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The Effect of the Trpv1 Agonist, Capsaicin, on the Developing Rat Brain: A Mini Review

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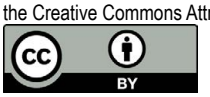

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Abstract

It has been shown previously that rats treated as neonates with capsaicin exhibited hyperactivity in a novel environment and had brain changes, including reduced brain weight, reduced hippocampal area, reduced cortical thickness and increased neuronal density in several cortical areas. These brain changes resembled those found in subjects with schizophrenia. This mini review discusses recent findings on the effects of capsaicin on hippocampal neurons and the role of TRPV1 channels in the central nervous system, which provide a possible explanation for the effects of capsaicin on the developing rat brain. Future studies on the role of TRPV1 channels in the brain hold great promise for further understanding of neuropsychiatric disorders.

Introduction

More than 40 years ago Jancsó et al[1,2] showed that treatment of neonatal rats with the vanilloid, capsaicin, the hot principle in chillies, produced life-long elimination of chemo sensitive primary afferent neurons and loss of chemogenic pain and neurogenic inflammation. Adult animals were less affected by capsaicin, exhibiting only a temporary loss of pain and inflammation. These observations followed on from the historic work of N Jancó who showed the desensitizing effect of capsaicin applied to sensory neurons[3]. At that time there was little understanding of the complexity of chemical neurotransmission. The concept of co-transmission was only beginning to evolve[4], and the role of neuropeptides was yet to be explored.

A few years earlier Chang and Leeman[5] had isolated a peptide from bovine hypothalamus and characterized it as substance P, a previously unidentified substance that had been discovered many years earlier by von Euler and Gaddum[6]. The discovery of the structure of substance P[7] opened an era of intensive investigation of its localization and role in the nervous system[8]. Over the next few years substance P was demonstrated to be responsible for antidromic vasodilatation and neurogenic inflammation[9] and to be released from the central synapses of small diameter primary afferent neurons on noxious stimulation[10].

During the early 1980s capsaicin treatment of neonatal rats was found to produce not only permanent loss of many unmyelinated primary afferent neurons, but also depletion of substance P in regions of termination of primary afferents in the spinal cord and medulla. However, substance P in higher central nervous system (CNS) regions appeared not to be affected[11]. Thus, the effect of capsaicin on the nervous system was considered to be limited mainly to action on primary afferent neurons.

TRPV1 channel – the capsaicin receptor

The discovery of the transient receptor potential vanilloid type 1 (TRPV1) channel, a heat activated, non-selective cation channel, as the site of action of capsaicin, was a major advance in the field[12,13]. The finding that responses to noxious heat and inflammatory pain were severely impaired in mice lacking the capsaicin receptor (then known as VR1)[14] led to great interest in the development of analgesic agents which acted on this new target[15-17].

The predominately primary afferent location of the site of action of capsaicin at first seemed to be confirmed when several studies showed little or very restricted localization of TRPV1 channels in the CNS[12,18,19]. Further studies using methods with increased sensitivity, however, showed that TRPV1 channels were not restricted to primary afferent neurons but were also widely distributed in the CNS, albeit at levels 20-30 times lower than those in the peripheral nervous system[20]. Thus, investigation of the role of TRPV1 channels and of the effects of capsaicin in the brain lagged behind studies of the peripheral actions.

Effect of neonatal capsaicin treatment on rat brain and behaviour

The observations that subjects with schizophrenia have deficits in pain sensation and flare responses to niacin prompted a study by Newson et al[21] of the effect of neonatal capsaicin treatment on rat brain and behaviour. At 5-7 weeks the rats treated as neonates with capsaicin had increased locomotor activity in a novel environment. The most striking finding, however, was that although they had normal body weight, the rats had reduced brain weight, reduced hippocampal and coronal cross-sectional areas, reduced cortical thickness and increased neuronal density in several cortical areas[21]. Some of these changes were found to persist into adulthood[22].

