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Integrative physiology of depression and antidepressant drug action: Implications for serotonergic mechanisms of action and novel therapeutic strategies for treatment of depression

Matthew W. Hale^a, Charles L. Raison^b, Christopher A. Lowry^{c,*}^a School of Psychological Science, La Trobe University, Melbourne 3086, Australia^b College of Medicine and College of Agriculture, University of Arizona, Tucson, AZ 85724, USA^c Department of Integrative Physiology and Center for Neuroscience, University of Colorado Boulder, Boulder, CO 80309-0354, USA

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ABSTRACT

Major depressive disorder (MDD) is predicted to be the second leading cause of disability worldwide by the year 2020. Currently available treatments for MDD are suboptimal. Only 50% of MDD patients recover in less than 12 weeks with adequate treatment, and up to 20% of patients will fail to adequately respond to all currently available interventions. Moreover, current treatments come at the cost of significant central nervous system (CNS) side effects, further highlighting the need for more effective treatments with fewer side effects. A greater mechanistic understanding of MDD and the actions of antidepressant drugs would provide opportunities for development of novel therapeutic approaches to treatment. With this aim in mind, we explore the novel, but empirically supported, hypothesis that an evolutionarily ancient thermoafferent pathway, signaling via the spinoparabrachial pathway from serotonergic sensory cells in the skin and other epithelial linings to serotonergic neurons and depression-related circuits in the brain, is dysfunctional in MDD and that antidepressant therapies, including antidepressant drugs and exercise, act by restoring its function.

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Abbreviations: BDNF, brain-derived neurotrophic factor; CNS, central nervous system; DR, dorsal raphe nucleus; DRC, dorsal raphe nucleus, caudal part; DRD, dorsal raphe nucleus, dorsal part; DRI, dorsal raphe nucleus, interfascicular part; DRV, dorsal raphe nucleus, ventral part; DRVL, dorsal raphe nucleus, ventrolateral part; MDD, major depressive disorder; NDRI, norepinephrine and dopamine reuptake inhibitor; NT-3, neurotrophin-3; SARI, serotonin antagonist and reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; *Tph1*, tryptophan hydroxylase 1; *Tph2*, tryptophan hydroxylase 2; Trpv4, transient receptor potential cation channel subfamily V member 4.

* Corresponding author at: Department of Integrative Physiology and Center for Neuroscience, 1725 Pleasant Street, Clare 114, 354 UCB, University of Colorado Boulder, Boulder, CO 80309-0354, USA. Tel.: 303 492 6029; fax: 303 492 0811.

E-mail address: christopher.lowry@colorado.edu (C.A. Lowry).

1. Introduction

Major depression is predicted to be the second leading cause of disability worldwide by the year 2020 (Murray & Lopez, 1996). The mean lifetime prevalence of major depressive episodes is 14.6%, and the 12 month prevalence is estimated to be 5.5% (Bromet et al., 2011; for review, see Kessler, 2012). In other words, in the United States alone, 17 million people will experience a major depressive episode in any one year. The economic burden of depression in the United States is considerable, \$83.1 billion in 2000 and increasing. Of the 2000 total, \$26.1 billion (31%) were direct medical costs, \$5.4 billion (7%) were suicide-related mortality costs, and \$51.5 billion (62%) were workplace costs (Greenberg et al., 2003). Individuals with depression have fewer years of schooling completed and lower family incomes that, on average, are about \$10,000 per year less than those of non-depressed counterparts, or \$300,000 over a lifetime (Smith & Smith, 2010). Only 50% of depressed patients recover in less than 12 weeks with adequate treatment (Keller et al., 1992) and treatment comes at the cost of significant central nervous system (CNS) side effects, indicating a need for more effective treatment with fewer side effects.

Convergent evidence suggests that brain serotonergic systems are dysregulated in patients with MDD, and that this contributes to the pathophysiology of MDD, while antidepressant therapy normalizes serotonergic function. The monoamine hypothesis of depression states that serotonergic systems are underactive in depression; however this hypothesis conflicts with empirical data that suggest that brain serotonergic activity may be increased in individuals with depression. For example, expression of tryptophan hydroxylase, the rate limiting enzyme in the biosynthesis of serotonin, is elevated in depressed patients (Bach-Mizrachi et al., 2006, 2008). Consistent with these observations, depressed patients have increased brain serotonin turnover, and brain serotonin turnover normalizes following successful antidepressant treatment (Barton et al., 2008). Finally, allelic variants of *tph2* may be genetic predictors of depression (Zill et al., 2004; Zhang et al., 2005; Haghghi et al., 2008), hopelessness (Lazary et al., 2012), suicide risk among depressed patients (Lopez de Lara et al., 2007), and responses to antidepressant treatment (Peters et al., 2004). Evidence suggests, however, that only a subset of brain serotonergic systems are dysregulated in depressed patients, specifically a subset located in the caudal part of the midbrain dorsal raphe nucleus (Bach-Mizrachi et al., 2006, 2008). As serotonergic neurons are topographically organized, with different populations of serotonergic neurons receiving different afferents and giving rise to unique patterns of neural output, this suggests that specific serotonergic circuits are dysregulated in MDD. A greater understanding of the functional properties of different anatomical and functional subsets of serotonergic neurons, some of which may have decreased, increased, or normal activity in depression, may resolve the paradox of the monoamine hypothesis and MDD. The questions are then, which circuits are dysregulated, and what are the mechanisms involved?

A reasonable hypothesis is that a subset of serotonergic neurons with projections to depression-related forebrain circuits, as defined by human imaging studies (Drevets et al., 2008; Price & Drevets, 2010) is dysregulated in patients with MDD. Based on studies in rodents, one such population of serotonergic neurons is located in the interfascicular part of the dorsal raphe nucleus (DRI) (Lowry et al., 2008; Hale & Lowry, 2011). As we will explain in this review, DRI serotonergic systems project to forebrain circuits implicated in the pathophysiology of MDD and are uniquely sensitive to environmental stimuli, including warm temperature, cold temperature, and peripheral immune signaling. Perhaps not by chance, MDD, and related affective disorders including bipolar disorder and seasonal affective disorder, are characterized by thermoregulatory (Souetre et al., 1988; Schwartz et al., 1997; Avery et al., 1999; Rausch et al., 2003) and immune imbalances (Leu et al., 2001; Raison et al., 2006; Munkholm et al., 2012). Importantly, both thermoregulatory and peripheral immune stimuli signal to the brain

via an afferent spinoparabrachial pathway (Buller et al., 2004; Nakamura & Morrison, 2010) and effective antidepressant therapies, including exercise, normalize thermoregulatory and immune signaling. In this review, we will first define different functional subsets of serotonergic neurons, and then focus on the idea that affective disorders, with a particular emphasis on MDD, involve dysregulation of a spinoparabrachial pathway relaying environmental signals to the brain, including DRI serotonergic neurons, while antidepressant therapy normalizes its function.

