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

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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 neurons3. At that time there was little understanding of the complexity of chemical neurotransmission. The concept of co-transmission was only beginning to evolve4, and the role of neuropeptides was yet to be explored.

A few years earlier Chang and Leeman5 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 Gaddum6. The discovery of the structure of substance P7 opened an era of intensive investigation of its localization and role in the nervous system8. Over the next few years substance P was demonstrated to be responsible for antidromic vasodilatation and neurogenic inflammation9 and to be released from the central synapses of small diameter primary afferent neurons on noxious stimulation10.

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 affected11. 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. The finding that responses to noxious heat and inflammatory pain were severely impaired in mice lacking the capsaicin receptor (then known as VR1) led to great interest in the development of analgesic agents which acted on this new target.

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. 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. 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. 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. Some of these changes were found to persist into adulthood.

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, was considered noteworthy. A subsequent investigation by Petrovszski et al. 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, 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. 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 Oreifej et al. has shown that peripheral mechanosensory neuron dysfunction induced by deletion during development of Mcp2 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, 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. 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. Stock et al. 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.

A recent study by Wang et al. 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. 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. Indeed, Wang et al. 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.\textsuperscript{21} The effects of capsaicin were absent in
TRPV1\textsuperscript{-/-} 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.\textsuperscript{32} Furthermore, administration of high doses of TRPV1
agonists leads to calcium overload and death of TRPV1
bearing neurons.\textsuperscript{22} Recent studies have shown that supra-
spinal neurons also exhibit desensitization to TRPV1
agonists.\textsuperscript{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, 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,\textsuperscript{1} in light of the
findings of Wang et al,\textsuperscript{31} it is proposed that the brain
changes in rats treated as neonates with capsaicin,\textsuperscript{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\textsuperscript{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.\textsuperscript{35-39} Marsch
et al\textsuperscript{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.\textsuperscript{41} TRPV1 channel activation
has also been found to trigger another form of synaptic
plasticity, interneuron long-term depression (LTD).\textsuperscript{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.\textsuperscript{43} Activation of TRPV1 channels
by capsaicin has also been found to decrease memory
impairment in a rat model of biliary cirrhosis,\textsuperscript{44} whereas
a TRPV1 antagonist was found to impair discrimination
between novel and familiar objects in rats.\textsuperscript{45}

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

Moreover, the finding by Stock et al\textsuperscript{48} 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.\textsuperscript{49} 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.\textsuperscript{33}

The revelation that anandamide, an endogenous
cannabinoid, is a TRPV1 agonist,\textsuperscript{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.\textsuperscript{48} 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.\textsuperscript{49} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{36}

**Future perspectives**

The discovery of the TRPV1 channel promised new
horizons in pain control\textsuperscript{15-17} and advances in treatment of
several other disorders.\textsuperscript{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\textsuperscript{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.

References


