That warm fuzzy feeling: brain serotonergic neurons and the regulation of emotion

CA Lowry
Department of Integrative Physiology, University of Colorado at Boulder, Boulder, CO, USA; Psychopharmacology Unit, University of Bristol, Bristol, UK.

SL Lightman
Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, Department of Clinical Sciences at South Bristol, University of Bristol, Bristol, UK.

DJ Nutt
Psychopharmacology Unit, University of Bristol, Bristol, UK.

Abstract

Whether lying on the beach in the midday sun on a Caribbean island, grabbing a few minutes in the sauna or spa after work, or sitting in a hot bath or Jacuzzi in the evening, we often associate feeling warm with a sense of relaxation and well-being. Even ‘working up a good sweat’, exercising or performing manual labour in the garden can have its rewards. Although we take these feelings for granted, convergent lines of evidence suggest that sensations of ‘warmth’ may alter neural circuits controlling cognitive function and mood, including serotonergic circuits, in addition to those directly involved in thermoregulatory cooling. One mechanism through which sensations of warmth may modulate neural circuits controlling cognitive function and mood is the activation of temperature-activated transient receptor potential (TRP) ion channels, including TRPv3 and TRPv4 which are active in the non-noxious thermal range, 27–42 °C, and subsequent activation of a subpopulation of brainstem serotonergic neurons. In this article, we explore the hypothesis that a subpopulation of serotonergic neurons are thermosensitive and form part of a thermoafferent pathway regulating physiology and behaviour. We also propose the novel hypothesis that dysregulation of this thermosensitive population of serotonergic neurons plays an important role in stress-related neuropsychiatric disorders, including anxiety and affective disorders.

Key words
hippocampus; medial prefrontal cortex; serotonergic; serotonin; thermosensitive; TRPv4

Introduction

Since Roman times, spa therapy or warm therapy has been used as treatment for a number of medical conditions including fibromyalgia, rheumatoid arthritis, osteoarthritis and chronic back pain (Karagulle and Karagulle, 2004; Kladny, 2005; Pittler, et al., 2006; Verhagen, et al., 2000). Spa therapy has also been used in the treatment of psoriasis and atopic dermatitis (Matz, et al., 2003; Tsankov and Kamarashev, 1996). In addition, spa therapy promotes a sense of well-being that we take for granted (of course feeling warm feels good). However, is it possible that there are biological mechanisms linking warmth or warm therapy to mechanisms in the brain controlling affect? The ability to sense and respond appropriately to changes in ambient temperature and body temperature is critical for the survival of every living organism. How does the body ‘sense’ these changes in temperature? More importantly, how does the brain ‘sense’ these changes in temperature and activate the appropriate thermoregulatory cooling mechanisms? Do afferent thermal signalling mechanisms alter the activity of other physiological or behavioural endpoints apart from thermoregulatory cooling? More specifically, do afferent thermal signalling mechanisms alter the activity of brainstem serotonergic neurons that have been implicated in both thermoregulatory cooling and other endpoints including regulation of cognitive function and mood? We address these questions in this article and consider the potential role of afferent thermal signals in regulation of mood and in the pathophysiology of stress-related disorders, including anxiety disorders and depression.
Temperature-sensitive proteins

Until recently, it was difficult to envision how sensations of ‘warmth’ could be transmitted from peripheral structures, such as the skin or the upper airways, to the brain. However, recent studies have identified temperature-sensitive proteins expressed in the skin and upper airways that are responsive to temperature in the range that is critical for responding to warm temperature. These proteins, responsive to temperatures in the range of 27–42 °C, are called temperature-activated transient receptor potential (TRP) ion channels 3 and 4 (TRPV3 and TRPV4) (Patapoutian, et al., 2003). As temperature rises, TRPV4 channel activity increases until it reaches a maximal activity at approximately 40–42 °C; channel activity declines precipitously as temperature rises further (Patapoutian, et al., 2003). TRPV3 channel activity increases at temperatures >33 °C (Patapoutian, et al., 2003). Both TRPV3 and TRPV4 are found in primary sensory neurons and specific cell types in the skin where they are thought to relay signals of warmth to sensory fibres (Patapoutian, et al., 2003).