2. Functional subsets of serotonergic neurons

Recent studies in rodents have defined multiple anatomically and functionally distinct subsets of serotonergic neurons in the dorsal raphe nucleus (DR), a midbrain structure that gives rise to extensive projections to forebrain circuits, including forebrain circuits modulating cognitive and affective function. In the current review, we propose that one of these subsets is particularly relevant to the cognitive and affective symptoms of MDD and to the mechanism of action of antidepressant therapies. Before discussing in detail the properties of the proposed antidepressant spinoparabrachial-DR system, it is important to contrast this system with other serotonergic systems, in order to understand why selectively activating a spinoparabrachial-DR system would be desirable, while activating other serotonergic systems would not.

The DR is the largest serotonergic nucleus in the brain and is the main source of forebrain-projecting serotonergic neurons (Azmitia & Gannon, 1986). The DR of the rat contains ~15,000 serotonergic neurons (Jacobs & Azmitia, 1992) and multiple lines of evidence suggest that they are topographically organized, with anatomically distinct groups of serotonergic neurons receiving synaptic input from specific forebrain and brainstem structures, and giving rise to anatomically distinct projections to forebrain and brainstem structures (for review, see Hale & Lowry, 2011). The patterns of afferent and efferent projections are highly organized, suggesting that there is precision in both the control of neuronal activity of subpopulations of serotonergic neurons and their output to forebrain and brainstem circuits. In addition, individual serotonergic neurons give rise to collateral or branched projections to anatomically distributed, but functionally related targets (Imai et al., 1986).

Different subregions of the DR control different physiological and behavioral processes. This is not a new observation and the functional neuroanatomical evidence presented below for several subregions of the DR is in broad support of a model of differential roles of serotonin in the control of conflict anxiety, panic-like responses, and processes associated with MDD proposed by Deakin, Graeff and colleagues (Graeff et al., 1996).

The rostral and ventral parts of the DR, (Fig. 1, blue shading) send projections to the caudate putamen, a brain region involved in motor function, learning and memory, and to sensorimotor cortical regions (for review, see Lowry et al., 2008) and it is likely that serotonergic neurons in this region play a role in sensorimotor function (Greenwood et al., 2005).

Activation of serotonergic neurons in the dorsal part of the DR (DRD) appears to facilitate conflict anxiety-like behavioral responses. Serotonergic neurons in the DRD (Fig. 1, yellow shading) send dense projections to limbic forebrain regions such as the basolateral (Ottersen, 1981; Hale et al., 2008) and central nuclei of the amygdala (Commons et al., 2003) and medial prefrontal cortex (Van Bockstaele et al., 1993) implicated in control of emotional states. The DRD is activated by stress- and anxiety-related stimuli including anxiogenic drugs (Abrams et al., 2005), social defeat (Gardner et al., 2005), uncontrollable stress (Grahn et al., 1999; Amat et al., 2005) and exposure to an open-field arena (Bouwknicht et al., 2007). Microinjection of urocortin 2 (Ucn 2), a stress- and anxiety-related neuropeptide, into the cerebral ventricles (Staub et al., 2005, 2006;

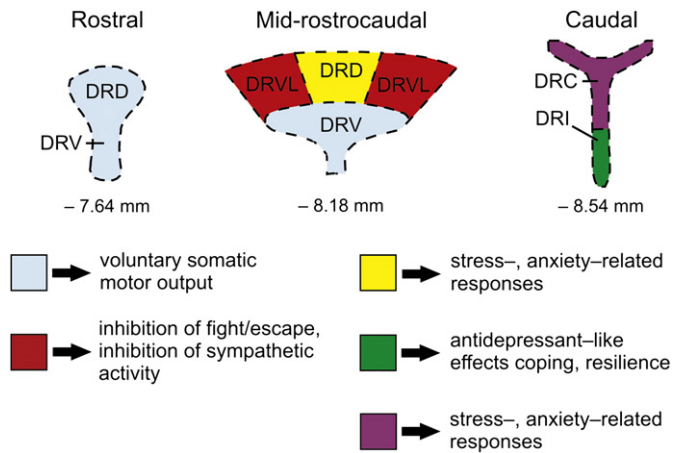


Fig. 1. Schematic illustrations of coronal sections of the rat dorsal raphe nucleus (DR) showing rostral, mid-rostrocaudal and caudal levels. Serotonin neurons in the DR can be divided into subregions based on anatomical, hodological (the pattern of afferent and efferent projections) and functional evidence. Each region controls different behavioral and physiological functions. Serotonergic neurons in the rostral and ventral parts of the dorsal raphe nucleus (DRV; shown in blue) project to the caudate putamen as well as sensorimotor cortical regions and may play a role in sensorimotor function. Serotonergic neurons in the dorsal and caudal parts of the dorsal raphe nucleus (DRD and DRC; shown in yellow and purple respectively) have been implicated in the control of anxious states while activation of serotonergic neurons in the dorsal raphe nucleus, ventrolateral part (DRVL) and in the adjacent ventrolateral part of the periaqueductal gray (VLPAG) is associated with inhibition of fight/flight-type behaviors and inhibition of sympathetic nervous system activity. Serotonergic neurons in the interfascicular part of the DR (DRI; shown in green), which have projections to the prefrontal cortex, hippocampus, and midline thalamus, are activated by warm temperature, cold temperature, and peripheral immune activation, and homologous neurons in humans may play an important role in pathophysiology of major depressive disorder and antidepressant effects.

Hale et al., 2010) or directly into the DR (Amat et al., 2004) increases activation of DRD serotonergic neurons and is associated with increased extracellular concentrations of serotonin in the basolateral nucleus of the amygdala (BLA) (Amat et al., 2004), a forebrain target of DRD serotonergic neurons (Hale et al., 2008). Hyperactivity of DRD serotonergic neurons projecting to the BLA is thought to underlie the anxiety state associated with learned helplessness (Christianson et al., 2010). Consequently, the nonselective facilitation of DRD serotonergic neurotransmission by centrally acting SSRIs and potentially other antidepressant therapies may underlie the increases of anxiety that are commonly associated with early phases of antidepressant therapy (for review, see Sinclair et al., 2009).

