11

Astrocyte CD38: Links to Neuroinflammation in HAND

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1. Introduction

Central nervous system (CNS) HIV-1 infection can lead to encephalitis (HIVE), which compromises brain function and presents clinically as HIV-associated dementia [HAD, (Navia et al., 1986; Price et al., 1988; Wiley and Achim, 1994; Brew et al., 1995; Grant, 2008; Letendre et al., 2008; Price and Spudich, 2008)], the most serious form of HIV-associated neurocognitive disorders [HAND, (Grant, 2008; Letendre et al., 2008)]. HAND is associated with various cognitive, behavioral and motor dysfunctions [for details refer (Ances and Ellis, 2007; Grant, 2008)]. Although initiation of combined antiretroviral therapy (cART) has been linked to cognitive improvement and decreased incidence of HAD (Brodt et al., 1997; Sacktor et al., 1999; Foley et al., 2008), the yearly incidence rates for milder forms of HAND are still as high as 10-25% (Woods et al., 2009), and the prevalence of HAD is on the rise due to longer life expectancy of HIV-1-infected individuals (Lindl et al., 2010).

The neuroinflammatory cascade associated with HAND, beginning with the infiltration of HIV-1-infected macrophages and immune activated microglial cells, likely reaches the endpoint of neurodegeneration via glial activation and changes in glial inflammatory responses (Kaul and Lipton, 2006). Reactive astrogliosis, the recruitment to and proliferation of astroglial cells at injury sites, is commonly observed during HIVE (Gonzales and Davis, 1988; Persidsky et al., 1996; Ridet et al., 1997; Wu and Schwartz, 1998; Petito et al., 1999). Astrocytes are the most abundant cell type in the CNS; and yet, their specific roles continue to be unraveled. Thus, characterization of molecules/pathways involving the activated astrocytes during HIVE and HAND, is of high interest.

CD38 expression on peripheral T lymphocytes is a marker for disease progression in HIV-1-infected patients (Savarino et al., 2000; Vigano et al., 2000; Kolber, 2008; Sinclair et al., 2008). CD38 is a 45-kD ectoenzyme involved in the synthesis of potent calcium- (Ca^{2+}) mobilizing agents, cyclic ADP ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP+) (Heidemann et al., 2005b; Banerjee et al., 2008). CD38 expression has been detected both in neurons and astrocytes in the cerebral cortex (Mizuguchi et al., 1995; Yamada et al., 1997), while it is primarily expressed by astrocytes in culture (Pawlikowska et al., 1996). Our group has shown that CD38 is one of the most upregulated molecules in IL-1β-activated astroglial cells *in vitro* and is also expressed by astrocytes in HIVE brain tissues

(Kou et al., 2009). However, very little is known about the role of CD38 in HAND. In this review, we will explore the possible mechanistic links between, astrocyte-CD38 upregulation, Ca^{2+} homeostasis and HIV-1 neuropathogenesis.

2. Neuroinflammation during HIVE and astrocytes

HIV-1 enters the brain early, after systemic infection of circulating T cells and macrophages, by crossing the blood brain barrier [BBB (Bell et al., 1998; Bell, 2004)]. Neurons are rarely infected by the virus (Price et al., 1988; Kaul et al., 2001; Ellis et al., 2007), thus most neuronal damage is due to indirect toxicity mediated by activated astrocytes and virus-infected and/or activated mononuclear phagocytes (MP, macrophage/microglia). However, viral proteins like HIV-1 Tat and gp120 released by infected MP may show direct neurotoxicity (Mauermann et al., 2008; Li et al., 2009). Pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6, have been implicated in HIV-1 neuropathogenesis (Dickson et al., 1991; Sebire et al., 1993; Gendelman and Tardieu, 1994; Persidsky et al., 1999). Indeed, IL-1β production is one of the first responses observed upon activation of immune cells including MP (Pellegrini et al., 1996). This suggests that immune cell activation during peripheral HIV-1 infection may provide soluble IL-1β that penetrates the BBB (Vitkovic et al., 2000a; Vitkovic et al., 2000b). Brain tissue and cerebrospinal fluid from HIVE patients (Gallo et al., 1991; Tyor et al., 1993; Vitkovic et al., 1995; Boven et al., 1999), as well as brain tissue from simian immunodeficiency virus infected rhesus monkeys (Lane et al., 1996), demonstrated elevated IL-1β levels. Various studies have shown links between IL-1β and astrocyte activation during HIVE (Blumberg et al., 1994; Kaul and Lipton, 2006; Peng et al., 2006). IL-1β is also known to stimulate release of neurotoxic molecules like reactive oxygen species and inducible nitric oxide synthase by astrocytes (Jana et al., 2005; Sharma et al., 2007). Our previous work showed IL-1β-mediated astrocyte Fas ligand expression and subsequent caspase activation in surrounding neurons *in vitro* (Deshpande et al., 2005). We have also shown the effects of IL-1β and HIV-1 gp120, leading to CD38 upregulation in primary astrocyte cultures (Banerjee et al., 2008) and increased CD38 mRNA and protein expression in HIVE brain (Kou et al., 2009). IL-1β-activated astrocytes are known to release cytokines like IL-6 and chemokines like CCL2, CXCL8 and RANTES (Lee and Aarhus, 1993; Zhao and Brinton, 2004; Sharma et al., 2007). Our work showed that CD38 is a partial regulator of chemokine and cytokine signaling by IL-1β-activated astrocytes, thus affecting the inflammatory milieu during HIVE (Kou et al., 2009). IL-1β has also been shown to mediate activation of mitogen activated protein kinases (MAPKs) in primary astrocyte cultures (Parker et al., 2002; Zhao et al., 2004). MAPKs belong to a family of serine threonine kinases [for details refer (Davis, 1995; Chang and Karin, 2001)]. These kinases are involved in inflammation, cell proliferation and differentiation in astrocytes (Rajan and McKay, 1998; Hua et al., 2002; Morita et al., 2003). It is also well established, that the prolonged activation of MAPKs and nuclear factor (NF)-κB may mediate inflammatory conditions during HIVE (Yi et al., 2004; Kaul and Lipton, 2006). Our studies have shown direct involvement of MAPK and NF-κB in the regulation of CD38 expression and signaling in primary astrocytes, thus indicating that CD38 may be a major molecule in astrocyte-mediated inflammatory signaling in HIVE brain (Mamik et al., In Press).