The resemblance between the brain changes found in rats treated as neonates with capsaicin, and those found in post-mortem human brains of subjects with schizophrenia[23], was considered noteworthy. A subsequent investigation by Petrovszski et al[24] of the behavioural changes in young rats treated with capsaicin showed that the animals had reduced memory function, as well as disturbances in thermoregulation and motor activity. These findings raised the possibility that rats treated during development with capsaicin might be an animal model of schizophrenia. However, sensory-motor gating was not affected in either study[22,24], indicating that in this regard the capsaicin treated rat did not exhibit one of the generally accepted characteristics of an animal model of schizophrenia.

Brain changes produced by neonatal capsaicin treatment – central or peripheral effect?

A major question that arises regarding the brain changes observed in rats treated as neonates with capsaicin is whether they were due to a central or peripheral action of capsaicin. The lack of a clear demonstration of the presence of TRPV1 channels in the CNS led Newson et al[21] to propose that the brain and behavioural changes seen in capsaicin treated rats were an indirect effect of the action of capsaicin on TRPV1 channels on primary afferent neurons, resulting in loss of sensory input to the brain, decreased synaptic density, and increased neuronal density. The primary afferent neuron would undoubtedly have been a significant site of action of capsaicin in neonatal rats and the importance of primary afferent input to brain development should not be dismissed. Indeed, a study by Orefice et al[25] has shown that peripheral mechanosensory neuron dysfunction induced by deletion during development of *Mecp2* or *Gabrb3*, genes associated with autism spectrum disorder in humans, resulted in social interaction deficits and anxiety-like behaviour in mice. Nevertheless, in light of more recent evidence of the presence of functional TRPV1 channels in the brain[20], it is considered most likely that neonatal capsaicin treatment produced brain changes by a direct action on central TRPV1 channels.

Role of TRPV1 channels in neuronal growth and development

Of particular relevance to the effects of neonatal capsaicin treatment on rat brain development are studies on the role of TRPV1 channels in neuronal growth and development[26]. The first studies that linked TRPV1 channels with neuronal development showed that TRPV1 channels were localised in neurites and growth cones where they were involved in the formation of filopodia in neurons[27]. Stock et al[28] showed that TRPV1 channels are expressed in mouse neural precursor cells during postnatal development but not in the adult. However, TRPV1 channel expression was induced in the adult by activities involving spatial learning and exercise. Furthermore, loss of TRPV1 channel expression in *Trpv1*-deficient (*Trpv1-/-*) mice led to an increase in proliferation of neural precursor cells[28].

A recent study by Wang et al[29] has shown that *Trpv1-/-* mice were more stress resilient than control animals. Furthermore, glucocorticoid receptor-mediated expression and activity of the chromatin-remodeling factor, histone deacetylase 2 (HDAC2), were reduced in *Trpv1-/-* mice[29]. HDAC2 has been shown to repress gene expression of cell-cycle-related genes involved in synaptic plasticity and neuronal differentiation. Thus, reduction in HDAC2 activity facilitated hippocampal neurogenesis[30]. Indeed, Wang et al[29] have suggested that HDAC2 is a molecular link between TRPV1 activity and stress

responses. In a further investigation, capsaicin was shown to reduce synaptic density in cultured primary hippocampal neurons, and to impair the proliferation, maturation and survival of neurons in the hippocampus of adult mice. These effects of capsaicin were mediated by HDAC2, which was elevated by capsaicin[31]. The effects of capsaicin were absent in *Trpv1-/-* mice, indicating that they were mediated by TRPV1 channels.

Capsaicin desensitization

One of the important characteristics of the action of capsaicin on primary afferent neurons is that the activation of TRPV1 channels is followed by a period of desensitization during which the cell is unresponsive to TRPV1 agonists[32]. Furthermore, administration of high doses of TRPV1 agonists leads to calcium overload and death of TRPV1 bearing neurons[33]. Recent studies have shown that supra-spinal neurons also exhibit desensitization to TRPV1 agonists[34]. Therefore, the resultant effects of capsaicin on the plasticity of particular neurons is likely to be a balance between the agonist action, desensitization and cell death. Treatment of neonatal rats with capsaicin would be expected to produce agonist action followed by prolonged desensitization and cell death of some TRPV1 bearing neurons. It is considered that cell death alone would be unlikely to explain the brain changes in rats treated as neonates with capsaicin[21], since neuronal density was increased in several cortical areas, indicating that synaptic density rather than cell number was reduced.

