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REVIEW ARTICLE

A concise review and update of the anatomical circuitry of itch

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Abstract

Chronic itch is a common, debilitating condition with major disease burden. Clinical management currently is based mainly on systemic antihistamines, steroids, anti-inflammatory drugs, antibiotics and lately biologics. These treatment strategies may have their own limitations and side effects. A critical and detail elucidation and understanding of the chronic itch scratch anatomical pathway is pivotal in designing new strategies in the management of this recalcitrant condition. Patients should also be informed about the anatomy and physiology of scratch which may enhance education, counselling and understanding of the condition. An integrated patient centre holistic approach should be adopted in management.

Keywords: Chronic Itch Scratch Pathway; Itch Specific Neurons; Central Nervous System; Cognition; Itch Inhibition Pathway; Education

Introduction

Hedonists enjoy itch while many chronically ill suffered the distressing symptoms and consequences of unrelieved scratchings or itchings of resistant skin diseases like atopic dermatitis (AD), chronic liver, renal diseases, internal malignancy and ketamine and opioids addictions. Scratching as a cognitive movement, reflect our body innate reaction to the hostile environment. It also evolved slowly becoming a body gesture mirroring what our mind thinks consciously or subconsciously in social and life circumstances. Major advances in neurosciences and molecular biology unveiled our human body has a system of complicated and structured morphological itch or pruritogenic pathway with important neuro-physiological functions; enhancing us to better adapt to a changing world and better survival advantages.

Our journey of itch starting from the outmost layer of our body integument; the epidermis; with its specialised keratinocytes which morphologically and functionally be regarded as the outermost sensors of the peripheral nervous system (PNS) [1]. Epidermal keratinocytes possessed the widely distributed transient receptor potential (TRP); TRPV 1 receptors readily receiving environmental noxious stimuli including, heat, chemicals, pain and itch [2,3]. These agonists activate depolarization signals through calcium (Ca^{++}) cation influx. Free nerve endings belong to the small neuro C fibres are posited between individual keratinocytes, sending neuronal signals through its afferent neurons joined by its counterparts of neuronal receptors of the PNS in the skin dermis. The discoveries of G protein C receptors (GPCR) protein interactors; Mrgrp receptors bring important insights that peripheral itch sensory inputs are not only histamine neurones mediated but non-histaminergic neuronal pathways existed [4, 5]. Previously, histamine was believed the only mediator interact with Histamine 1 (H1) receptor to release histamine to result pruritic signals. H1 was shown to interact with TRPV 1 transmitting pruritic neuronal signals to the central nervous system (CNS) [2]. The non-histaminergic neuronal pathway is more complicated and not completely elucidated; involved afferent neurons possessing other neuronal receptors like TRPA 1, protease activated protein (PAR 2), Endothelial 1, Thymic stromal lymphopoietin (TSLP) and serotonin receptors [6,7]. MrgprA3, MrgprC11 and $MrgprD^{+}$ expressed neurones located in the epidermis activated by Ser-Leu-Ile-Gly-Arg-Leu (SLIGRL) and β-alainine respectively relaying exclusive non-histaminergic itch to the dorsal root of ganglion (DRG) of the CNS [8]. On the other hand, MrgprA3 and MrgprC11 interact with TRPV 1 and TRP ankyrin 1 (TRPA1) in the epidermis transmit histaminergic and non-histaminergic pruritic signals to the CNS [9,7]. While superficial stimulation of noxious stimuli like cowhage initiate itch; deeper stimulation especially in the dermis of these neuronal receptors result pain. This give rise to the idea itch sensation is transmitted through a polymodal C fibre neuron with low intensity transmit itch while high intensity propagates pain perception [2]. The spatial linear model postulated that different distinctive anatomical pathways between itch and pain existed in the transmission and perception of itch and pain sensations [2]. At this junction, one may assume both model exists and can explain different

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scientific findings using different methodologies. Nonetheless, it is generally agreed that a subset of itch specific neuron exists exclusively transmit pruritic signal peripherally to the spinal cord of CNS [10]. Currently, two voltage gated depolarization signals; one involved Ca^{++}cation and the other sodium (Na^{+}) cation have been identified; in the transmission of itch [10]. The latter may mediate through the glutamate N-methy-D-aspartate receptor (NMDA) receptor pathway to the CNS.