3. Calcium in glial biological functions and HAND

Astrocytes can sense, respond to, and modulate neuronal activity (Cotrina and Nedergaard, 2005; Heidemann et al., 2005a). They provide crucial support for neurons and the other CNS cells through diverse functions, ranging from the production of neurotrophic factors to the elimination of neurotoxins (Ransom et al., 2003). Their ability to respond vigorously to diverse neural insults is commonly referred to as reactive astrogliosis, astrocytosis or astrocyte activation (Eng and Ghirnikar, 1994). Astrogliosis is associated with HAND and also observed in HIV-1 gp120 transgenic mice (Kaul et al., 2001). Since astrocytes are not electrically excitable, they sense changes in the microenvironment through receptors on their plasma membranes. Activation of these transmembrane receptors or ion channels and intracellular endoplasmic reticulum (ER) receptors, as well as mitochondrial Na^+/Ca^{2+} exchangers, increases intracellular calcium concentration ($[Ca^{2+}]_i$) [for details review (Cotrina and Nedergaard, 2005; Reyes and Parpura, 2009)]. Depending on the amplitude, spatial resolution and duration of Ca^{2+} response, genes are up or downregulated (Berridge et al., 2003). Change in free $[Ca^{2+}]_i$ also results in secretion of glutamate and other neuro-active compounds (peptides, eicosanoids, neurotrophins) into the microenvironment. These substances modulate the activity of juxtaposed neurons and other astrocytes (Cotrina and Nedergaard, 2005). In addition, Ca^{2+} waves are also used for long-distance communication between astrocytes via gap junction proteins, which in turn can be modulated by IL-1β (John et al., 1999).

After a physiological task is completed, the cytosolic Ca^{2+} levels return to normal by extrusion of Ca^{2+} either via Na^+/Ca^{2+} exchangers or plasma membrane Ca^{2+}-ATPases (Rojas et al., 2004; Rojas et al., 2007), while Ca^{2+} mobilized from internal stores return to normal via sarco/ER Ca^{2+}-ATPase (Bers, 2002; Wang et al., 2006; Liu et al., 2007). Some recent reports show that mitochondrial Ca^{2+} uniporter may also act as a sink to trap off the excess $[Ca^{2+}]_i$ (Reyes and Parpura, 2008, 2009). Thus, the physiological levels of free $[Ca^{2+}]_i$ are tightly controlled. However, Ca^{2+} overload triggered by excessive influx through plasma membrane voltage and receptor-operated channels, by metabotropic receptors or Ca^{2+} released from intracellular pools, may lead to HIV-1-induced neurotoxicity (Nath and Geiger, 1998; Holden et al., 1999). Mobilization of intracellular Ca^{2+} pools is an important modulator of apoptosis in various cells, including T cells, ventricular myocytes, and cerebellar granule cells (Khan et al., 1996; Jayaraman and Marks, 1997; Lin and Leonard, 1997; Felzen et al., 1998; Herbein et al., 1998). Furthermore, it has been associated with HIV-1 gp120-induced neuronal cell death *in vitro* (Meucci et al., 1998).

4. CD38 function and Ca^{2+} homeostasis

It has been suggested that there is more than one substrate for the enzymatic activity of CD38, including nicotinamide adenine dinucleotide (NAD+) and nicotinamide adenine dinucleotide phosphate (NADP) in astrocytes (Berthelier et al., 1998; Deaglio et al., 2001; Antonelli and Ferrannini, 2004; De Flora et al., 2004; Heidemann et al., 2005a). The CD38-catalyzed cleavage of the nicotinamide-ribose bond eventually leads to the production of cADPR (Berthelier et al., 1998). Despite the fact that CD38 is a very inefficient cyclase because ADPR produced by hydrolysis of cADPR is the major end product (Lee and Aarhus, 1993), it has been demonstrated that this small amount of cADPR is still biologically relevant (Partida-Sanchez et al., 2003).

NADP+, the major alternate substrate to NAD+, leads to the formation of NAADP+ by CD38 primarily in acidic conditions (Heidemann et al., 2005b). While some recent reports have shown that hydrolysis of NAD+ to adenosine may increase $[Ca^{2+}]_i$ in astrocytes (Doengi et al., 2008; Okuda et al., 2010), both cADPR and NAADP+ are potent Ca^{2+} mobilizing metabolites (Lee, 2001; Antonelli and Ferrannini, 2004; De Flora et al., 2004; Heidemann et al., 2005a). These secondary messengers generated by CD38 lead to intracellular Ca^{2+} release by various mechanisms. NAADP+ has been shown to mobilize Ca^{2+} from inositol 1,4,5 trisphosphate (IP3) receptors (IP3R) in astrocytes (Heidemann et al., 2005b), ryanodine (Ry) receptors (RyR) in T cells (Dammermann and Guse, 2005; Steen et al., 2007), or from other uncharacterized intracellular Ca^{2+} stores (Mandi and Bak, 2008). However, cADPR is primarily involved in release of intracellular Ca^{2+} through RyRs in various cell types including myocytes, fibroblasts, smooth muscle cells, T cells, neuronal cells and astrocytes (Bruzzone et al., 2003; Partida-Sanchez et al., 2003; Kunerth et al., 2004; Hashii et al., 2005; Fliegert et al., 2007; Jude et al., 2008). cADPR can also be involved in the extracellular Ca^{2+} influx in T cells and neuroblastoma-derived neuronal cells (Partida-Sanchez et al., 2001; Amina et al., 2010). These evidences suggest that CD38 is a primary regulator of Ca^{2+} signaling in various cell types, including astrocytes.