Although hippocampal neuronal density was not investigated in the study by Newson et al[21], in light of the findings of Wang et al[31], it is proposed that the brain changes in rats treated as neonates with capsaicin[21], were produced by prolonged TRPV1 agonist activity by capsaicin resulting directly or indirectly in prolonged activation of cellular pathways that lead to reduced neuronal arborisation. The finding that TRPV1 channels were expressed at greater densities in the early developmental period[19,28] might explain the prolonged agonist action of capsaicin in neonatal animals and thus their greater vulnerability.

Role of TRPV1 channels in neuropsychiatric disorders

The possible role of TRPV1 channels in the central nervous system and in neuropsychiatric disorders has been increasingly studied over the past fifteen years[35-39]. Marsch et al[40] showed that TRPV1 knock-out mice exhibited less fear, anxiety and hippocampal long- term potentiation (LTP) than wild type mice. In agreement with this study was the finding that acute administration of a TRPV1 agonist improved cognitive performance of rats in passive avoidance learning tasks[41]. TRPV1 channel activation has also been found to trigger another form of synaptic plasticity, interneuron long-term depression (LTD)[42]. Both LTP and LTD are considered to be involved in the formation of stable memories. The TRPV1 agonists, capsaicin and resiniferatoxin, facilitated LTP and suppressed LTD in rat hippocampal slices, and exerted a protective effect against the effects of stress on synaptic plasticity and spatial memory formation[43]. Activation of TRPV1 channels by capsaicin has also been found to decrease memory impairment in a rat model of biliary cirrhosis[44], whereas a TRPV1 antagonist was found to impair discrimination between novel and familiar objects in rats[45].

The role of TPVPV1 channels in neurogenesis, synaptic plasticity, learning and memory requires further investigation. Although Marsch et al[40] found reduced LTP in TRPV1 knock- out mice, other investigators have reported increased LTP in TRPV1 knock-out mice[46].

Moreover, the finding by Stock et al[28] of increased neurogenesis in TRPV1 knock-out mice would be expected to result in increased synaptic plasticity, enhanced LTP and enhanced learning and memory, which would seem to be at odds with studies showing that knock-out mice have reduced LTP[40]. However, the discrepancy might be explained by the finding of less differentiation of neural precursor cells into neurons and glia in TRPV1 knock-out animals[33].

The revelation that anandamide, an endogenous cannabinoid, is a TRPV1 agonist[47], provided a further dimension and added complexity to studies on vanilloids in health and disease. In the hippocampal dentate gyrus, TRPV1 channel activation by endogenous anandamide has been found to trigger postsynaptic LTD[46]. Cross-talk between the endocannabinoid and endovanilloid receptor systems, whereby the cannabinoid CB1 receptor sensitizes TRPV1 receptors to anandamide, has been demonstrated in primary afferent neurons[48]. A balance or interplay between the endocannabinoid and endovanilloid systems at central synapses involved in learning, memory and cognition has been found in several studies[49,50].

Furthermore, some of the effects of cannabinoids in rats, including apathetic and impulsive patterns of behaviour, have been shown to be partially mediated by TRPV1 channels[51]. The complex interactions between the endocannabinoid and endovanilloid systems at central synapses involved in learning, memory and cognition require further elucidation and should prove of considerable importance in advancing understanding of neuropsychiatric disorders[36].

Future perspectives

The discovery of the TRPV1 channel promised new horizons in pain control[15-17] and advances in treatment of several other disorders[52,53]. However, the multifunctional nature of the TRPV1 channel also poses considerable

challenges for targeted drug design. Recent studies on the molecular mechanism of activation of the TRPV1 channel by capsaicin[54,55] may provide clues for new approaches to drug design.

Although investigation of the roles of vanilloids and cannabinoids in brain function is at an early stage, it holds the promise of greater understanding of the responses of the central nervous system to sensory input and stressors. The exploitation of such understanding to provide therapeutic advances for currently poorly understood brain and neuropsychiatric disorders remains a tantalizing possibility.

Conflict of Interest

The author declares no conflict of interest.

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