Recent studies have also described TRPV3 and TRPV4 expression in the brain, for example, in the substantia nigra where they regulate midbrain dopaminergic neuronal activity (Guattee, et al., 2005) and the hippocampus, where they also regulate neuronal activity (Shibasaki, et al., 2007). TRPV3 and TRPV4 expression in brain may contribute to activation of thermoregulatory cooling mechanisms. For example, during intense exercise, jugular venous blood temperature in humans can reach 39.5 °C, 0.2 °C higher than the peripheral blood temperature (Nybo, et al., 2002), temperatures that would be expected to cause maximal activation of TRPV4.

Thermosensitivity of brainstem serotonergic neurons

One mechanism through which warm temperature could affect mood is via control of brain neuropeptidergic systems implicated in regulation of mood, such as serotonergic systems. Brainstem serotonergic neurons, via actions on 5-HT1A and 5-HT2 receptors, are thought to play an important role in thermoregulation, specifically in the defence against hyperthermia (Hedlund and Sutcliffe, 2004). In contrast to this widely accepted role for serotonergic systems in thermoregulatory cooling, the issue of whether or not the neuronal firing rates of brainstem serotonergic neurons are responsive to warm temperature remains somewhat controversial. Early studies found evidence that neuronal firing rates of neurons in the midbrain raphe complex are thermosensitive and that firing rates are maximal when body temperature approaches life-threatening levels (Weiss and Aghajanian, 1971; Dickenson, 1977; Jahns, 1976). However, subsequent studies suggested that serotonergic neurons in the dorsal raphe nucleus (DR), which provides the serotonergic innervation of the majority of the forebrain, were not thermosensitive (Fornal, et al., 1987). Using in vivo recording in behaving cats, Fornal, et al. reported that neither exposure of cats to elevated ambient temperature nor treatment with the synthetic pyrogen, muramyl dipeptide, altered the neuronal firing rates of serotonergic neurons in vivo, even though they clearly induced thermoregulatory cooling responses. Since this time, there has been a paucity of studies on the potential role of serotonergic neurons in the brain as thermosensors. However, these in vivo studies involved recordings from relatively few neurons, whereas there are approximately 15,000 serotonergic neurons in the DR. It remains possible that a subset of serotonergic neurons within the midbrain raphe complex is thermosensitive. Indeed, studies that have identified thermosensitive neurons in the brainstem raphe complex of the cat brain in vivo have found a high density within a subregion of the DR called the interfascicular part of the dorsal raphe nucleus (DRI). This is interesting because the DRI contains a population of serotonergic neurons (Type II serotonergic neurons) with unique electrophysiological properties and behavioural correlates (Rasmussen, et al., 1984). The existence of a thermosensitive subpopulation of serotonergic neurons, clustered in a specific region of the midbrain raphe complex, could explain why some studies have identified thermosensitive neurons in the midbrain raphe complex, whereas others have not.

The DRI region contains a subpopulation of thermosensitive neurons that initiate thermoregulatory cooling

Studies in anaesthetized cats found evidence that neurons in the DRI region are responsive to local increases in brain temperature (Cronin and Baker, 1976, 1977b). Local heating of the DRI region results in physiological cooling responses in cats, including increased respiration and increased nasal mucosal temperature (two of the most important mechanisms regulating peripheral heat loss in the cat) (Cronin and Baker, 1977a). Stimulation of the midline DR alters the neuronal activity of thermosensitive neurons in the ventrobasal thalamus (Gottschlich, et al., 1984) and medial preoptic area (Werner and Bienek, 1985) (areas that are critical for thermoregulatory responses), whereas lesions of the caudal, but not the rostral, midbrain raphe complex completely prevent thermal responses in the ventrobasal thalamus (Gottschlich and Werner, 1985) and medial preoptic area (Werner and Bienek, 1990). Together, these findings are consistent with the hypothesis that the DRI, which is included in the caudal midbrain raphe complex, is critical for normal thermal responses. These observations are consistent with projections from the caudal median raphe nucleus/DRI region to the ventrobasal thalamus (Peschanski and Besson, 1984) and medial preoptic area (Tillet, et al., 1993).