5. Astrocyte glutamate production vs. glutamate uptake in HAND

Astrocytes are known to regulate glutamate homeostasis in CNS [for details review (Hamilton and Attwell, 2010)]. In the HIV-1-infected brain, multiple factors may impair astrocyte regulation of Ca^{2+} and glutamate levels. Gendelman and co-workers first reported high levels of arachidonic acid and cytokines such as TNF-α and IL-1β, in HIVE brain tissue (Gendelman et al., 1994), which likely lead to reduced glutamate uptake and increased Ca^{+2}-mediated release of glutamate by astrocytes (Parpura et al., 1994; Bezzi et al., 1998). It has also been shown that HIV-1 gp120 may indirectly contribute to impaired astrocyte-glutamate uptake *in vitro* (Schneider-Schaulies et al., 1992; Benos et al., 1994). Thus, in addition to glutamate release, dysreguation of $[Ca^{+2}]_i$ in astrocytes may also contribute to HIV neuropathogenesis through impaired glutamate uptake. Impaired glutamate uptake can lead to further increases in the extracellular glutamate levels. Enhanced glutamate levels in turn activate N-methyl-D-aspartic acid (NMDA) receptors causing increased levels of intracellular Ca^{2+} in neurons as shown both in cultured neurons and acute brain slices (Kaul et al., 2001), and can eventually lead to neuronal apoptosis or necrosis. Excess glutamate may also lead to lipid peroxidation and eventually affect both astrocyte and neuronal viability (Visalli et al., 2007).

Under normal physiological conditions, astrocytes selectively regulate extracellular levels of glutamate to maintain homeostasis in the neuronal microenvironment mainly through glutamate transporters (Rothstein et al., 1996). Previous work on primary human astrocytes has shown downregulation of excitatory amino acid transporter 2 (EAAT2) upon activation of astrocytes with HIV-1 gp120, leading to reduction in glutamate uptake (Wang et al., 2003). Glutamate transporter activity and inhibition of glutamate uptake can also be mediated by MAPKs and NF-κB in astrocytes (Abe and Saito, 2001; Jayakumar et al., 2006). Our laboratory showed that CD38 expression and function in astrocytes, is primarily regulated by NF-κB and MAPKs (Mamik et al., In Press). Thus, it is relevant to propose that CD38 levels may affect astrocyte-mediated glutamate homeostasis during neuroinflammatory conditions.

Both RyR and IP3R blockers can reduce excess glutamate release by astrocytes (Hua et al., 2004; Reyes and Parpura, 2009). This suggests that perhaps both IP3R and RyR may be involved in the increase in $[Ca^{2+}]_i$, an event that plays a major role in glutamate release. We have previously reported CD38-cADPR-mediated increase in $[Ca^{2+}]_i$ in activated astrocytes. Our data suggests that elevated CD38 level leads to production of excess cADPR, which may eventually result in higher Ca^{2+} in activated astrocytes during HIVE (Banerjee et al., 2008). As previously reported by De Flora's group, this rise in $[Ca^{2+}]_i$ by CD38 may lead to increased release of glutamate by astrocytes (Verderio et al., 2001). Studies by Bezzi and co-workers showed that cultured astrocytes may trigger $[Ca^{2+}]_i$-dependent release of