Serotonergic neurons in the ventrolateral part of the DR (DRVL) and in the adjacent ventrolateral part of the periaqueductal gray (VLPAG) appear to form part of an anti-panic-like system (Johnson et al., 2004, 2008). Consistent with this hypothesis, serotonergic neurons in the DRVL (Fig. 1; red shading) receive strong input from brain regions associated with control of autonomic nervous system function and send output to the dorsolateral periaqueductal gray and rostroventrolateral medulla, brainstem regions important for central autonomic control. Consistent with these findings, DRVL/VLPAG serotonergic neurons are part of a sympathomotor command system, controlling both somatic motor and sympathetic function (Kerman et al., 2006). Serotonergic signaling arising from the DRVL/VLPAG serotonergic neurons is thought to inhibit panic like responses through projections to the dorsal periaqueductal gray, where serotonin inhibits elicited panic via actions on 5-HT_{1A} and 5-HT_{2A} receptors (Pobbe & Zangrossi, 2005; de Oliveira et al., 2011; Pobbe et al., 2011) and through projections to the ventrolateral medulla, where serotonin inhibits sympathetic outflow (Davies et al., 2007; for review, see Johnson et al., 2004). In support of this model, we have found in a rat model of panic disorder involving i.v. infusion of sodium lactate

that these serotonergic neurons are highly activated by sodium lactate in control rats, but fail to be activated by sodium lactate in panic-prone rats (Johnson et al., 2008). Thus, activation of this specific subpopulation of serotonergic neurons would be predicted to inhibit panic symptoms. We have shown that serotonergic neurons in the DRVL are also activated by exposure to warm (37 °C) ambient temperature (Hale et al., 2011), which influences autonomic outflow controlling thermoregulatory effector systems. Facilitation of serotonergic neurotransmission by DRVL/VLPAG serotonergic neurons could be beneficial in MDD, particularly in patients with comorbid panic disorder (Gorman & Coplan, 1996).

The caudal part of the DR (DRC; Fig. 1, purple shading) is located at the caudal-most aspect of the DR, ventral to the cerebral aqueduct, and contains serotonergic neurons that project to the cerebral ventricles, as well as to the ependymal lining of the ventricles, circumventricular organs, and periventricular structures (Lind, 1986; Mikkelsen et al., 1997; Simpson et al., 1998). In addition to these ventricular and periventricular projections, the DRC sends projections to the ventral hippocampus (Imai et al., 1986), basolateral nucleus of the amygdala (Ottersen, 1981; Hale et al., 2008), central nucleus of the amygdala (Halberstadt & Balaban, 2006; Usunoff et al., 2006) and the infralimbic and prelimbic cortices (Van Bockstaele et al., 1993). Like the DRD, serotonergic neurons in DRC are strongly activated by emotion-related stimuli (Abrams et al., 2005; Staub et al., 2005, 2006; Hale et al., 2010). Dysregulation of this ventricle-projecting group of serotonergic neurons may be particularly relevant to studies demonstrating altered concentrations of serotonin and serotonin metabolites in the cerebrospinal fluid of patients with MDD (Lester, 1995; Mann, 2003).

A final subregion of the DR, the DRI (Fig. 1; green shading), projects to forebrain structures implicated in control of cognitive and affective function and has been associated with antidepressant-like effects (Lowry et al., 2007). Studies in rats indicate that the DRI innervates the dorsal and ventral hippocampus (Pasquier & Reinoso-Suarez, 1978; Bobillier et al., 1979; Wyss et al., 1979; Köhler & Steinbusch, 1982; Köhler et al., 1982), the medial septum (Köhler et al., 1982; McKenna & Vertes, 2001), entorhinal cortex (Köhler & Steinbusch, 1982) as well as cortical structures, including cortical Areas 17 and 18a/b (Waterhouse et al., 1986, 1993) and the barrel field cortex (Kirifides et al., 2001). A study of the efferent projections of the DRI (then referred to as the nucleus centralis superior) of cats revealed projections to the ventrolateral and dorsal periaqueductal gray, interpeduncular nucleus, lateral and dorsal hypothalamus, lateral and medial habenula, centromedial, intermediodorsal and periventricular thalamus, lateral septum, nucleus accumbens, medial amygdala and hippocampus (Taber Pierce et al., 1976). Studies in rhesus monkeys have revealed that DRI neurons contribute to the innervation of regions of the prefrontal cortex, including the dorsolateral prefrontal cortex, medial orbital cortex, inferior convexity, frontal pole, and anterior cingulate cortex (Porrino & Goldman-Rakic, 1982). This subregion of the DR is the focus of this review and will be considered in detail later. Briefly, the DRI is activated by peripheral immune activation, warm temperature, and cold temperature, stimuli that have all been shown to signal via the spinoparabrachial pathway to the brain (for references, see below). We hypothesize that the afferent limb of the spinoparabrachial pathway is dysregulated in MDD, and that antidepressants restore its function. One prediction of this hypothesis is that MDD will be associated with dysregulation of thermoregulation, particularly reflex thermoregulatory cooling mechanisms. Therefore, next we consider evidence for dysregulation of thermoregulation, including thermoregulatory cooling, in MDD.

3. Depressed patients have dysfunction of thermoregulatory cooling

Depressed patients have dysfunction of thermoregulatory cooling mechanisms, suggesting that either the afferent limb of thermal

signaling, its integration, or efferent control of thermoregulatory cooling is dysfunctional in MDD. It has been known since the 1960s that depressed patients sweat less well than healthy patients, and that sweating normalizes upon clinical recovery (Ward et al., 1983; Ward & Doerr, 1986). Incredibly, Ward and colleagues proposed in 1986 that daytime resting skin conductance (an indirect measure of sweating) was a potentially sensitive and specific marker for depression (Ward & Doerr, 1986). Mean skin conductance levels were significantly lower in individuals with depression compared with “stressed” and “non-stressed” controls and low daytime resting skin conductance levels was highly predictive of MDD (Ward et al., 1983; Ward & Doerr, 1986). Consistent with the hypothesis that depressed patients have dysfunction of thermoregulatory cooling mechanisms, several lines of evidence suggest that individuals with affective disorders have elevated body temperature. Patients with depression show elevated nocturnal temperatures compared with healthy controls, which decrease following clinical recovery (e.g., following either: ECT, antidepressant drug treatment or spontaneous recovery) (Avery et al., 1982). A similar increase in nocturnal temperature is also observed in the depressed phase of bipolar disorder (Souetre et al., 1988) and seasonal affective disorder (Schwartz et al., 1997). Despite a higher nocturnal temperature in depressed patients, there is no concomitant increase in nighttime sweating (Avery et al., 1999). As well as an increased nocturnal temperature, evidence suggests that individuals with MDD also have higher daytime (morning) temperature (Rausch et al., 2003) and that increased body temperature in general is predictive of MDD and also associated with the short form of the promoter region of the serotonin-transporter-linked polymorphic region (5-HTTLPR) (Rausch et al., 2003). Together, these previous studies suggest that thermoregulatory cooling mechanisms are dysfunctional in depressed patients. Furthermore, as mentioned above they are restored by antidepressant therapy.

