Cell Death and Differentiation (2006) 13, 534–536

www.nature.com/cdd

Meeting Report

The crucial role of neuronal plasticity in pain and cell death

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Cell Death and Differentiation (2006) **13,** 534–536. doi:10.1038/sj.cdd.4401848; published online 13 January 2006

Workshop on Apoptosis in Biology and Medicine. Parghelia (VV) Italy, 25–26 May 2005

Severe pain is a major health care problem, since almost 20% of the European population, actually, suffers from chronic or intermittent pain, that results in suffering and disability for patients and increasing economic loss for society. Only 1/3 of patients receive pain relief from current analgesics, like opiates, nonsteroidal anti-inflammatory drugs, local anaesthetics, tricyclic antidepressants and anticonvulsants, including carbamazepine and gabapentin. Therefore, it seems notable that recent developments in the understanding of the mechanisms that, individually or collectively, produce pain have disclosed new potential therapeutic targets for the development of more effective drugs.

During the last decade, Parghelia (Calabria, Italy), harboured the 'Workshop on Apoptosis In Biology and Medicine', which VIII edition (25th May 2005), gathered together scientists and PhD students to discuss the most recent advances in neuroplasticity in pain and cell death.

The main topic of this congress was the 'nociceptive system', involved in the conduction of pain stimuli from the periphery to the brain. Today, it's quite clear that, after tissue injury or inflammation, plastic changes can take place in the periphery, in the spinal cord and in higher brain centres, and that neuroplasticity, as well as processes of cell death, contribute to pain perception and to the development and maintenance of chronic pain syndromes.

In the opening lecture, Dr. SA Lipton (USA) presented a broad range overview of the latest acquisitions in the molecular mechanisms underlying neurodegenerative diseases, based on his more than 15 years research in this field. He emphasized the role of excitotoxicity in triggering neuronal cell death pathways involved in a wide range neurological disorders, such as stroke, Alzheimer's and Parkinson's diseases, HIV-related dementia, and also neuropathic pain. Death pathways are triggered by excessive stimulation of the NMDA receptors that may result in necrosis (strong receptor hyperactivity) or in apoptosis (moderate receptor hyperactivity). Interestingly, in this context, Dr. Lipton further characterized the process of apoptotic cell death highlighting the importance of matrix metalloproteinase (MMP) and showing how *S*-nitrosylation-mediated activation of MMP-9 results in neuronal apoptosis.[1]

Finally, the presentation shifted to the description of NMDA receptor antagonists as potential pharmacological tools to reduce excitotoxic neuronal death. Importantly, memantine, an open-channel blocker with a relatively fast off-rate, preferentially blocks excessive NMDA receptor activity without disrupting normal activity, thus resulting in minimal side effects. Indeed, human clinical trials have documented that memantine represents an effective and well-tolerated drug for the treatment of Azheimer's disease, vascular dementia, HIV-associated dementia, glaucoma and neuropathic pain and it was recently approved in both Europe and the USA for the treatment of the Alzheimer's disease. Excitingly, preclinical studies show that NitroMemantines, second-generation memantine derivatives, display greater neuroprotective properties, while retaining the clinical safety of their precursor.[2]

The role of p73 in neuronal plasticity has been highlighted by Dr. G Melino (Rome, Italy and Leicester, UK). This gene belongs to the p53 family, pivotal in DNA damage; indeed, the structural and functional similarity with p53 and p63 is remarkable.[3] Nonetheless, p73 knockout mice show severe neuronal abnormalities, with abnormalities in the development of the central nervous system.[4] *In vitro*, p73 is able to regulate the differentiation of neuronal cells[5] as well as that of oligodendrocyte precursors.[6] The gene for p73 contains two different promoters, which allow transcription of two protein isoforms: a full-length transactivating (TAp73) isoform with proapoptotic function, and a shorter isoform (DeltaNp73), which lacks the N-terminal transactivating domain and displays antiapoptotic activity.[7] The protein stability of p73 is achieved by Ubiquitin–Proteasome degradation system mediated by the Nedd-4-like Itch[8] and Nedd-8[9] E3 ligases, affecting the balance between the two protein isoforms and thus controlling proliferation and cell death.[10]