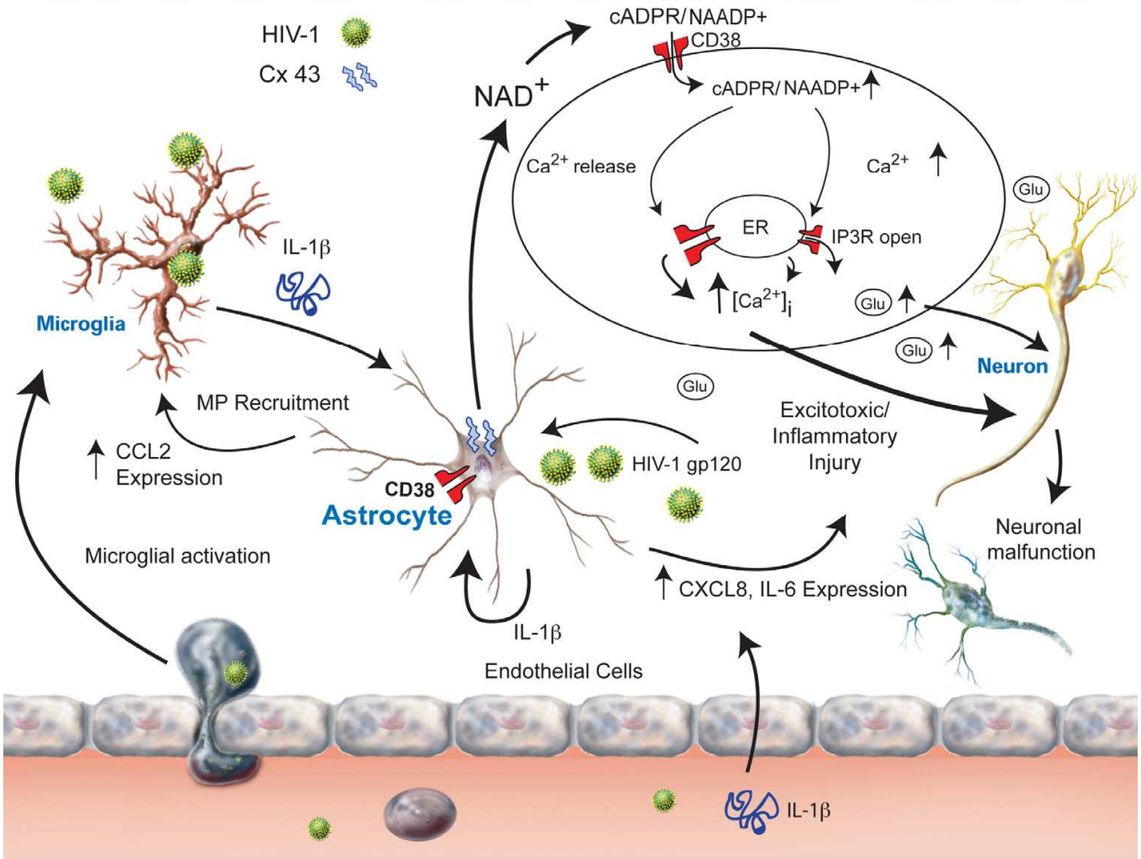


Fig. 1. Schematic representation of CD38-mediated astrocyte-neuron interactions. In HIVE, virus-infected macrophages cross the blood-brain barrier and initiate inflammatory processes in the brain including microglial activation. Activated macrophages and microglia produce IL-1β, which along with viral protein HIV-1 gp120 leads to activation of astrocytes. Inflammatory responses of activated astrocytes may include upregulation of molecules detrimental to neural homeostasis. One of these pathways includes CD38 upregulation, which produces Ca^{2+}-mobilizing metabolites like NAD+. NAD+ upon release through Connexin 43 (Cx 43) hemichannels is hydrolyzed and transported back into the cell as cADPR by membrane bound CD38. cADPR and NAADP+ may regulate release of $[Ca^{2+}]_i$. Astrocyte-mediated release of glutamate and other inflammatory mediators (IL-6 and CXCL8) into the synapse may ultimately lead to excitotoxic neuronal injury.

glutamate, which may lead to NMDA receptor-mediated increased Ca^{+2} levels in neurons (Bezzi et al., 1998). The above evidences suggest that the initial release of glutamate due to increase in $[Ca^{+2}]_i$ by astrocytes, may be influencing the prolonged higher Ca^{2+} levels in neurons during HAND. Taken together, CD38/cADPR-mediated rise of $[Ca^{2+}]_i$ in activated astrocytes (Banerjee et al., 2008) may contribute to increased extracellular glutamate levels, resulting in neuronal excitotoxicity during HAND.

6. Conclusion

6.1 Role of astrocyte-CD38 in HAND: Possible mechanisms

Astrocytes are capable of generating complex changes in $[Ca^{2+}]_i$, allowing them to communicate with each other and with neighboring neuronal cells. The CD38/cADPR system is involved in regulating $[Ca^{2+}]_i$ homeostasis in astrocytes (Banerjee et al., 2008). A paracrine model of interaction has been suggested, involving NAADP+ and cADPR, leading to glutamate-release by astrocytes, affecting neurons (Verderio et al., 2001; De Flora et al., 2004). Our previous data demonstrate that in HIV-1 CNS disease, astrocytes express elevated levels of CD38 (Kou et al., 2009), thus activating these paracrine pathways. The possible connections between HIV-1 infection, neuroinflammation and astrocyte activation, which result in CD38 upregulation and dysregulation of Ca^{2+}/glutamate homeostasis and culminate in neuronal injury (Fig. 1).

7. Acknowledgement

The authors would like to thank Ms. Kathleen Borgmann, Ms. Radhika Suryadevara and Ms. Manmeet Mamik for their suggestions and editing help. We would also like to acknowledge our collaborators Drs. Timothy Walseth, Mathur Kannan and Keshore Bidasee for insightful discussions on CD38 biology.

8. References

Abe, K., and Saito, H. (2001). Possible linkage between glutamate transporter and mitogen-activated protein kinase cascade in cultured rat cortical astrocytes. Journal of neurochemistry 76, 217-223.

Amina, S., Hashii, M., Ma, W.J., Yokoyama, S., Lopatina, O., Liu, H.X., Islam, M.S., and Higashida, H. (2010). Intracellular calcium elevation induced by extracellular application of cyclic-ADP-ribose or oxytocin is temperature-sensitive in rodent NG108-15 neuronal cells with or without exogenous expression of human oxytocin receptors. Journal of neuroendocrinology 22, 460-466.

Ances, B.M., and Ellis, R.J. (2007). Dementia and neurocognitive disorders due to HIV-1 infection. Semin Neurol 27, 86-92.

Antonelli, A., and Ferrannini, E. (2004). CD38 autoimmunity: recent advances and relevance to human diabetes. J Endocrinol Invest 27, 695-707.

Banerjee, S., Walseth, T.F., Borgmann, K., Wu, L., Bidasee, K.R., Kannan, M.S., and Ghorpade, A. (2008). CD38/cyclic ADP-ribose regulates astrocyte calcium signaling: implications for neuroinflammation and HIV-1-associated dementia. J Neuroimmune Pharmacol 3, 154-164.

Bell, J.E. (2004). An update on the neuropathology of HIV in the HAART era. Histopathology 45, 549-559.

Bell, J.E., Brettle, R.P., Chiswick, A., and Simmonds, P. (1998). HIV encephalitis, proviral load and dementia in drug users and homosexuals with AIDS. Effect of neocortical involvement. Brain 121, 2043-2052.

Benos, D.J., Hahn, B.H., Bubien, J.K., Ghosh, S.K., Mashburn, N.A., Chaikin, M.A., Shaw, G.M., and Benveniste, E.N. (1994). Envelope glycoprotein gp120 of human immunodeficiency virus type 1 alters ion transport in astrocytes: implications for AIDS dementia complex. Proc Natl Acad Sci U S A 91, 494-498.

Berridge, M.J., Bootman, M.D., and Roderick, H.L. (2003). Calcium signalling: dynamics, homeostasis and remodelling. Nat Rev Mol Cell Biol 4, 517-529.