We propose that the dysfunction of thermoregulatory cooling in depressed patients involves deficient afferent signaling from peripheral serotonergic sensory cells, and that antidepressant therapy restores it. Peripheral, serotonergic, sensory cells include Merkel cells in the skin, neuroepithelial endocrine cells in the airways, and enterochromaffin cells in the gut. As these cells are involved in relaying homeostatic environmental signals (including temperature) to the brain, and are targets of commonly used antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) it is possible that MDD involves dysregulation of both peripheral and central serotonergic systems, while successful antidepressant therapy normalizes function of both. Consistent with the hypothesis that both peripheral and central serotonergic systems are involved in the pathophysiology of MDD, a number of studies suggest that allelic variants in TPH1, which is expressed in peripheral tissue (in addition to allelic variants in TPH2, listed above) may be genetic predictors of MDD (Nash et al., 2005; Gizatullin et al., 2006).

3.1. Chronic stress in animal models results in chronic hyperthermia

Chronic stress is a risk factor for the development of neuropsychiatric illnesses, including MDD, and in rodent models, chronic stress is associated with a chronic hyperthermia (Ushijima et al., 2006). Repeated social defeat stress induces a chronic elevation in body temperature in mice (Keeney et al., 2001) and in rats (Hayashida et al., 2010). In rats, this chronic stress-induced hyperthermia is associated with increased immobility in the forced swim test (Hayashida et al., 2010). In addition, rats exposed to three days of variable stress (including exposure to the forced swim test, an elevated platform and restraint on consecutive days) during a critical period in adolescence results in long-term alterations in body temperature control (Yee et al., 2011).

Exercise, which is known to increase resilience to stressors (Greenwood & Fleshner, 2008), increases core temperature. However this increase occurs during the active phase of the light/dark cycle, corresponding with the peak body temperature, resulting in an increase in the amplitude of the body temperature diurnal rhythm

(Shido et al., 1997; Sugimoto et al., 1998). Chronic stress on the other hand increases body temperature during the inactive phase, corresponding with the trough, resulting in a decrease in the amplitude, or a flattening, of the body temperature diurnal rhythm (Hayashida et al., 2010). Interestingly, this 24 h body temperature profile resembles the 24 h body temperature profile of individuals with depression (Avery et al., 1982), the depressed phase of bipolar disorder (Souetre et al., 1988) and the depressed phase of seasonal affective disorder (Schwartz et al., 1997). It would be of interest to determine if chronic-stress induced hyperthermia could be ameliorated with either exercise or antidepressant drug treatment.

4. A spinoparabrachial pathway provides homeostatic signals to the central nervous system

In this review we propose the potentially transformative hypothesis that an evolutionarily ancient thermoafferent pathway, signaling from serotonergic sensory cells in the skin and other epithelial linings (e.g. Merkel cells in the skin, neuroepithelial endocrine cells in the airways, and enterochromaffin cells in the gut), via the spinoparabrachial pathway, is dysfunctional in patients with major depressive disorder (MDD) and that antidepressant therapies, including antidepressant drugs and exercise, act by restoring the function of this thermoafferent pathway. This hypothesis challenges the existing paradigm that antidepressant therapies must directly target the CNS.

According to the monoamine hypothesis of depression, brain monoaminergic systems are dysfunctional and antidepressant drugs act within the brain to facilitate monoaminergic function. In the case of serotonergic systems, it is thought that increases in extracellular serotonin concentrations in the region of somatodendritic serotonin 1A (5-hydroxytryptamine_{1A}; 5-HT_{1A}) autoreceptors lead to, over time, a functional desensitization of 5-HT_{1A} autoreceptors in the DR and consequently an increase in neuronal firing rates of serotonergic neurons and serotonergic neurotransmission. We propose a refinement of this hypothesis, that the therapeutic effects of antidepressant drugs are dependent on increased neurotransmission of DRI serotonergic neurons, specifically. This could be achieved either by decreasing 5-HT_{1A} autoreceptor-mediated inhibition, by increasing excitatory synaptic input (e.g. from the spinoparabrachial pathway), or both.

Acute antidepressant treatment may be ineffective because antidepressant drugs such as SSRIs increase 5-HT_{1A} receptor-dependent autoinhibition of serotonergic neuronal firing rate, which prevents their ability to increase extracellular serotonin concentrations in some forebrain target regions. For example in the prefrontal cortex, acute SSRI treatment increases serotonin concentration in the medial prefrontal cortex, but not in the dorsolateral prefrontal cortex, whereas acute SSRI treatment combined with the 5-HT_{1A} receptor antagonist, WAY-100635, or chronic SSRI treatment does increase extracellular serotonin concentrations in the dorsolateral prefrontal cortex (Beyer & Cremers, 2008). One hypothesis therefore is that only after downregulation or functional desensitization of 5-HT_{1A} autoreceptors in the DR, processes that take time, are SSRIs able to increase extracellular concentrations in these regions. Changes in postsynaptic serotonin receptors, for example the serotonin type 2A receptor, may also be important in the effectiveness of SSRIs (Lucae et al., 2010). Another hypothesis would be that SSRI-dependent plasticity in the afferent arm of the spinoparabrachial pathway, a process that may also take time, is important in the expression of antidepressant-like properties of SSRIs.

5. Activation of a putative antidepressant spinoparabrachial/serotonergic pathway by environmental stimuli

In 2007, we discovered that preimmunization and subsequent challenge of mice with the nonpathogenic, saprophytic mycobacterium, *Mycobacterium vaccae*, activates a specific subpopulation of serotonergic