The likelihood that a subpopulation of serotonergic neurons is temperature sensitive is supported by the finding that exposure of rats to elevated ambient temperature increases the expression of c-Fos, a marker of intracellular neuronal responses, in the DR, although it was not determined if these
neurons were serotonergic or whether they were restricted to the DRI region (Bratincsák and Palkovits, 2004). Also consistent with the existence of a thermosensitive subpopulation of serotonergic neurons within the DRI, the water temperature used in the forced swim test (a test commonly used to detect antidepressant-like properties of drugs) determines the amount of serotonin release in the hippocampus, a main target of DRI serotonergic neurons (Köhler and Steinbusch, 1982; Linthorst, et al., 2007). In this test, higher temperatures result in greater serotonin release in the hippocampus, as would be expected if a subset of serotonergic neurons projecting to the hippocampus was temperature sensitive. Thus, DRI serotonergic neurons may be part of a feedback system to initiate thermoregulatory cooling following increased cutaneous or core body temperature, as might occur following exercise, stress or immune activation (e.g., following induction of fever).

**Beyond thermoregulation**

Unfortunately, the specific afferent input to the DRI has not yet been determined. This is an important objective for future studies. The efferent projections of DRI serotonergic neurons have been determined in part. As mentioned above, anatomical studies suggest that the DRI serotonergic neurons project to the ventrobasal thalamus (Peschanski and Besson, 1984) and medial preoptic area/anterior hypothalamus (Taber Pierce, et al., 1976; Tillet, et al., 1993), consistent with a potential role in thermoregulatory cooling. However, DRI serotonergic neurons also project specifically to a distributed system implicated in the regulation of mood and in the pathophysiology of depression, including the medial prefrontal cortex (mPFC), frontal, cingulate, and entorhinal cortices, hippocampus and midline thalamus (Lowry, et al., 2008; Drevets, et al., 2008). It seems unlikely, based on the widespread distribution of DRI serotonergic fibres innervating the forebrain, that the function of DRI serotonergic neurons is limited to a role in thermoregulation.

**The DRI is independently regulated**

Previous studies found that the DRI is the sole location of a subpopulation of serotonergic neurons referred to as Type II serotonergic neurons. Type II serotonergic neurons are unique in that, unlike classic or Type I serotonergic neurons, their neuronal firing rates are not tightly correlated with levels of behavioural arousal or motor activity (Rasmussen, et al., 1984). In addition, Type II serotonergic neurons have unique electrophysiological responses to phasic auditory and visual stimulation (Rasmussen, et al., 1984). In a series of studies, we have recently shown that serotonergic neurons in the region of the DRI, but not elsewhere, are activated following peripheral immune activation following injection of the bacterial antigen, *Mycobacterium vaccae* (Lowry, et al., 2007). This activation of DRI serotonergic neurons was associated with an increase in serotonin and serotonin metabolism in the mPFC, a forebrain target of DRI serotonergic neurons, and was temporally associated with antidepressant-like effects in the forced swim test (Lowry, et al., 2007).

How does peripheral immune activation result in such a selective activation of a small subpopulation of serotonergic neurons? Our working hypothesis is that peripheral immune activation, via localised release of immune signalling molecules in the periphery, either directly or indirectly activates sensory nerve fibres that relay a signal, via multisynaptic connections, to the DRI. We induced peripheral immune activation in two different ways. The first was induction of a localised immune activation in the upper airways and lungs. The second was induction of immune activation following subcutaneous injection. Because both were effective in activating DRI serotonergic neurons, it suggests that multiple sensory pathways may converge on DRI serotonergic neurons. The weight of the evidence suggests that activation of the vagus nerve, a sensory nerve that innervates thoracic and abdominal ganglia, is neither necessary nor sufficient for these effects (Lowry, et al., 2007). An alternative possibility, apart from the vagus nerve, is that sensory fibres travelling to the spinal cord (Coleridge and Coleridge, 1984) relay the signal from the bronchopulmonary system to the brainstem raphe complex. If this is the case, signals arising from the bronchopulmonary system and skin may converge on the brainstem raphe complex via spinal pathways. The ability of both peripheral immune activation and thermal activation to selectively activate neurons in the very specific region of the DRI has led us to hypothesize that these stimuli converge on the same afferent pathway. Immune activation enhances both TRPV3 (Hu, et al., 2006) and TRPV4 signalling (Alessandri-Haber, et al., 2005, 2006, 2008), providing a mechanistic basis for how peripheral immune activation and cutaneous heating could provide convergent signals to selectively activate DRI serotonergic neurons and regulate emotional behaviour. Indeed, a recent study found that selective activation of TRPV3 had anxiolytic and antidepressant effects in a number of behavioural tests in mice (Moussaieff, et al., 2008). This hypothetical model is illustrated in Figure 1.