The discussion then shifted from the molecular mechanisms to the 'spatial and temporal control of neuronal cell

death', which was the topic of Dr. L Berliocchi (UK). In neurons, axons and cell bodies degenerate by active and regulated mechanisms resembling apoptotic features. This axonal degeneration and the subsequent loss of synaptic connectivity also contribute to neurological symptoms of many disorders, as multiple sclerosis, stroke, traumatic brain and spinal cord injury, peripheral neuropathies and chronic neurodegenerative diseases. Interestingly, synaptic loss seems to be an early event in these diseases and may even appear before any detectable neuronal loss. By using a model of axonal degeneration elicited by botulinum toxin C (BoNT/C), Dr. Berliocchi showed that two neurodegenerative events, distinct in space and time, can be observed in cerebellar granule cells: (i) an early neurite degeneration, which occurs independently of trophic stimulation and the activation of death-signalling kinases, and which does not involve the apoptosis-executing machinery (caspases); and (ii) a late apoptotic termination of the cell bodies, which is prevented by kinase inhibition and involves cytochrome *c* release and caspase activation. The compartmentalization of the two degenerative events is emphasized by the selective recognition and removal of different regions in degenerating neurons. The data suggest that widespread synaptic damage caused by BoNT/C in central neurons can initiate spatially and temporally different degenerative programmes that recapitulate many relevant features found in human neurodegenerative disorders.[11]

In his presentation on the modulation of chronic stress effects by the prefrontal cortex (PFC) in major psychiatric disorders, Dr. AA Grace (USA) outlined the mechanisms that allow the medial PFC to regulate the activity and plasticity of the basolateral amygdala (BLA). The amygdala exhibits a high degree of plasticity in models of tetanic, pharmacologically induced and behavioural long-term modification of synaptic transmission and such a neuroplasticity seems to underlie associative learning and some neurological and psychiatric disorders. Data from Dr. Grace's laboratory show that chronic stress produces an increase in baseline firing and population activity, as well as a potent increased response to foot shock (noxious stimulus) in the BLA. By contrast, the central nucleus of the amygdala (CeA) shows reduced baseline-firing rate, reduced population activity, increased response to foot shock, but habituation to repeated foot shock in response to chronic stress. Interestingly, PFC appears to exert a pivotal regulation of this stress response. In fact, PFC lesions result in reduced baseline firing of CeA, reduced effect of chronic stress and reduced response to foot shock in stressed animals by activating inhibitory interneurones in BLA. So, since the amygdala plays a significant role in different types of emotional-affective behaviours, stimulation of PFC, results in reduced, inappropriate emotional response to acute stimuli.

Furthermore, we know that stress plays a crucial role in many psychiatric disorders, such as schizophrenia and the lack of PFC activation, which occurs during schizophrenia, might result in the reduced ability to regulate stress response in patients, thus providing a potential target, that is, regulation of PFC activity, for future therapeutics.[12]

Since accumulating evidence suggests that the amygdala also plays an important role in the emotional-affective component of pain, the discussion turned into a description of the molecular and neuroanatomical mechanisms underlying neuronal plasticity in relation to pain. Indeed, Dr. S Hunt (UK) highlighted the correlation between 'pain and memory'. He pointed out that pain is sustained by both peripheral and central events and that several mechanisms occurring at brain level may modulate the experience of pain. Therefore, although a series of changes occurs at the spinal cord level following a noxious stimulation, actually the pain experience results from the brain itself and its control on the spinal cord. Thus, as a consequence, the link between the pain experience and the injury is often variable. Furthermore, a strong stimulation of pain fibres may result in the establishment of long-term potentiation (LTP) recorded from the dorsal horn of the spinal cord. Such form of synaptic plasticity could establish an important link between acute and chronic pain, providing to be a pivotal mechanism involved in the development and maintenance of chronic pain.

Another interesting talk on neuronal plasticity in pain was provided by Dr. M Malcangio (UK), who focused on the role of 'neurotrophins as modulators of the first pain synapse'. Recent studies indicate that, in addition to their role as survival factors, neurotrophins can modulate the synaptic efficacy of the first pain synapse between primary sensory and dorsal horn neurones. In particular, NGF seems to be pronociceptive, since it increases substance P release from the dorsal horn of the spinal cord and reduces the threshold for thermal hyperalgesia. In contrast, NT-3 inhibits substance P release in the dorsal horn of the spinal cord and induces mechanical hypoalgesia. However, while NT-3 modulates the synaptic efficacy acutely, NGF does it chronically. BDNF, another important neurotrophin known to be involved in the induction of LTP in the hippocampus, is responsible for plasticity also in the dorsal spinal horn, where it is released by sensory neurones following noxious stimuli. Interestingly, BDNF elicits this effect via phosphorylation of the NR1 subunit of the NMDA receptor.[13] Thus, LTP-like phenomenon may occur in the dorsal horn of the spinal cord as a result of BDNF release from nociceptive terminals.