neurons in the DRI (Lowry et al., 2007). Meanwhile, a previous clinical trial using *M. vaccae* for treatment of cancer found that treatment with *M. vaccae* increased quality of life scores, including increased emotional health, increased cognitive function, and decreased pain (O'Brien et al., 2004). We reasoned that the beneficial effects of *M. vaccae* on quality of life scores in cancer patients could be related to the activation of DRI serotonergic neurons, and set out to define potential mechanisms. Of particular interest, serotonergic neurons in the DRI and in the dorsal part of the median raphe nucleus, which are developmentally linked to DRI serotonergic neurons (Jensen et al., 2008; Bang et al., 2012), project specifically to a distributed system implicated in affective control and in the pathophysiology of depression (Drevets et al., 2008; Lowry et al., 2008). In follow up studies, we demonstrated that treatment with *M. vaccae* increased serotonergic activity in the medial prefrontal cortex (mPFC) and had antidepressant-like behavioral effects in the forced swim test (FST) in mice (Lowry et al., 2007). Experimental evidence suggested that spinal, and not vagal, afferents were involved (Lowry et al., 2007). Therefore, we explored the possibility that activation of spinal afferent pathways could activate DRI serotonergic neurons and have antidepressant-like effects. Independent electrophysiologic recording studies conducted in the 1970s had found that cutaneous warming could activate brainstem serotonergic neurons (for review, see Lowry et al., 2009), particularly those within the DRI region. In recent studies, we've confirmed that exposure to either warm or cold ambient temperature, both of which signal to the brain via the spinoparabrachial pathway (Nakamura & Morrison, 2010), activates DRI serotonergic neurons (Hale et al., 2011; Kelly et al., 2011). Thus, we've identified convergent effects of thermal signals and peripheral immune activation on DRI serotonergic neurons, both of which are now known to signal via spinoparabrachial pathways to the brain (Buller et al., 2004; Nakamura & Morrison, 2010). It should be noted here that although glutamatergic projections from the lateral parabrachial nucleus to the DR have been described (Lee et al., 2003), direct evidence that this glutamatergic projection is activated by thermal stimuli is lacking. Demonstrating a causal role for the lateral parabrachial nucleus in the activation of DRVL/VLPAG and DRI serotonergic neurons by warm temperature is an important objective for future studies. We have documented that c-Fos expression in the external lateral part of the lateral parabrachial nucleus (a thermosensitive subdivision) is correlated with c-Fos expression in serotonergic neurons in the DRVL/VLPAG and DRI subdivisions of the DR (Kelly et al., 2011), but a direct causal link has not yet been established.

As discussed above, inoculation with *M. vaccae* increases serotonergic activity in the mPFC and is associated with antidepressant-like behavioral effects in the FST (Lowry et al., 2007); however, critical experiments that would demonstrate that DRI serotonergic neurons are necessary for antidepressant-like effects have not yet been done, and will require targeted lesions or temporary inactivation of these cells. This is an important goal for future research.

Next we consider mechanisms through which the spinoparabrachial pathway relays environmental stimuli from the periphery to the CNS, and the potential involvement of peripheral serotonergic sensory systems.

6. Peripheral serotonergic cells as biosensors

Although much is known about serotonergic neurons in the brainstem raphe complex, less is known about serotonergic systems in the periphery, which account for the majority of serotonin in the body. Brain serotonergic neurons express *tph2* (Walther et al., 2003), while peripheral serotonergic cells express *tph1* (Patel et al., 2004). Both isoforms catalyze the rate-limiting enzymatic step in the biosynthesis of serotonin. What is perhaps underappreciated by most researchers is that many of the peripheral serotonergic systems are

sensory cells that form synaptic contacts with afferent fibers, typically sensory neurons with cell bodies in dorsal root ganglia, or sensory ganglia of cranial nerves. Because these sensory serotonergic cells are typically located in the epithelium, at the interface between the environment and the body, peripheral serotonergic systems have the potential to relay a number of sensory modalities to the CNS. We propose that these peripheral serotonergic systems function as “biosensors”, sensing environmental stimuli and relaying information to the brain. For example, serotonergic Merkel cells, located deep in the epidermis, express the temperature-sensitive ion channel transient receptor potential cation channel subfamily V member 4 (TRPV4) (Suzuki et al., 2003; Boulais, Pennec, et al., 2009; Boulais, Pereira, et al., 2009), a channel that is warm-sensitive (~27–39.5 °C), osmosensitive, and mechanosensitive (sensitive to light touch; Fig. 2). In addition, the response of TRPV4 to sensory stimuli can be sensitized by proinflammatory cytokines, such as tumor necrosis factor alpha (TNF- α ; Kochukov et al., 2009), suggesting that the same signaling system may relay signals of both warm temperature and peripheral immune activation to the CNS. Serotonergic neuroepithelial endocrine cells within the bronchopulmonary system, which have reciprocal synapses with sensory fibers, are believed to be hypoxia sensors (Cutz & Jackson, 1999; Fu et al., 2002). The transient receptor potential (TRP) cation channel TRPA1, which is activated by pungent compounds or cold temperature, is highly expressed in serotonergic enterochromaffin cells in the gastrointestinal system, and controls gastrointestinal motility (Nozawa et al., 2009). Sensory serotonergic cells in taste buds are stimulated by bitter, sweet, or sour (acid) tastants (Huang et al., 2005). Serotonin serves as a neurotransmitter in this sensory system and SSRIs alter taste thresholds (Heath et al., 2006). In the retina, amacrine cells (interneurons) synthesize serotonin and bipolar neurons accumulate serotonin, likely through active transport of serotonin via the serotonin transporter, and metabolize serotonin released from amacrine neurons (Ghai et al., 2009). These are just a few of many examples of the ways that serotonin signaling is central to the functioning of peripheral sensory pathways. Thus,

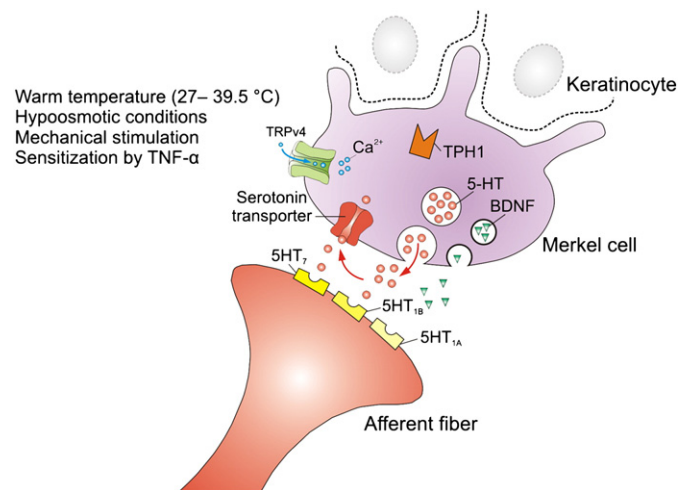


Fig. 2. Schematic illustration of a Merkel cell, located deep in the epidermis. Merkel cells express the temperature-sensitive ion channel transient receptor potential cation channel subfamily V member 4 (TRPV4), a channel that is warm-sensitive (~27–39.5 °C), osmosensitive, and mechanosensitive (sensitive to light touch). The response of TRPV4 to sensory stimuli can be sensitized by proinflammatory cytokines, such as tumor necrosis factor alpha (TNF α), suggesting that the same signaling system may relay signals of both warm temperature and peripheral immune activation to the CNS. Merkel cells synthesize serotonin and express the serotonin transporter, suggesting that, like serotonergic neurons in the brain, they are targets of the SSRI class of antidepressant drugs. Abbreviations: 5-HT_{1A}, 5-hydroxytryptamine receptor type 1A; 5-HT_{1B}, 5-hydroxytryptamine receptor type 1B; 5-HT₇, 5-hydroxytryptamine receptor type 7; BDNF, brain-derived neurotrophic factor; TNF- α , tumor necrosis factor alpha; TRPV4, temperature-sensitive ion channel transient receptor potential cation channel subfamily V member 4; TPH1, tryptophan hydroxylase 1.

serotonergic cells in the retina, the cutaneous membrane and other epithelial tissues (all interfaces between the environment and the organism) serve as biosensors that detect or modulate multiple modalities of sensory stimuli. Through afferent signaling, these serotonergic cells can relay this information to the CNS.

