Review

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Neuronal TRP channels: thermometers, pathfinders and life-savers

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Cation channels of the TRP superfamily are widely expressed in the nervous system, and important progress has been made in elucidating the gating properties and physiological roles of neuronal TRPs. Recent studies have firmly established the role of temperature-sensitive TRPs (thermoTRPs) as the principal molecular thermometers in the peripheral sensory system, and provided the first molecular insight into the mechanisms underlying the exquisite thermo- and chemosensitivity of these channels. Moreover, accumulating evidence implicates TRP channels in the development of the central nervous system. In particular, Ca^{2+} influx via TRPC channels appears to be a critical component of the signalling cascade that mediates the guidance of growth cones and survival of neurons in response to chemical cues such as neurotrophins or Netrin-1.

Introduction to the TRP superfamily

The TRP superfamily consists of proteins with six transmembrane domains (6TM) related to the product of the *Drosophila trp* (*t*ransient *r*eceptor *p*otential) gene. TRP proteins assemble as homo- or heterotetramers to form cation-permeable ion channels [1]. Based on sequence homology, the 28 mammalian TRPs are classified into six subfamilies: TRPC, TRPV, TRPM, TRPA, TRPP and TRPML [1,2]. A seventh subfamily, TRPN, has members in lower vertebrates and invertebrates only.

Members of the TRP superfamily are expressed in probably all mammalian organs and cell types, and in recent years great progress has been made in elucidating their involvement in health and disease [3]. Here we review current knowledge of the mode of action and physiological role of TRP channels in the nervous system, particularly focussing on their function in peripheral and central thermo- and chemosensation.

TRPs as peripheral thermosensors

Thermosensing can be considered as the most elementary sense, as it is absolutely crucial for our survival [4,5]. A prompt reaction to contact with noxiously cold or hot objects is crucial to prevent acute, potentially fatal, injury. Moreover, to maintain the core body temperature around 37°C, heat production and heat loss must equal in the steady state. This requires the permanent monitoring and integration of thermal information from skin (through peripheral thermoreceptors) and deep body structures (through central thermoreceptors), and the ensuing initiation of reflexes that promote heat production or heat loss [5].

Sensory nerve fibres that convey thermal information from the head and body arise from cell bodies in trigeminal (TG) and dorsal root ganglia (DRG) [6]. These peripheral sensory nerves are subdivided into three main categories. C-type fibres are characterised by small cell bodies, the lack of myelin sheets and slow conduction velocities. Both C-type and medium-sized, myelinated and more rapidly conducting Aδ-type fibres are responsible for conveying painful signals, including noxious cold or heat. The largest cell bodies of TG and DRG give rise to Aβ-type fibres. These are myelinated, rapidly conducting primary sensory fibres that convey nonnoxious signals, including warm or cool temperatures [6]. A subset of the TRP superfamily, dubbed thermoTRPs, is highly sensitive to temperature, and several thermoTRPs essentially serve as molecular thermometers in different cell populations of the peripheral sensory system [1] (Figure 1a,b).

TRPs in heat sensation

Excitation of heat-sensitive TG and DRG neurons results from the activation of nonselective cation channels (Figure 1c). Knowledge of the molecular bases of thermosensation has experienced an explosive growth since the cloning of the capsaicin receptor TRPV1, now a decade ago [5,7]. Under basal conditions and at the resting potential of a sensory neuron, TRPV1 starts conducting significant inward cation current when temperatures rise above ~43°C [5]. In line herewith, TRPV1-deficient mice specifically lack the subset of TG and DRG neurons that is excited by moderate heat (average threshold ~43°C) [8,9]. Although there is some discussion as to whether TRPV1 is involved in the acute response to painful heat stimuli [8–10] (see Table 1 for a summary of thermosensory behaviour in thermoTRP knockout mice), it is well established that sensitisation of TRPV1 by inflammatory mediators such as bradykinin, nerve growth factor (NGF) and prostaglandins underlies the heat hyperalgesia that one experiences in injured and/or inflamed tissue [8,9]. Moreover, TRPV1 is activated by exogenous chemicals that evoke a burning sensation, including vanilloid compounds, acid, ethanol, antifungal drugs such as clotrimazole and certain spider toxins [7,11,12].

The capsaicin-insensitive homologue TRPV2 is considered an attractive molecular candidate to explain the activation of large capsaicin-insensitive neurons at