Recent studies highlighted that the dopaminergic mesolimbic system plays an important role in regulating nociception. Indeed, transient receptor potential vanilloid 1 (TRPV1) antagonists are able to induce antihyperalgesic effects in animal models of inflammatory and neuropathic pain. In this context, Dr. NB Mercuri (Italy) highlighted the 'synaptic modulation of dopamine neurons by vanilloid receptors' and its possible involvement in the modulation of pain.[14] He explained that activation of TRPV1 in the ventral tegmental area (VTA) increases the firing rate of rat dopamine neurones, a phenomenon strictly related to enhanced glutamatergic transmission. In addition, either activation of VTA TRPV1 receptors or noxious stimuli results in a transient increase of extracellular dopamine levels in the nucleus accumbens. This confirms that the mesolimbic dopaminergic system may be involved in the control of pain perceptions via stimulation of TRPV1 receptors in VTA.

In line with the idea that the endocannabinoid system is potently involved in pain modulation, Dr. M Maccarrone (Italy) focused on 'endocannabinoids, pain and peripheral mirrors'. As known, Cannabis has been used for centuries to treat different pathological conditions, including pain[15] and

Dr. Maccarrone introduced his lecture giving an overview of the latest discoveries in this field. In particular, activation of cannabinoid receptors (CB1 and CB2), as well as inhibition of fatty acid amide hydrolase, an enzyme involved in endocannabinoid degradation, represent attractive strategies to promote analgesia in both inflammatory and neuropathic pain, as documented by recent experimental and clinical evidence.[16] Also migraine, another important chronic and disabling illness, depends on the endocannabinoid system, as proved by the increasing in degradation and intracellular transport of these lipids occurring in platelets from female patients. Hopefully, cannabinoid mimetics may represent effective pharmacological tools for the treatment of this disease. The neuroanatomical and neurochemical mechanisms leading to hypersensitivity of the trigeminal pathway occurring in migraine was finely described by Dr. C Tassorelli (Italy) in her talk entitled 'the role of plasticity in migraine pain: hints from basic and clinical science'.[17]

Finally, a constructive moment for the meeting was represented by the poster session, which challenged the PhD students to present and discuss their data with scientists coming from top ranking European and USA research institutions. Thus, overall the meeting allowed the participants to initiate stimulating interactions, which will result in setting new experiments to improve our understanding of the mechanisms involved in neuronal plasticity in pain and cell death.

Acknowledgements

The VIII Workshop on Apoptosis in Biology and Medicine (25–26 May 2005, Parghelia, VV, Italy) has been organized with the financial support of The Ministry of University Research and Technology (PRIN 2004053099_004 to GB), The Calabria Region, The Universities of Calabria at Cosenza and Magna Graecia at Catanzaro, and The National Council for Research (CNR) ISN, Section of Catanzaro, Italy.

1. Gu Z *et al.* (2002) Science 297: 1186–1190
2. Lipton SA (2004) Neurorx 1: 101–110
3. Melino G *et al.* (2003) Trends Biochem. Sci. 28: 663–670
4. Yang A *et al.* (2000) Nature 404: 99–103
5. De Laurenzi V *et al.* (2000) J. Biol. Chem. 275: 15226–15231
6. Billion N *et al.* (2004) Development 131: 1211–1220
7. Melino G *et al.* (2002) Nat. Rev. Cancer 2: 605–615
8. Rossi ML *et al.* (2005) EMBO J. 24: 836–848
9. Bernassola F *et al.* (2004) J. Exp. Med. 199: 1545–1557
10. Oberst A *et al.* (2005) BBRC 331: 707–712
11. Berliocchi L *et al.* (2005) J. Cell Biol. 168: 607–618
12. Grace AA and Rosenkranz JA (2002) Physiol. Behav. 77: 489–493
13. Slack SE *et al.* (2004) Eur. J. Neurosci. 20: 1769–1778
14. Marinelli S *et al.* (2005) Neuropsychopharmacology 30: 864–870
15. Notcutt W *et al.* (2004) Anaesthesia 59: 440–452
16. Cravatt BF and Lichtman AH (2004) J. Neurobiol. 61: 149–160
17. Buzzi MG *et al.* (2003) Cephalalgia 23 (Suppl 1): 1–14