**Thermosensitive serotonergic neurons: a novel mechanism for regulation of emotional behaviour?**

Figure 1 illustrates our working model for how warm temperature in the skin or epithelial lining of the airways modulates, via DRI serotonergic neurons, neural circuits controlling emotional behaviour; 1) Cutaneous temperature receptors, predominantly nonmyelinated C fibres, are free nerve endings in the dermal and epidermal skin layers. Non-noxious, warm-sensitive thermoreceptors, with neuronal cell bodies in the dorsal root ganglia, express the temperature-activated TRP ion channels TRPV3 (~34 °C and above) and TRPV4 (~27–42 °C)
(Patapoutian, et al., 2003) and relay warm signals to lamina I of the spinal cord. 2) Free nerve endings are also observed within the epithelial lining of the trachea and lungs (Adriaensen and Scheurmann, 1993; Cutz and Jackson, 1999) where TRPV4 is abundant (Delany, et al., 2001). The cell bodies of primary sensory afferents innervating the epithelial lining of the upper airways and lungs are mainly located in the nodose and jugular ganglia of the vagus nerve but approximately 20% are located in the T1-T5 dorsal root ganglia, mainly at the T2-T3 levels (Dalsgaard and Lundberg, 1984). 3) Warm-sensitive neurons are present in lamina I of the dorsal horn (dark grey shading) and give rise to a direct contralateral spi-nothalamic projection to the ventrobasal thalamus (Andrew and Craig, 2001). 4) Neurons within lamina I of the spinal cord project, via fibre tracts in the ventrolateral funiculus, to the midline raphe magnus nucleus (RMg); lesions of RMg

**Figure 1** Hypothetical model in which the interfascicular part of the dorsal raphe nucleus is a critical component of a non-noxious, warm-sensitive, cutaneous thermoafferent pathway regulating emotional behaviour. ac, anterior commissure; DRC, dorsal raphe nucleus, caudal part; DRI, dorsal raphe nucleus, interfascicular part; mlf, medial longitudinal fasciculus; RMg, raphe magnus nucleus; ROb, raphe obscurus nucleus; RPa, raphe pallidus nucleus. Scale bar, 1 mm.
abolish the responses of both hypothalamic and thalamic responses to cutaneous heating (Taylor, 1982). Neurons within the RMg are responsive to cutaneous warming with a peak response at ~39 °C (Dickenson, 1977), a temperature response profile that is similar to that of TRPv4 (Patapoutian, et al., 2003). 5) Ascending projections from the RMg innervate the medial reticular formation and strongly innervate the region lateral and ventral to the medial longitudinal fasciculi (mlf) in the region of the DRI (Bobillier, et al., 1976). This suggests that neurons in the medial reticular formation (Petrovicky, 1981) or local interneurons in the region of the DRI relay signals from the RMg to the DRI. 6) The DRI region is a critical part of afferent pathways regulating thermoregulatory cooling (Consolazione, et al., 1984; Gottschlich and Werner, 1985; Werner and Bieneck, 1985, 1990), but serotonergic neurons in the DRI also project to forebrain limbic structures regulating emotional behaviour (Lowry, et al., 2008).

