2002). Due to its widespread distribution in the whole body (Kurtz et al., 2002; Page et al., 2003), HK-1 is involved in different physiological and pathophysiological functions involving immune regulation (Zhang et al., 2006; Murthy et al., 2007), respiratory (Groneberg et al., 2006) and endocrine functions (Pennefather et al., 2004), as well as malignancies (Palma, 2006).

The gene structures, splice variants and receptor selectivity have extensively been reviewed (Nelson and Bost, 2004; Page, 2005, 2006), but synthesis of the expression and functional data of the last 10 years are lacking. Furthermore, it is also important to compare its characteristics with SP to get a deeper insight in the different cellular mechanisms. Since the structures of HK-1 and SP are almost 50% identical, it was not possible to differentiate them with classical immune assays. More sophisticated immunological methods (Jin et al., 2009), as well as advanced, modern molecular biological and analytical techniques might be promising tools to differentiate between the expression patterns of the two peptides. They also help to reevaluate several functions originally thought to be related to SP and reconsider the drug developmental potentials of tachykinins.

2. Structure, forms, receptor affinity

The Tac4 gene can be found in mice, rats, rabbits and humans, but isoforms of the peptide products are different compared to the Tac1-encoded SP and NKA having highly conservated structure in different strains (Table 1). The Tac4 gene encodes only one peptide, which is the rat/mouse hemokinin-1 (r/mHK-1), while in case of the human TAC4 gene the transcription is much more complicated. Four different splice variants of this gene are known, α, β, γ and δTAC4, which encode the different peptides. The αTAC4 is responsible for endokinin A and C (EKA and C) transcription, the β type encodes EKB and D, and both γ and δTAC4 encode EKB (Page et al., 2003). Furthermore, an additional peptide, the human HK-1 (hHK-1) and its fragment, the hHK-1(4-11), are encoded by this gene (Kurtz et al., 2002; Page, 2005). Due to their structural homology to other tachykinins (FXGLM-NH_2) r/m or hHK1, EKA and B belong to the classical tachykinin family, but EKC and D are classified to tachykinin gene-related peptides characterized by the GLL-NH_2 motif (Page et al., 2003).

It would be important to know whether the expression patterns and functions of rodent or human HK-1 (and endokinins:EKs) are sex-related, but unfortunately in most animal studies only one sex was involved without any comparison. In some studies, both male and female human samples were involved, but in these cases no differences were indicated between them (e.g.: Dai et al., 2012; Liu et al., 2011; Grassin-Delyle et al., 2010).

The receptor selectivity of HK-1 was first described in 2001 showing that it is a full agonist at the tachykinin NK1 receptor (Morteau et al., 2001). Further experiments showed that HK-1 is a full agonist at all NK receptors, but similarly to SP it has a remarkable selectivity to NK1. Additionally, it was less potent than SP, NKA and NKB at these classical tachykinin receptors in isolated organs (urinary bladder, pulmonary artery and ileum), but it induced dose-dependent reduction of blood pressure and salivation with similar potency to SP (Bellucci et al., 2002). Similar observations regarding HK-1 as an NK1-preferential agonist were made by Kurtz et al. (2002) on Chinese hamster ovary (CHO) cells and Camarda et al. (2002) in different isolated vessel systems. SP and HK-1 also similarly activated astrocytoma cells through the NK1 receptor (Berger and Paige, 2005). During the investigation of scratching behavior in rats it turned out that intrathecal administration of EKA/B or SP caused strong cross-desensitization to SP, but if HK-1 was administered first there was only a weak cross-desensitization to EKA/B and SP (Naono et al., 2007). The human peptides, EKA and B also showed the greatest affinity to the NK1 receptor, but interestingly, EKC and D had minimal or no affinity to any of the presently known tachykinin receptors (Page et al., 2003). The hHK-1 and its C-terminal part bound to the human NK1 receptor, and both Gs and Gq signalling could be activated (Gq seems to be predominant), but NK1 desensitization and internalization was only weakly affected (Mou et al., 2011). There was only one paper investigating the structure-NK1-binding relationship of hHk1 with 2D NMR spectroscopy. This showed that the C-terminal region is inserted into the transmembrane part of the receptor, while the N-terminal region is responsible for the binding to the extracellular loops and help the insertion of C-terminal region (Ganjiwale and Cowsik, 2015). Although the complexity and the functions of the different NK1 receptor sub-types ("classic", "septide-sensitive" and "new NK1 sensitive") are also not fully understood (reviewed in detail in Page, 2005; Newton and Page, 2007), and their significance in mediating the HK-1 effects is also unknown.

There is an increasing number of experimental data suggesting the presence of an own "hemokinin"-receptor. All these data provide only indirect evidence, since they were obtained from different systems, where the effects of HK-1 were different from that of SP or could not be blocked by NK1 antagonists. First it was suggested that SP and HK-1 act via different pathways, since HK-1 had significant effects on B lymphopoesis, which actions were not observed in case of SP (Zhang et al., 2000). In animal models, SP reduced the latency of thermal stimulation-induced pain in rats, but HK-1 could not exert this effect (Endo et al., 2006). The above described cross-desensitization properties of SP,

Table 1
Tac1 and Tac4 gene locations and the encoded peptides.

		Tac1/TAC1	Tac4/TAC4
Gene location	Mouse	6 A1	11 D
	Rat	4q21	10q31
	Human	7q21-q22	17q21.33
Encoded peptides	Mouse/rat	SP (RPKPQQFFGLM-NH_2); NKA (HKTDSFVGLM-NH_2)	r/mHK-1 (RSRTRQFYGLM-NH_2)
	Human	SP (RPKPQQFFGLM-NH_2); NKA (HKTDSFVGLM-NH_2)	hHK-1 (TGKASQFFGLM-NH_2); hHK-1 (4-11) (ASQFFGLM-NH_2); EKA (DGGEEQTLSTEAETWVIVALEEGAGPSIQLQLQEVKTGKASQFFGLM-NH_2); EKB (DGGEEQTLSTEAETWEGAGPSIQLQLQEVKTGKASQFFGLM-NH_2); EKC (KKAYQLEHTFQGLL-NH_2); EKD (VGAYQLEHTFQGLL-NH_2)

Tac1, Tac4: genes encoding mouse and rat substance P (SP), Neurokinin A (NKA), and hemokinin-1 (m/rHK-1); TAC1/TAC4: genes encoding human SP and NKA, hemokinin-1 (hHK-1) and endokinins A-D (EKA. EKB, EKC, EKD).

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