Bers, D.M. (2002). Cardiac excitation-contraction coupling. Nature 415, 198-205.

Berthelier, V., Tixier, J.M., Muller-Steffner, H., Schuber, F., and Deterre, P. (1998). Human CD38 is an authentic NAD(P)+ glycohydrolase. Biochem J 330 (Pt 3), 1383-1390.

Bezzi, P., Carmignoto, G., Pasti, L., Vesce, S., Rossi, D., Rizzini, B.L., Pozzan, T., and Volterra, A. (1998). Prostaglandins stimulate calcium-dependent glutamate release in astrocytes. Nature 391, 281-285.

Blumberg, B.M., Gelbard, H.A., and Epstein, L.G. (1994). HIV-1 infection of the developing nervous system: central role of astrocytes in pathogenesis. Virus Res 32, 253-267.

Boven, L.A., Gomes, L., Hery, C., Gray, F., Verhoef, J., Portegies, P., Tardieu, M., and Nottet, H.S. (1999). Increased peroxynitrite activity in AIDS dementia complex: implications for the neuropathogenesis of HIV-1 infection. J Immunol 162, 4319-4327.

Brew, B.J., Rosenblum, M., Cronin, K., and Price, R.W. (1995). AIDS dementia complex and HIV-1 brain infection:clinical-virological correlation. Ann Neurol 38, 563-570.

Brodt, H.R., Kamps, B.S., Gute, P., Knupp, B., Staszewski, S., and Helm, E.B. (1997). Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. Aids 11, 1731-1738.

Bruzzone, S., Kunerth, S., Zocchi, E., De Flora, A., and Guse, A.H. (2003). Spatio-temporal propagation of Ca2+ signals by cyclic ADP-ribose in 3T3 cells stimulated via purinergic P2Y receptors. The Journal of cell biology 163, 837-845.

Chang, L., and Karin, M. (2001). Mammalian MAP kinase signalling cascades. Nature 410, 37-40.

Cotrina, M.L., and Nedergaard, M. (2005). Intracellular calcium control mechanisms in glia. Neuroglia (BOOK), 229-239.

Dammermann, W., and Guse, A.H. (2005). Functional ryanodine receptor expression is required for NAADP-mediated local Ca2+ signaling in T-lymphocytes. The Journal of biological chemistry 280, 21394-21399.

Davis, R.J. (1995). Transcriptional regulation by MAP kinases. Mol Reprod Dev 42, 459-467.

De Flora, A., Zocchi, E., Guida, L., Franco, L., and Bruzzone, S. (2004). Autocrine and paracrine calcium signaling by the CD38/NAD+/cyclic ADP-ribose system. Ann N Y Acad Sci 1028, 176-191.

Deaglio, S., Mehta, K., and Malavasi, F. (2001). Human CD38: a (r)evolutionary story of enzymes and receptors. Leuk Res 25, 1-12.

Deshpande, M., Zheng, J., Borgmann, K., Persidsky, R., Wu, L., Schellpeper, C., and Ghorpade, A. (2005). Role of activated astrocytes in neuronal damage: potential links to HIV-1-associated dementia. Neurotox Res 7, 183-192.

Dickson, D.W., Mattiace, L.A., Kure, K., Hutchins, K., Lyman, W.D., and Brosnan, C.F. (1991). Microglia in human disease, with an emphasis on acquired immune deficiency syndrome. Lab Invest 64, 135-156.

Doengi, M., Deitmer, J.W., and Lohr, C. (2008). New evidence for purinergic signaling in the olfactory bulb: A2A and P2Y1 receptors mediate intracellular calcium release in astrocytes. The FASEB journal : official publication of the Federation of American Societies for Experimental Biology 22, 2368-2378.

Ellis, R., Langford, D., and Masliah, E. (2007). HIV and antiretroviral therapy in the brain: neuronal injury and repair. Nat Rev Neurosci 8, 33-44.

Eng, L.F., and Ghirnikar, R.S. (1994). GFAP and astrogliosis. Brain pathology 4, 229-237.

Felzen, B., Shilkrut, M., Less, H., Sarapov, I., Maor, G., Coleman, R., Robinson, R.B., Berke, G., and Binah, O. (1998). Fas (CD95/Apo-1)-mediated damage to ventricular myocytes induced by cytotoxic T lymphocytes from perforin-deficient mice: a major role for inositol 1,4,5-trisphosphate. Circ Res 82, 438-450.

Fliegert, R., Gasser, A., and Guse, A.H. (2007). Regulation of calcium signalling by adenine-based second messengers. Biochemical Society transactions 35, 109-114.

Foley, J., Ettenhofer, M., Wright, M., and Hinkin, C.H. (2008). Emerging issues in the neuropsychology of HIV infection. Current HIV/AIDS reports 5, 204-211.

Gallo, P., Laverda, A.M., De Rossi, A., Pagni, S., Del Mistro, A., Cogo, P., Piccinno, M.G., Plebani, A., Tavolato, B., and Chieco-Bianchi, L. (1991). Immunological markers in the cerebrospinal fluid of HIV-1-infected children. Acta Paediatr Scand 80, 659-666.

Gendelman, H., and Tardieu, M. (1994). Macrophages/microglia and the pathophysiology of CNS injuries in AIDS. J of Leukocyte Biology 56, 387-388.

Gendelman, H.E., Genis, P., Jett, M., Zhai, Q.H., and Nottet, H.S. (1994). An experimental model system for HIV-1-induced brain injury. Adv Neuroimmunol 4, 189-193.

Gonzales, M.F., and Davis, R.L. (1988). Neuropathology of acquired immunodeficiency syndrome. Neuropathol Appl Neurobiol 14, 345-363.

Grant, I. (2008). Neurocognitive disturbances in HIV. Int Rev Psychiatry 20, 33-47.