Potential role for TRPv4 in activation of brain serotonergic neurons by cutaneous or whole body heating

A temperature response profile similar to that of TRPv4 (27–42 °C, with maximal responses of approximately 39 °C) was observed in the firing rates of neurons within the brainstem raphe complex in response to cutaneous heating in rats (Dickenson, 1977). A subsequent study described similar effects of cutaneous heating on neuronal firing rates of raphe neurons, predominantly in the median raphe nucleus, which merges with the DRI caudally (Jahns, 1976). Body heating in the range of 37–39 °C, using an infrared lamp that is also likely to elevate cutaneous temperature, increases firing rates of neurons in the DRI, with peak firing rates at approximately 39 °C (Weiss and Aghajanian, 1971). However, other studies failed to identify neuronal responses to elevated body temperature (Bramwell, 1974; Fornal, et al., 1987), suggesting that perhaps only a subset of raphe neurons is thermosensitive. Identification of thermosensitive neurons in the midbrain raphe complex in some studies but not others is consistent with the hypothesis that a subset of serotonergic neurons is part of an afferent thermosensitive pathway. The temperature response profile of a subset of serotonergic neurons in the brainstem raphe complex is consistent with a role for TRPv4.

TRPv4 as a multimodal signal transduction system, warmth, hyposmosotic stimulation, mechanostimulation and inflammation

TRPv4 was originally identified as an osmosensitive calcium channel (Delany, et al., 2001; Strotmann, et al., 2000; Wissenbach, et al., 2000; Liedtke, et al., 2000; Guler, et al., 2002). TRPv4 therefore is a multimodal signalling channel. These signalling modalities are interdependent. Heat-evoked, TRPv4-mediated responses are greater in hyposmotic conditions and reduced in hyperosmotic conditions (Guler, et al., 2002). Recent studies also suggest that inflammatory mediators interact to increase TRPv4 signalling. For example, injection of inflammatory mediators (prostaglandin E2, serotonin) into peripheral receptive fields of mice increases responses of identified C fibres to hypotonic stimulation and this effect is abrogated in TRPv4-null mice (Chen, et al., 2007). In addition, wild-type, but not TRPv4-null mice, respond to inflammatory mediators with decreased threshold responses to mechanical stimulation (Chen, et al., 2007; Alessandi-Haber, et al., 2006, 2008). TRPv4 also appears to contribute to thermosensation and thermoregulation in vivo under noninjury conditions, as TRPv4-null mice respond by selecting warmer floor temperatures than wild-type mice (Lee, et al., 2005). Cell swelling, heat and chemical agonists activate TRPv4 via different mechanisms (Vriens, et al., 2004), and therefore, these stimuli may have additive or synergistic effects.

Antidepressant and anxiolytic effects of TRPv3 and TRPv4 activators

If activation of thermoafferent pathways and DRI serotonergic neurons is relevant to regulation of anxiety and mood, we would predict that activation of TRPv3 or TRPv4, either using direct chemical agonists or exposure to warmth or hyposmotic conditions, would have anxiolytic or antidepressant-like effects on behaviour. Several lines of evidence support this hypothesis. Perhaps the most striking finding is that inceosol acetate, a selective TRPv3 activator derived from the Boswellia resin, used for millennia as incense, has anxiolytic effects in the elevated plus maze and antidepressant-like effects in the forced swim test (Mousaieff, et al., 2008), effects that are absent in TRPv3-null mice. Disruption of myoinositol regulation, an abundant solute involved in osmotic balance, has been proposed as a potential mechanism underlying pathology in bipolar depression (Harwood, 2005; Silverstone, et al., 2005), whereas inositol triphosphate (IP-3), derived from myoinositol, sensitises TRPv4 to the mechano- and osmotransducing messenger 5’-6’-epoxy-eicosatrienoic acid (Fernandes, et al., 2008). In addition, a number of mood-stabilizing drugs (oxcarbazepine (Cilli and Algun, 2002), carbamazepine (Van, et al., 1994)) and antidepressant drugs (Wright and Schroeter, 2008) can induce a hypoosmotic state induced by hyponatremia (and therefore activate TRPv4 signalling), including escitalopram (Grover, et al., 2007; Coveyou and Jackson, 2007), citalopram (Bavbek, et al., 2006), mirtazapine (Bavbek, et al., 2006), venlafaxine (Romero, et al., 2007), fluvoxamine (Arizon, et al., 2002), paroxetine (Arizon, et al., 2002), bupropion (Bagley and Yaeger, 2005), lofepramine (Wylie, et al., 1989) and sertraline (Bouman, et al., 1997), while case studies suggest that hyponatremia can induce a manic state (Baar, 1994). The brain is particularly vulnerable to reductions in plasma osmolarity, such as those that occur during hypona-
Tremia (Fisher, et al., 2008), and therefore even mild hyponatremic conditions may affect TRPV4 signalling pathways.