The impact of these sensory serotonergic systems on central serotonin functions is not clear. One possible exception is a potential role of CO₂/acidic pH-sensitive peripheral serotonergic systems signaling to brain serotonergic neurons. We have shown that hypercapnia, which results in acute elevation of blood pH and signaling via chemoreceptors in the periphery, strongly activates DRVL/VLPAG and DRI serotonergic neurons (Johnson et al., 2005), a pattern that is remarkably similar to that observed following exposure to either cold (Kelly et al., 2011) or warm (Hale et al., 2011) temperature. Although there is no direct evidence that peripheral serotonergic systems mediate this signal, one hypothesis is that serotonergic neurons, collectively, function as CO₂/pH sensors (Richerson, 2004), and therefore it is likely that serotonergic cells in peripheral chemosensory organs are activated by CO₂/acidic pH. Consistent with this hypothesis, serotonin is stored in carotid body receptors (glomus type 1 cells) (Habeck et al., 1994; Oomori et al., 1994) and is released during chemoexcitation (Zhang & Nurse, 2000; Zhang et al., 2003).

Peripheral serotonergic cells are dependent on growth factors, including brain-derived neurotrophic factor (BDNF) (LeMaster et al., 1999) and neurotrophin-3 (NT-3) (Sieber-Blum et al., 2004), which is highly enriched in serotonergic Merkel cells, for their innervation and proliferation. Merkel cells are known to synthesize serotonin (Tachibana et al., 2005) and express the serotonin transporter (Nordlind et al., 2008), suggesting that, like serotonergic neurons in the brain, they may be targets of the SSRI class of antidepressant drugs. Patients with MDD have altered expression of neurotrophic factors (Duman et al., 1997; Duman & Monteggia, 2006; Otsuki et al., 2008). Peripheral BDNF and NT-3 concentrations are low in depressed patients (Duman & Monteggia, 2006), and allelic variation in the NT-3 receptor, p75 has been associated with major depression (Fujii et al., 2011). Evidence from transgenic mouse models involving disruption of the BDNF signaling pathways supports the interaction between BDNF and the antidepressant effects of SSRIs (for review, see Martinowich et al., 2007). Mice lacking TrkB receptors in the fore-brain or overexpressing a truncated form of the TrkB receptor (TrkB.T1; which show reduced TrkB activation in brain) are resistant to the behavioral effects of SSRI antidepressant drugs (Saarelainen et al., 2003). Interestingly, TrkB receptor knockout mice show reduced density of Merkel cells in glabrous skin compared with WT controls (Perez-Pinera et al., 2008).

We propose that depressed patients, who have decreased concentrations of peripheral BDNF and NT-3 (Duman & Monteggia, 2006), suffer from a lack of sensory input from these multimodal signaling systems (temperature, chemical stimulation, taste). This may relate to one of the core symptoms of MDD, “markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).” A lack of sensory stimulation may lead to disengagement from the environment, which may secondarily lead to a number of symptoms characteristic of MDD. Indeed, depressed patients are reported to have increased activity of the CNS default mode network, a network of brain regions associated with introspection, and have difficulty disengaging this network and shifting to neural circuits associated with engagement with the environment (Drevets et al., 2008).

We propose that serotonergic biosensors are nature's antidepressant pathways, using serotonin as a neurotransmitter to activate, via multisynaptic pathways, specific neural circuits in the brain. At the evolutionary level, exposure of an organism to environmental extremes of warm or cold temperature, CO₂ or O₂ concentrations, pH, osmolality, tastants, or mechanosensory stimuli, would be expected

to demand a shift from introspection to engagement with the environment in order to assess the risk posed by these conditions and to engage in behaviors designed to restore bodily homeostasis. In addition, because peripheral serotonergic sensory cells express the serotonin transporter, they are, like brain serotonergic neurons, targets of the SSRI class of antidepressant drugs. We propose that activation of peripheral serotonergic biosensors activates sensory pathways (cranial nerve II for illuminance stimuli (Shen & Semba, 1994; Cajochen et al., 2005), cranial nerve VII, IX for taste, spinal afferents giving rise to a spinoparabrachial pathway for warm temperature in the skin) that, via multisynaptic pathways, converge on specific subpopulations of serotonergic neurons in the DR that mediate antidepressant responses. We predict that activation of serotonergic gustatory cells, serotonergic gut enterochromaffin cells, serotonergic bronchopulmonary neuroepithelial endocrine cells, or serotonergic Merkel cells will also engage lateral parabrachial nucleus pathways and brainstem serotonergic systems, but this would require specific experimental approaches to address each sensory modality. In the case of gut enterochromaffin cells (ECs), however, indirect evidence suggests that activation of ECs may signal to the parabrachial nucleus. The lateral parabrachial nucleus is an important component of the gut-brain axis, and processes gastrointestinal sensory information (Castex et al., 1998). In rats, infection with *Campylobacter jejuni* increases c-Fos expression in the lateral parabrachial nucleus in the absence of any measurable peripheral immune activation (serum concentrations of TNF- α , IL-1 β and IL-6) (Gaykema et al., 2004). Following infection with *C. jejuni* in humans, a subset of patients goes on to develop post-infection irritable bowel syndrome. These patients show increased numbers of serotonin containing ECs compared with patient controls (asymptomatic after infection) and healthy controls, and also show increased anxiety and depression scores compared with controls (Dunlop et al., 2003).

The role for peripheral serotonergic biosensors in central serotonergic pathways and antidepressant effects is not yet clearly established, and further experimental evidence is required to demonstrate that activation of peripheral serotonin biosensors leads to activation of the lateral parabrachial nucleus and serotonergic neurons in the brainstem raphe complex. This hypothesis could be tested using local application of SSRI drugs to peripheral targets, followed by assessment of neuronal activity in the lateral parabrachial nucleus and serotonergic neurons in the brainstem raphe complex.