Hamilton, N.B., and Attwell, D. (2010). Do astrocytes really exocytose neurotransmitters? Nature reviews Neuroscience 11, 227-238.

Hashii, M., Shuto, S., Fukuoka, M., Kudoh, T., Matsuda, A., and Higashida, H. (2005). Amplification of depolarization-induced and ryanodine-sensitive cytosolic Ca2+ elevation by synthetic carbocyclic analogs of cyclic ADP-ribose and their antagonistic effects in NG108-15 neuronal cells. J Neurochem 94, 316-323.

Heidemann, A.C., Schipke, C.G., and Kettenmann, H. (2005a). Extracellular application of NAADP+ induces Ca2+ signaling in astrocytes in situ. J Biol Chem.

Heidemann, A.C., Schipke, C.G., and Kettenmann, H. (2005b). Extracellular application of nicotinic acid adenine dinucleotide phosphate induces Ca2+ signaling in astrocytes in situ. J Biol Chem 280, 35630-35640.

Herbein, G., Mahlknecht, U., Batliwalla, F., Gregersen, P., Pappas, T., Butler, J., O'Brien, W.A., and Verdin, E. (1998). Apoptosis of CD8+ T cells is mediated by

macrophages through interaction of HIV gp120 with chemokine receptor CXCR4. Nature 395, 189-194.

Holden, C.P., Haughey, N.J., Nath, A., and Geiger, J.D. (1999). Role of Na+/H+ exchangers, excitatory amino acid receptors and voltage-operated Ca2+ channels in human immunodeficiency virus type 1 gp120-mediated increases in intracellular Ca2+ in human neurons and astrocytes. Neuroscience 91, 1369-1378.

Hua, L.L., Zhao, M.L., Cosenza, M., Kim, M.O., Huang, H., Tanowitz, H.B., Brosnan, C.F., and Lee, S.C. (2002). Role of mitogen-activated protein kinases in inducible nitric oxide synthase and TNFalpha expression in human fetal astrocytes. J Neuroimmunol 126, 180-189.

Hua, X., Malarkey, E.B., Sunjara, V., Rosenwald, S.E., Li, W.H., and Parpura, V. (2004). C(a2+)-dependent glutamate release involves two classes of endoplasmic reticulum Ca(2+) stores in astrocytes. J Neurosci Res 76, 86-97.

Jana, M., Anderson, J.A., Saha, R.N., Liu, X., and Pahan, K. (2005). Regulation of inducible nitric oxide synthase in proinflammatory cytokine-stimulated human primary astrocytes. Free Radic Biol Med 38, 655-664.

Jayakumar, A.R., Panickar, K.S., Murthy Ch, R., and Norenberg, M.D. (2006). Oxidative stress and mitogen-activated protein kinase phosphorylation mediate ammonia-induced cell swelling and glutamate uptake inhibition in cultured astrocytes. The Journal of neuroscience : the official journal of the Society for Neuroscience 26, 4774-4784.

Jayaraman, T., and Marks, A.R. (1997). T cells deficient in inositol 1,4,5-trisphosphate receptor are resistant to apoptosis. Mol Cell Biol 17, 3005-3012.

John, G.R., Scemes, E., Suadicani, S.O., Liu, J.S., Charles, P.C., Lee, S.C., Spray, D.C., and Brosnan, C.F. (1999). IL-1beta differentially regulates calcium wave propagation between primary human fetal astrocytes via pathways involving P2 receptors and gap junction channels. Proc Natl Acad Sci U S A 96, 11613-11618.

Jude, J.A., Wylam, M.E., Walseth, T.F., and Kannan, M.S. (2008). Calcium signaling in airway smooth muscle. Proceedings of the American Thoracic Society 5, 15-22.

Kaul, M., Garden, G.A., and Lipton, S.A. (2001). Pathways to neuronal injury and apoptosis in HIV-1-associated dementia. Nature 410, 988-993.

Kaul, M., and Lipton, S.A. (2006). Mechanisms of neuroimmunity and neurodegeneration associated with HIV-1 infection and AIDS. J Neuroimmune Pharmacol 1, 138-151.

Khan, A., Soloski, M., Sharp, A., Schilling, G., Sabatini, D., Li, S., Ross, C., and Snyder, S. (1996). Lymphocyte apoptosis: mediation by increased type 3 inositol 1,4,5-triphosphate receptor. Science 273, 503-507.

Kolber, M.A. (2008). CD38+CD8+ T-cells negatively correlate with CD4 central memory cells in virally suppressed HIV-1-infected individuals. Aids 22, 1937-1941.

Kou, W., Banerjee, S., Eudy, J., Smith, L.M., Persidsky, R., Borgmann, K., Wu, L., Sakhuja, N., Deshpande, M.S., Walseth, T.F., *et al.* (2009). CD38 regulation in activated astrocytes: implications for neuroinflammation and HIV-1 brain infection. J Neurosci Res 87, 2326-2339.

Kunerth, S., Langhorst, M.F., Schwarzmann, N., Gu, X., Huang, L., Yang, Z., Zhang, L., Mills, S.J., Zhang, L.H., Potter, B.V., *et al.* (2004). Amplification and propagation of

pacemaker Ca2+ signals by cyclic ADP-ribose and the type 3 ryanodine receptor in T cells. J Cell Sci 117, 2141-2149.

Lane, T.E., Buchmeier, M.J., Watry, D.D., and Fox, H.S. (1996). Expression of inflammatory cytokines and inducible nitric oxide synthase in brains of SIV-infected rhesus monkeys: applications to HIV- induced central nervous system disease. Mol Med 2, 27-37.

Lee, H.C. (2001). Physiological functions of cyclic ADP-ribose and NAADP as calcium messengers. Annu Rev Pharmacol Toxicol 41, 317-345.

Lee, H.C., and Aarhus, R. (1993). Wide distribution of an enzyme that catalyzes the hydrolysis of cyclic ADP-ribose. Biochimica et biophysica acta 1164, 68-74.