TRPV4, DRI serotonergic systems and antidepressant-like activity

As mentioned above, peripheral injection with M. vaccae increases serotonin metabolism in the mPFC while at the same time inducing antidepressant-like behavioural responses. This begs the question of 1) whether or not other antidepressant treatments also activate DRI serotonergic neurons and increase serotonergic activity in the mPFC and 2) whether or not the antidepressant effects of these treatments are in part dependent on activation of this serotonergic circuit. Evidence suggests that the answer to the first question is yes, but the answer to the second remains to be determined.

Acute administration of antidepressant drugs increases serotonin release in the mPFC and this effect is amplified following chronic treatment, suggesting that M. vaccae and antidepressant drugs may target the same group of serotonergic neurons. For example, intraperitoneal injections of the selective serotonin reuptake inhibitors (SSRIs) citalopram, fluoxetine and fluvoxamine, the serotonin noradrenaline reuptake inhibitor (SNRI) venlafaxine and the tricyclic antidepressant (TCA) imipramine increase extracellular serotonin concentrations in the mPFC in rats (Jordan, et al., 1994; Mochizuki, et al., 2002; Muraki, et al., 2001). The selective noradrenaline reuptake inhibitor (NRI) reboxetine (although it is selective for modulation of noradrenaline reuptake) increases serotonergic cell firing rates in the DR and increases extracellular serotonin concentrations within the rat mPFC (Linner, et al., 2004). Chronic treatment with SSRIs results in facilitation of serotonin release in forebrain limbic circuits (reviewed in (Adell, et al., 2002)). Meanwhile, chronic treatment with lithium increases baseline extracellular serotonin concentrations in the mPFC and potentiates the effects of citalopram or milnacipran, an SNRI (Kitauchi, et al., 2005; Muraki, et al., 2001). Even novel (‘nonserotonergic’) drugs including (1R,2R,3R,5R)-2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (MGS0039), a selective group II metabotropic glutamate receptor (mGluR) antagonist with antidepressant-like effects in rodent models, increase serotonin release in the mPFC that persists for up to 3 h (Karasawa, et al., 2005a,b, 2008). Because taste buds also express serotonin neurotransmission in the brain by potentiating signalling in primary sensory pathways. Supporting this hypothesis, presynaptic (Type III) cells in mouse taste buds, which sense sour (acid) taste, also synthesize and release serotonin signalling in primary sensory pathways. Supporting this hypothesis, presynaptic (Type III) cells in mouse taste buds, which sense sour (acid) taste, also synthesize and release serotonin (Huang, et al., 2005a,b, 2008). Because taste buds also express the serotonin transporter (Ren, et al., 1999; Dvoryanchikov, et al., 2007), we would predict that antidepressants would alter taste thresholds. Indeed, this has been shown to be the case in human volunteers (Heath, et al., 2006).

Antidepressant drugs and peripheral serotonergic systems

TRPV4 is expressed in neurosensory cells, including inner-ear hair cells, sensory neurons, and Merkel cells, sensory cells found in the epidermis of the skin and some parts of the mucosa (stratum germinativum). Because of their strong innervation by sensory nerve fibres, Merkel cells traditionally have been proposed to be mechanoreceptors (Andres and von Düring, 2008). The presence of TRPV4 in this cell type is consistent with a mechanosensory function, but it also suggests that Merkel cells respond to thermal signals, hypoosmotic conditions and inflammation. The presence of TRPV4 in this specific cell type is interesting as Merkel cells synthesize both serotonin and the serotonin transporter (Nordlund, et al., 2008), suggesting that SSRI antidepressants could potentiate Merkel cell signalling to sensory fibres by preventing reuptake of serotonin from the synaptic space, thus facilitating activation of 5-HT receptors on sensory fibres. According to this model, antidepressants could activate DRI serotonergic neurons and serotonin neurotransmission in the brain by potentiating signalling in primary sensory pathways. Supporting this hypothesis, presynaptic (Type III) cells in mouse taste buds, which sense sour (acid) taste, also synthesize and release serotonin (Huang, et al., 2005a,b, 2008). Because taste buds also express the serotonin transporter (Ren, et al., 1999; Dvoryanchikov, et al., 2007), we would predict that antidepressants would alter taste thresholds. Indeed, this has been shown to be the case in human volunteers (Heath, et al., 2006).