The itch signals through its afferent neurons then synapse with neurons in the DRG with the Gastrin Protein C Receptors (GPCR) inter-relay pruritic neuronal signals contralateral to the opposite side of the same level of DRG of the spinal cord. Many studies have confirmed the gatekeeper role of GPCR as an anatomical identifiable pruritic receptor protein in the transmission of itch from the peripheral nervous system to the CNS [11]. Interestingly, an inhibitory inter - neuronal pathway $Bhlhb5^{+}$ (B5-I) inhibits the transduction of itch through downregulation of TRP channels with the release of a kappa opioid receptor ligand neuropeptides called dynorphin; to impede pruritus [12]. A vast array of inflammatory mediators like prostaglandins, bradykinin, substance P (SP), nerve growth factors (NGF), cytokines, insulin, serotonin, noradrenaline (NA), interferon-ϒ (IFN-ϒ), histamine 1 to 4, proteases and toll like receptors and its ligands secreted by immunological activated mast cells, T lymphocytes, keratinocytes, granulocytes and macrophages [13, 14]. Many other mediators that may promote itch in the DRG are Substance P (SP), cytokines, interleukins like IL-31 and natriuretic polypeptide b (Nppb) expressed in a subset of TRPV 1 neurons. Recent evidences, suggested that chronic itch promote glial cell proliferation and increase in astrocytes especially following induction of the body inflammasome in the CNS during chronic pruritus [15, 16].

The thalamus and midbrain which control many vital functions of our body like sleep and autonomic nervous system is the centre of pruritus in the CNS. The contralateral ascending spinothalamic tract relay histaminergic and non-histaminergic pruritogenic signals to the inner structures of the brain [17]. Hedonic scratch activated the primary somatosensory S1 areas of the cerebral cortex gave the perception of pleasantness of pruritus in the cingulate cortex which decided the movement of scratching from the motor cortex [18, 19]. The midbrain, ventral tegmental area, striatum, nucleus accumbens, caudate nucleus, ventromedial prefrontal cortex, insula and claustrum are all shown by functional magnetic resonance imaging (f-MRI) studies to be activated in this rewarding circuitry [20-