Letendre, S., McCutchan, J.A., and Ellis, R.J. (2008). Neurologic Complications of HIV Disease and Their Treatment. Top HIV Med 16, 15-22.

Li, W., Li, G., Steiner, J., and Nath, A. (2009). Role of Tat protein in HIV neuropathogenesis. Neurotoxicity research 16, 205-220.

Lin, J.X., and Leonard, W.J. (1997). Signaling from the IL-2 receptor to the nucleus. Cytokine Growth Factor Rev 8, 313-332.

Lindl, K.A., Marks, D.R., Kolson, D.L., and Jordan-Sciutto, K.L. (2010). HIV-associated neurocognitive disorder: pathogenesis and therapeutic opportunities. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology 5, 294-309.

Liu, X.L., Miyakawa, A., Aperia, A., and Krieger, P. (2007). Na,K-ATPase generates calcium oscillations in hippocampal astrocytes. Neuroreport 18, 597-600.

Mamik, M.K., Banerjee, S., Walseth, T.F., Hirte, R., Tang, L., Borgmann, K., and Ghorpade, A. (In Press). HIV-1 and IL-1β regulate astrocytic CD38 through mitogen-activated protein kinases and nuclear factor-κB signaling mechanisms. J Neuroinflammation.

Mandi, M., and Bak, J. (2008). Nicotinic acid adenine dinucleotide phosphate (NAADP) and Ca2+ mobilization. Journal of receptor and signal transduction research 28, 163-184.

Mauermann, M.L., Angius, D., Spinner, R.J., Letendre, L.J., Amrami, K.K., and Dyck, P.J. (2008). Isolated granulocytic sarcoma presenting as a brachial plexopathy. Journal of the peripheral nervous system : JPNS 13, 153-156.

Meucci, O., Fatatis, A., Simen, A.A., Bushell, T.J., Gray, P.W., and Miller, R.J. (1998). Chemokines regulate hippocampal neuronal signaling and gp120 neurotoxicity. Proc Natl Acad Sci U S A 95, 14500-14505.

Mizuguchi, M., Otsuka, N., Sato, M., Ishii, Y., Kon, S., Yamada, M., Nishina, H., Katada, T., and Ikeda, K. (1995). Neuronal localization of CD38 antigen in the human brain. Brain Res 697, 235-240.

Morita, M., Higuchi, C., Moto, T., Kozuka, N., Susuki, J., Itofusa, R., Yamashita, J., and Kudo, Y. (2003). Dual regulation of calcium oscillation in astrocytes by growth factors and pro-inflammatory cytokines via the mitogen-activated protein kinase cascade. J Neurosci 23, 10944-10952.

Nath, A., and Geiger, J. (1998). Neurobiological aspects of human immunodeficiency virus infection: neurotoxic mechanisms. Prog Neurobiol 54, 19-33.

Navia, B.A., Jordan, B.D., and Price, R.W. (1986). The AIDS dementia complex: I. Clinical features. Annals of Neurology 19, 517-524.

Okuda, H., Higashi, Y., Nishida, K., Fujimoto, S., and Nagasawa, K. (2010). Contribution of P2X7 receptors to adenosine uptake by cultured mouse astrocytes. Glia 58, 1757-1765.

Parker, L.C., Luheshi, G.N., Rothwell, N.J., and Pinteaux, E. (2002). IL-1 beta signalling in glial cells in wildtype and IL-1RI deficient mice. Br J Pharmacol 136, 312-320.

Parpura, V., Basarsky, T.A., Liu, F., Jeftinija, K., Jeftinija, S., and Haydon, P.G. (1994). Glutamate-mediated astrocyte-neuron signalling. Nature 369, 744-747.

Partida-Sanchez, S., Cockayne, D.A., Monard, S., Jacobson, E.L., Oppenheimer, N., Garvy, B., Kusser, K., Goodrich, S., Howard, M., Harmsen, A., *et al.* (2001). Cyclic ADP-ribose production by CD38 regulates intracellular calcium release, extracellular calcium influx and chemotaxis in neutrophils and is required for bacterial clearance in vivo. Nat Med 7, 1209-1216.

Partida-Sanchez, S., Randall, T.D., and Lund, F.E. (2003). Innate immunity is regulated by CD38, an ecto-enzyme with ADP-ribosyl cyclase activity. Microbes Infect 5, 49-58.

Pawlikowska, L., Cottrell, S.E., Harms, M.B., Li, Y., and Rosenberg, P.A. (1996). Extracellular synthesis of cADP-ribose from nicotinamide-adenine dinucleotide by rat cortical astrocytes in culture. J Neurosci 16, 5372-5381.

Pellegrini, P., Berghella, A.M., Di Loreto, S., Del Beato, T., Di Marco, F., Adorno, D., and Casciani, C.U. (1996). Cytokine contribution to the repair processes and homeostasis recovery following anoxic insult: a possible IFN-gamma-regulating role in IL- 1beta neurotoxic action in physiological or damaged CNS. Neuroimmunomodulation 3, 213-218.

Peng, H., Erdmann, N., Whitney, N., Dou, H., Gorantla, S., Gendelman, H.E., Ghorpade, A., and Zheng, J. (2006). HIV-1-infected and/or immune activated macrophages regulate astrocyte SDF-1 production through IL-1beta. Glia 54, 619-629.

Persidsky, Y., Ghorpade, A., Rasmussen, J., Limoges, J., Liu, X.J., Stins, M., Fiala, M., Way, D., Kim, K.S., Witte, M.H., *et al.* (1999). Microglial and astrocyte chemokines regulate monocyte migration through the blood-brain barrier in human immunodeficiency virus-1 encephalitis. Am J Pathol 155, 1599-1611.