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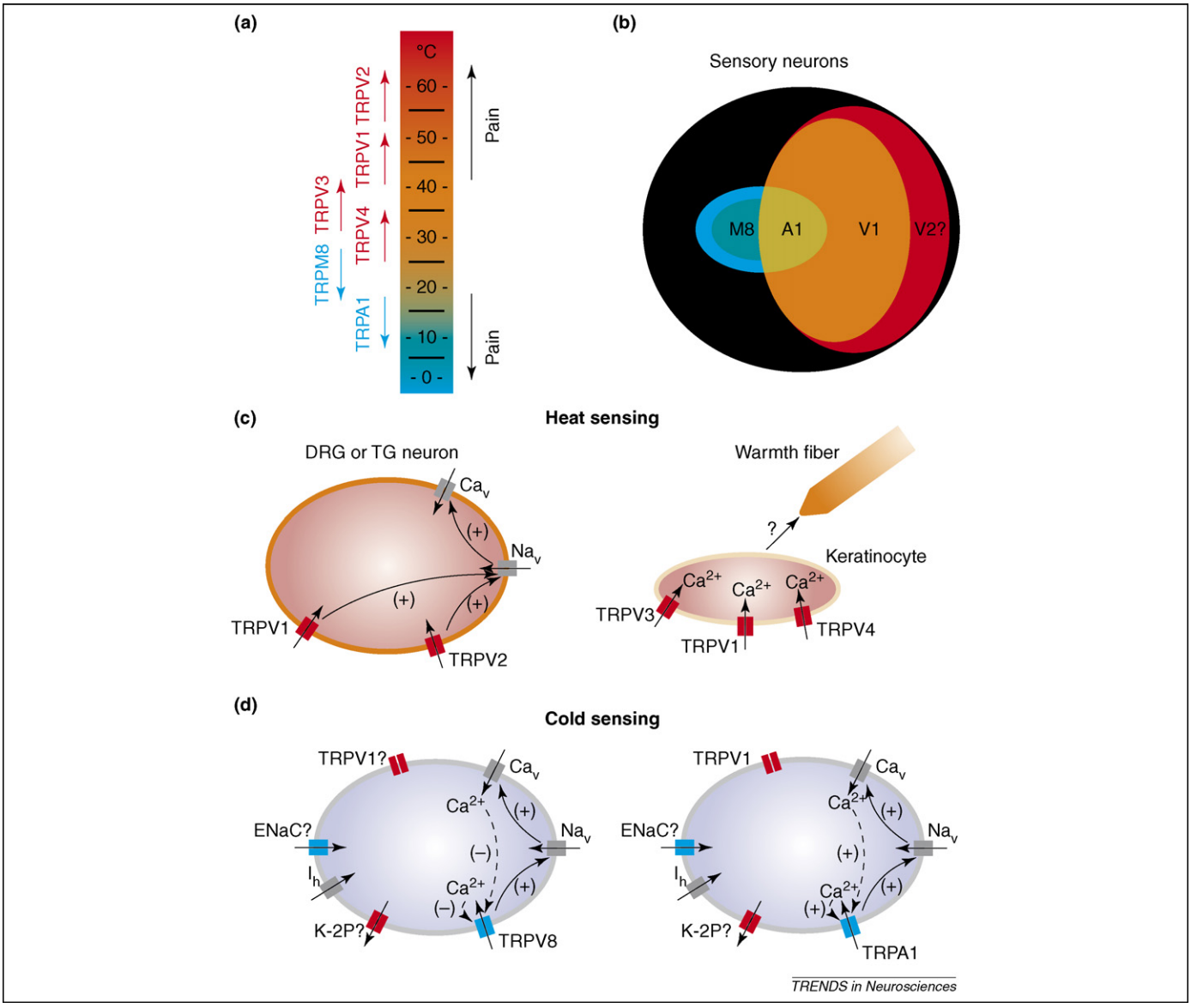

Figure 1. TRP channels in hot and cold sensation. **(a)** Diagram showing the temperature range of activation of the TRP channels involved in thermosensation. **(b)** Composition of the population of sensory neurons (DRG or TG) according to their thermal and agonist sensitivities. The ensemble of warm- and hot-sensitive neurons (red) contains the capsaicin-sensitive fraction expressing TRPV1 (orange). The cold-sensitive population (blue) contains the menthol-responsive cells expressing TRPM8 or TRPA1 (green). TRPA1-positive neurons are also activated by heat and capsaicin and can convey burning cold sensation. **(c)** Strong heat is detected by TRPV1 and/or TRPV2 in nociceptive nerve fibres. Activation of these channels causes cell depolarisation that triggers the opening of voltage-gated Na^+ and Ca^{2+} channels. Warmth is detected through the activation of TRPV3 and TRPV4 expressed in epithelial skin cells (keratinocytes), which excite sensory nerves via unknown paracrine signals. **(d)** Cool temperatures are primarily sensed by activation of TRPM8 and the consequent activation of voltage-gated Na^+ and Ca^{2+} channels. Ca^{2+} influx leads to desensitisation of TRPM8 channels through depletion of cellular PtdIns(4,5)P_2 [72]. Noxious cold can activate TRPA1 channels in a subset of nociceptive, TRPV1-expressing fibres. The activity-induced rise in intracellular Ca^{2+} further promotes channel opening [34,73]. The tetrodotoxin-insensitive voltage-gated Na^+ channel $Na_V1.8$, whose inactivation properties are resistant to cooling, is required for excitability at noxiously cold temperatures [74].

temperatures above ~50°C, as well as the residual nocifensive response to noxious heat stimuli in TRPV1-deficient mice [5]. However, some caution might be appropriate because heat-induced activation of TRPV2 is not fully understood and TRPV2-deficient mice have not yet appeared in the literature.

Two more related heat-activated channels, TRPV3 and TRPV4, exhibit already significant activity at body

Table 1. Thermosensation and thermoregulation in thermoTRP knockout mice

Response		TRPV1$^{-/-}$	TRPV3$^{-/-}$	TRPV4$^{-/-}$	TRPM8$^{-/-}$	TRPA1$^{-/-}$
Hot	Acute heat response	(+) (–)	(+)	(+)	(–)	(–)
	Heat hyperalgesia	(+)	(–)	(+)	ND	ND
Cold	Acute cold response	ND	ND	ND	(+)	(–) (+)
	Cold hyperalgesia	ND	ND	ND	(–) (+)	ND
	Chemical cooling	ND	ND	ND	(+)	(+)
Other	Temperature selection	(–)	(+)	(+)	(–)	ND
	Core temperature	(–)	(–)	(–)	(–)	ND
Selected references		[8,9]	[14]	[13,75]	[23–25]	[36,37]

(+) = significant difference from WT; (–) = no significant difference from WT; ND = not determined.