Antidepressants and thermoregulatory cooling

Activation of the DRI region induces thermoregulatory cooling mechanisms (Cronin and Baker, 1977a). Consistent with a potential relationship between temperature, serotonin and mood, excessive sweating (an important thermoregulatory cooling mechanism in humans) has been associated with antidepressant drugs. It is likely that other sites and other neurotransmitter systems are involved. Notably, many antidepressant drugs increase noradrenaline release in the mPFC and other limbic structures, and antidepressant drugs also increase extracellular serotonin concentrations in the hippocampus (SSRI, paroxetine; (Hajos-Kocsok, et al., 2000)), another target of DRI serotonergic neurons (Azmitia, 1981). The DRI gives rise to a majority of the median raphe forebrain bundle tract, travelling within the ventromedial part of the medial forebrain bundle to the prefrontal cortex, frontal, cingulate, and entorhinal cortices, hippocampus and midline thalamus, suggesting that activation of DRI serotonergic neurons is likely to modulate circuits well beyond the mPFC (reviewed by (Lowry, 2002; Lowry, et al., 2008)).
antidepressant treatment including TCAs, selective serotonin-reuptake inhibitors and venlafaxine (Marcy and Britton, 2005).

Time for the sauna?

Since ancient times, professional charcoal burners in Japan entered the charcoal kilns after the burners had finished burning charcoal in order to enjoy a sauna, typically at temperatures between 40 and 50 °C (Jo, 2005). In South Korea, the same kiln procedure, called jjimjilbang (zzimzilbang), has been used for promoting health and improving the sense of well-being (Jo, 2005). Perhaps not surprisingly, sauna therapy in uncontrolled intervention studies results in self-reported decreases in anxiety and increases in mood (Hayasaka, et al., 2008). The potential for thermal activation of serotonergic systems suggests that controlled studies, perhaps involving manipulation of afferent thermal pathways, of the effects of elevated ambient temperatures on anxiety and mood are warranted.

Taking the waters

The use of thermal baths for treatment of clinical conditions has been used since the time of Hippocrates (Frosch, 2007). The consequences of these thermal signals on physiology and neural systems regulating emotional states are unclear. Nevertheless, spa bathing at 42 °C decreases salivary cortisol levels (Toda, et al., 2006), suggesting that it can influence stress-related physiology.

Summary and conclusions

In this review, we propose a hypothetical model for how elevations in peripheral temperature, immune stimulation, as well as local changes in osmotic conditions, can signal to the central nervous system to activate a subpopulation of brainstem serotonergic neurons in the DRI. These DRI serotonergic neurons are likely to play a role in thermoregulatory responses, but are also likely, via widespread connections to limbic forebrain structures, to play a role in cognitive function and mood. Activation of DRI serotonergic neurons may play an important role in physiological and behavioural responses during conditions with altered cutaneous or core temperature, such as intense exercise or exposure to warm ambient temperatures. Investigation of anatomical and functional properties of DRI serotonergic neurons is an important research objective for future studies as it may lead to new treatment approaches in depression and anxiety.

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Note added in proof: Since this article was written, Williams and Bargh (Science [2008] 322; 606–607) have shown that experiences of warm cutaneous temperature influence affective state, altering a person’s impressions of and prosocial behavior toward others, without any awareness of these influences.

References

Chen, X, Alessandri-Haber, N, Levine, JD (2007) Marked attenuation of inflammatory mediator-induced C-fiber sensitization for