7. Serotonergic systems and resilience

What are the key psychological processes that the serotonergic biosensory pathways normally mediate such that dysregulation of the sensory pathways results in depression? The hypothesis that in depression there is a dysregulation of the serotonin biosensory cells and pathways, which normally serve to sense environmental changes and respond to restore bodily homeostasis, is consistent with Deakin and Graeff's (1991) suggestion that serotonergic systems are primarily involved in adaptive responses to aversive stimuli. Deakin and Graeff (1991) suggest that serotonergic systems play an important role in minimizing the impact of aversive events on behavior and adapting to aversive stimuli and that depression may correspond to a failure in the mechanism of adaptation and resilience to aversive events (Deakin, 1996). The suggestion that serotonergic systems throughout the body are important components of resilience mechanisms is supported by the evidence that exercise alters serotonergic neurotransmission and promotes resilience (Greenwood & Fleshner, 2011). Similarly, resilience and adaptation to adverse events in rodents can be promoted by returning animals to group housing following exposure to an aversive stimulus and Deakin (1996) hypothesized that this may in fact be mediated by tactile or warmth stimuli, both of which would signal the brain via serotonergic Merkel cells in the skin.

8. Antidepressant drugs induce thermoregulatory cooling

Antidepressant drugs induce thermoregulatory cooling (sweating) in humans, consistent with the idea that thermoregulatory function may be relevant to antidepressant drug action, or a biomarker of successful antidepressant drug action. Induction of thermoregulatory cooling seems to be a common effect of all antidepressant therapies. For example, diverse classes of antidepressant drugs, including SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), norepinephrine dopamine reuptake inhibitors (NDRIs), serotonin antagonist and reuptake inhibitors (SARIs), and tricyclic antidepressants (TCAs) induce excessive sweating (Marcy & Britton, 2005; Demling et al., 2010). Indeed, a number of ongoing clinical trials are designed to prevent excessive sweating in depressed patients being treated with SSRIs. Even electroconvulsive therapy has been shown to induce a delayed increase in the number of active sweat glands, coinciding with clinical recovery (Bagg & Crookes, 1966).

9. Integrative nature of temperature, circadian and sleep physiology

Temperature, circadian and sleep physiology are integrated at neurophysiological and behavior levels. Sleep quality is best when it occurs as core temperature is decreasing and skin temperature is increasing (Raymann et al., 2005, 2008; Van Someren, 2006). There is also a sleep-induced decrease in temperature independent of changes in activity or in circadian timing (Lack et al., 2008). Both circadian and sleep processes contribute to the observed amplitude and mean daily level of body temperature. Findings from experimental studies show bi-directional influences between temperature and sleep such that manipulation of core and skin temperatures can improve or disrupt sleep and disturbed sleep can alter body temperature (for review, see Harvey, 2011). Sleep and temperature physiology are disturbed in patients with MDD and sleep disruption negatively influences quality of life in patients with MDD (Bunney & Potkin, 2008; Harvey, 2011).