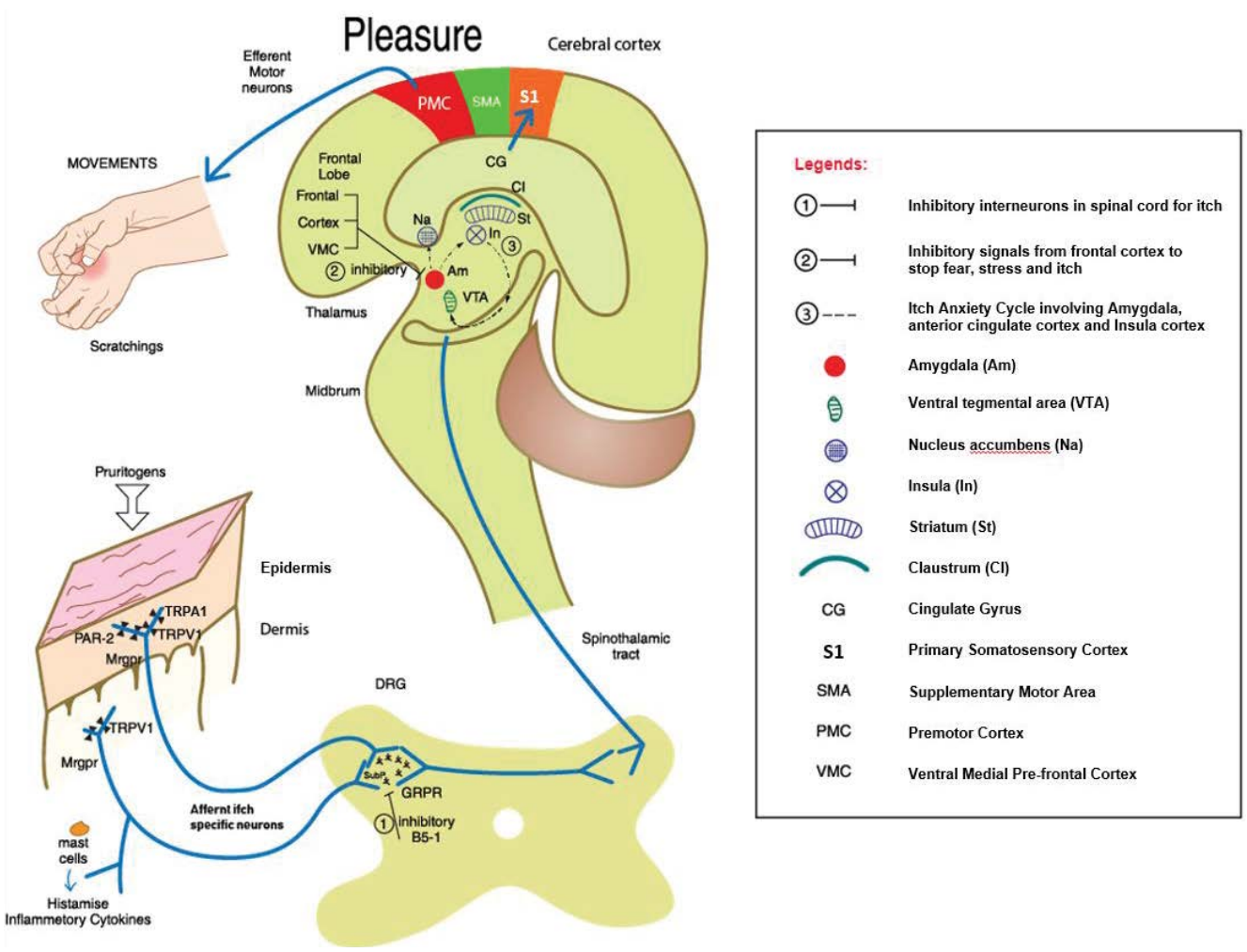

Figure 1: Diagrammatic illustration of the chronic itch – scratch – CNS – cognition pathway.

24]. A significant important insightful finding suggested that, an itch- anxiety circuitry existed in the primitive part of our inner brain, involving the hippocampus; its adjacent anatomical structures like amygdala, anterior cingulate cortex and insula cortex during itch and anxiety [25-28]. Subcallosal gray matter and nucleus accumbens of the brain are anatomically and physiologically activated in depression during chronic scratchings. (10) Conversely, specific anatomical areas of the prefrontal cortex can execute inhibitory signals to amygdala to suppress fear, anxiety, stress and chronic itch via a top down regulation through co-ordination of different cognitive domains in the cerebral cortex. [25] Claustrum may have a role to interocept and positively affect cognition especially in addictive behaviour. (10) Imbalance of various brain neurotransmitters like GABAs, serotonin, noradrenaline and dopamine has been implicated in mediating chronic itch in the brain through this complicated multi-dimensional pruritic circuitry. [10, 25] The diagrammatic representation of the itch-scratch brain cognitive pathway is illustrated in (Figure 1).

In sum, chronic itch and its sensory perception involves a very specific networking system that is far more sophisticated than one believed in the past. One must go beyond; critically review our existing paradigm. As in chronic pruritus, the role of the CNS, cognition and new peripheral mediators are anatomically and functionally evident. This enables a possible new top down approach in management of these distressing chronic diseases. Academicians have a responsibility to inform and educate their peers and stakeholders on this. Injudicious use of prescribing systemic antihistamines in treating children and adult with chronic pruritus due to chronic AD, cholestasis, uraemia, lymphoma, psycho-dermatosis and substances abuse is common and non-evidence based. Practitioners, health care managers and stakeholders concerned should be educated and informed; starting from scratch; the anatomical pathway of chronic itch and scratch.

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