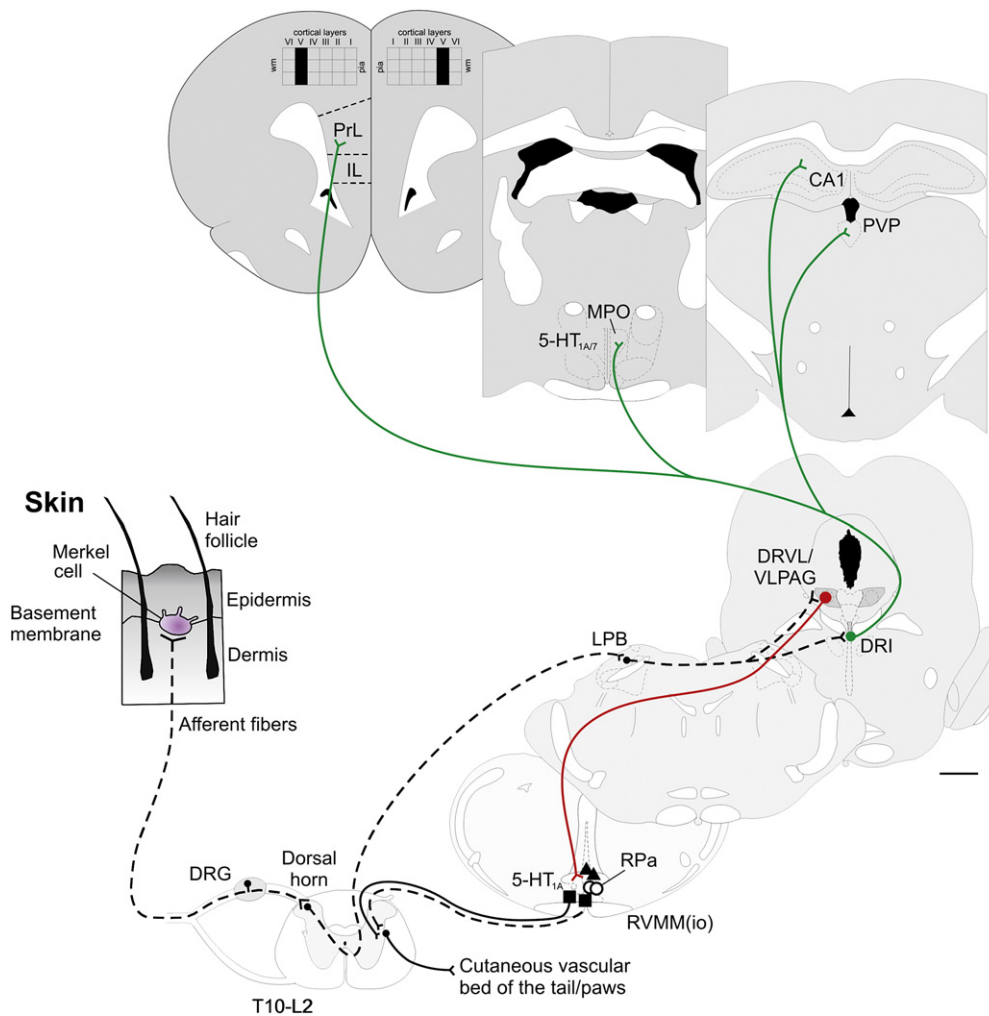


Fig. 3. Hypothetical model of warm cutaneous temperature-induced activation of a spinoparabrachial pathway, leading to activation of subsets of anxiolytic- and antidepressant-related serotonergic neurons (Adapted with permission, from Fig. 12 of Hale et al., 2011). Warm temperature activates TRPV4 channels (multimodal sensory channels) inducing an influx of calcium and release of serotonin from Merkel cells deep in the epidermis. Serotonin activates 5-HT receptors on sensory afferents, leading to activation of sensory fibers projecting to the spinal cord. Spinal neurons relay the signal to the lateral parabrachial nucleus (LPB) in the brainstem. Glutamatergic neurons in the LPB project to the dorsal raphe nucleus, activating serotonergic neurons in the 1) ventrolateral part of the dorsal raphe nucleus (DRVL)/ventrolateral periaqueductal gray (VLPAG; red lines; implicated in inhibition of anxiety/panic-like responses and inhibition of sympathetic outflow from the ventral medulla, and 2) interfascicular part of the dorsal raphe nucleus (DRI; green lines), which project to forebrain limbic structures implicated in major depression. Serotonin acts in the prelimbic part of the medial prefrontal cortex, via 5-HT_{2A} receptors, to activate layer V pyramidal neurons, which are known to project back to the dorsal raphe nucleus to inhibit anxiety-promoting serotonergic neurons in a model of learned helplessness (not shown), thus demonstrating how the afferent thermosensory system may influence “top-down” regulation of depression circuits, for example during cognitive behavioral therapy (CBT), mindfulness-based cognitive therapy (MBCT), behavioral activation (BA) therapy, etc. Abbreviations: 5-HT, serotonin; 5-HT_R, 5-HT receptors; CA1, CA1, cornu ammonis 1 region of the dorsal hippocampus; DRG, dorsal root ganglion; IL, infralimbic cortex; MPO, medial preoptic nucleus; PrL, prelimbic cortex; PVP, paraventricular thalamic nucleus, posterior part; RPa, raphe pallidus nucleus; RVMM(io), rostral ventromedial medulla (inferior olive level).

These data are consistent with previous studies showing that 1) patients with seasonal affective disorder in winter during depression have blunted thermoregulatory cooling but have thermoregulatory cooling that is similar in efficiency to control subjects after successful antidepressant response to phototherapy (Arbisi et al., 1989). Anterograde and retrograde tract tracing experiments have demonstrated that the retina sends direct projections to the DRVL/VLPAG region (Shen & Semba, 1994; Fite et al., 1999). These retinal projections are intermingled with serotonergic neurons in the DRVL/VLPAG (Shen & Semba, 1994), and as mentioned above, serotonergic neurons in this region are thought to control autonomic function (Kerman et al., 2006); 2) ECT increases the circadian amplitude of core body temperature, and decreases mean core body temperature, particularly during the nighttime thermoregulatory cooling period (Szuba et al., 1997); and 3) thermoregulatory cooling, as evidenced by the number of active sweat glands in depressed patients, increases upon clinical recovery, but not earlier, following ECT (Bagg & Crookes, 1966). We hypothesize that these relationships are due to dysfunction of the afferent signaling arm of the thermoregulatory system in MDD, specifically the warm afferent system projecting to the lateral parabrachial nucleus (LPB) and, secondarily, to the DRVL/VLPAG and DRI subsets of serotonergic neurons that have been implicated in anxiolytic and antidepressant actions, respectively, and to the normalization of warm afferent signaling following treatment (Fig. 3).

10. Potential relevance to non-pharmacological antidepressant action, such as exercise

Previous studies have shown that chronic exercise increases peripheral BDNF (Goekint et al., 2011). Although the source of this peripheral BDNF is not yet certain, we hypothesize that chronic exercise increases BDNF synthesis and release from Merkel cells and other serotonergic biosensors. Of potential interest, previous studies have shown that warm temperature potentiates exercise-induced increases in peripheral BDNF (Goekint et al., 2011). Increased BDNF leads to both the proliferation of Merkel cells (LeMaster et al., 1999) and increased innervation of Merkel cells by sensory afferents (Haerberle et al., 2004). Other neurotrophic factors, e.g. NT-3, are also expressed by Merkel cells (Sieber-Blum et al., 2004), and are involved in the maintenance of innervation of Merkel cells.

Several lines of evidence suggest that chronic exercise improves thermoregulatory cooling efficacy. Trained athletes tend to sweat more than untrained controls (Ichinose-Kuwahara et al., 2010) even when exercising at a moderate intensity (Cramer et al., 2012).

It should be noted here that studies of the effectiveness of exercise for the treatment of affective disorders have provided mixed results. A recent large randomized control trial showed that a physical activity intervention, consisting of face-to-face meetings and telephone consultations with trained physical activity facilitators, increased physical activity, but did not improve outcomes for depression (Chalder et al., 2012). Despite this, recent meta-analyses have provided some support for the effectiveness of exercise in the treatment of depression (Herring et al., 2012; Rimer et al., 2012); however these benefits may be short term (Krogh et al., 2011). Further research is required to determine the optimal type, intensity and duration of physical activity that are required to produce antidepressant effects.

11. Implications for novel therapeutic strategies for treatment of depression

The hypothesis that dysregulation of a thermoafferent signaling pathway, from serotonergic sensory cells in the skin and other epithelial linings to mood-related brain regions, is associated with the pathophysiology of MDD suggests several novel therapeutic strategies. Evidence suggests that whole body hyperthermia (WBH) has antidepressant effects in cancer patients for at least 72 h following WBH (Koltyn

et al., 1992) and recent evidence suggests that thermal therapy with far-infrared sauna improves quality of life scores among patients with type II diabetes mellitus (Beever, 2010).

12. Summary

In this review we explored the highly novel, but empirically supported, hypothesis that serotonergic biosensors in the skin and other epithelial linings of the body are nature's antidepressant pathways, using serotonin as a neurotransmitter to activate specific neural circuits in the brain associated with control of cognitive and affective function. We propose the potentially transformative hypothesis that a spinoparabrachial pathway, relaying sensory information from temperature-sensitive, serotonergic sensory cells in the skin and other epithelial linings to brain mesolimbic serotonergic systems, is dysfunctional in patients with major depressive disorder (MDD), and that antidepressant therapies act by restoring its function. Briefly, we propose that warm temperature acts via TRPV4 ion channels to induce synaptic release of serotonin from sensory serotonergic cells (e.g. Merkel cells) in the cutaneous membrane. Serotonin acts within the sensory synapse to activate serotonin receptors on sensory receptors in the dorsal root or cranial ganglia, resulting in activation of a thermosensitive spinoparabrachial pathway. Because sensory serotonergic cells express the high affinity, low capacity serotonin transporter, they, like serotonergic neurons in the brain, are targets of the selective serotonin reuptake inhibitor (SSRI) class of antidepressant drugs. Activation of the warm-sensitive spinoparabrachial pathway in turn activates glutamatergic neurons within the LPB that project to specific subpopulations of serotonergic neurons in the DR previously implicated in antidepressant-like responses.

13. Conclusions

In conclusion, further studies of thermoregulatory function in MDD, and the response to antidepressant therapies, are warranted. The hypothesis outlined here provides a hypothetical framework for how therapies that affect thermoafferent signaling, such as currently used antidepressant drugs, whole-body infrared heating, or chronic exercise may have therapeutic effects. Further clinical trials involving therapies that directly target thermoafferent signaling pathways are warranted.

Conflict of interest

MWH declares no conflict of interest. In the previous 12 months Dr. Raison has served as a consultant to PamLab and Bristol Myers Squibb. He has developed and presented slides for promotional disease state programs for PamLab. In the previous 3 years, CAL has consulted for Enlight Biosciences.

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