Persidsky, Y., Limoges, J., McComb, R., Bock, P., Baldwin, T., Tyor, W., Patil, A., Nottet, H.S., Epstein, L., Gelbard, H., *et al.* (1996). Human immunodeficiency virus encephalitis in SCID mice. Am J Pathol 149, 1027-1053.

Petito, C.K., Kerza-Kwiatecki, A.P., Gendelman, H.E., McCarthy, M., Nath, A., Podack, E.R., Shapshak, P., and Wiley, C.A. (1999). Review: neuronal injury in HIV infection. J Neurovirol 5, 327-341.

Price, R.W., Brew, B., Sidtis, J., Rosenblum, M., Scheck, A.C., and Cleary, P. (1988). The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex. Science 239, 586-592.

Price, R.W., and Spudich, S. (2008). Antiretroviral therapy and central nervous system HIV type 1 infection. J Infect Dis 197 Suppl 3, S294-306.

Rajan, P., and McKay, R.D. (1998). Multiple routes to astrocytic differentiation in the CNS. J Neurosci 18, 3620-3629.

Ransom, B., Behar, T., and Nedergaard, M. (2003). New roles for astrocytes (stars at last). Trends Neurosci 26, 520-522.

Reyes, R.C., and Parpura, V. (2008). Mitochondria modulate Ca2+-dependent glutamate release from rat cortical astrocytes. The Journal of neuroscience : the official journal of the Society for Neuroscience 28, 9682-9691.

Reyes, R.C., and Parpura, V. (2009). The trinity of Ca2+ sources for the exocytotic glutamate release from astrocytes. Neurochemistry international 55, 2-8.

Ridet, J.L., Malhotra, S.K., Privat, A., and Gage, F.H. (1997). Reactive astrocytes: cellular and molecular cues to biological function. Trends Neurosci 20, 570-577.

Rojas, H., Colina, C., Ramos, M., Benaim, G., Jaffe, E.H., Caputo, C., and DiPolo, R. (2007). Na+ entry via glutamate transporter activates the reverse Na+/Ca2+ exchange and triggers Ca(i)2+-induced Ca2+ release in rat cerebellar Type-1 astrocytes. Journal of neurochemistry 100, 1188-1202.

Rojas, H., Ramos, M., and Dipolo, R. (2004). A genistein-sensitive Na+/Ca2+ exchange is responsible for the resting [Ca2+]i and most of the Ca2+ plasma membrane fluxes in stimulated rat cerebellar type 1 astrocytes. The Japanese journal of physiology 54, 249-262.

Rothstein, J.D., Dykes-Hoberg, M., Pardo, C.A., Bristol, L.A., Jin, L., Kuncl, R.W., Kanai, Y., Hediger, M.A., Wang, Y., Schielke, J.P., *et al.* (1996). Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. Neuron 16, 675-686.

Sacktor, N.C., Lyles, R.H., Skolasky, R.L., Anderson, D.E., McArthur, J.C., McFarlane, G., Selnes, O.A., Becker, J.T., Cohen, B., Wesch, J., *et al.* (1999). Combination antiretroviral therapy improves psychomotor speed performance in HIV-seropositive homosexual men. Multicenter AIDS Cohort Study (MACS). Neurology 52, 1640-1647.

Savarino, A., Bottarel, F., Malavasi, F., and Dianzani, U. (2000). Role of CD38 in HIV-1 infection: an epiphenomenon of T-cell activation or an active player in virus/host interactions? Aids 14, 1079-1089.

Schneider-Schaulies, J., Schneider-Schaulies, S., Brinkmann, R., Tas, P., Halbrugge, M., Walter, U., Holmes, H.C., and Ter Meulen, V. (1992). HIV-1 gp120 receptor on CD4-negative brain cells activates a tyrosine kinase. Virology 191, 765-772.

Sebire, G., Emilie, D., Wallon, C., Hery, C., Devergne, O., Delfraissy, J.F., Galanaud, P., and Tardieu, M. (1993). In vitro production of IL-6, IL-1 beta, and tumor necrosis factor-alpha by human embryonic microglial and neural cells. J Immunol 150, 1517-1523.

Sharma, V., Mishra, M., Ghosh, S., Tewari, R., Basu, A., Seth, P., and Sen, E. (2007). Modulation of interleukin-1beta mediated inflammatory response in human astrocytes by flavonoids: implications in neuroprotection. Brain Res Bull 73, 55-63.

Sinclair, E., Ronquillo, R., Lollo, N., Deeks, S.G., Hunt, P., Yiannoutsos, C.T., Spudich, S., and Price, R.W. (2008). Antiretroviral treatment effect on immune activation reduces cerebrospinal fluid HIV-1 infection. Journal of acquired immune deficiency syndromes 47, 544-552.

Steen, M., Kirchberger, T., and Guse, A.H. (2007). NAADP mobilizes calcium from the endoplasmic reticular Ca(2+) store in T-lymphocytes. The Journal of biological chemistry 282, 18864-18871.

Tyor, W.R., Glass, J.D., Baumrind, N., McArthur, J.C., Griffin, J.W., Becker, P.S., and Griffin, D.E. (1993). Cytokine expression of macrophages in HIV-1-associated vacuolar myelopathy [see comments]. Neurology 43, 1002-1009.

Verderio, C., Bruzzone, S., Zocchi, E., Fedele, E., Schenk, U., De Flora, A., and Matteoli, M. (2001). Evidence of a role for cyclic ADP-ribose in calcium signalling and neurotransmitter release in cultured astrocytes. J Neurochem 78, 646-657.

Vigano, A., Saresella, M., Villa, M.L., Ferrante, P., and Clerici, M. (2000). CD38+CD8+ T cells as a marker of poor response to therapy in HIV-infected individuals. Chem Immunol 75, 207-217.

Visalli, V., Muscoli, C., Sacco, I., Sculco, F., Palma, E., Costa, N., Colica, C., Rotiroti, D., and Mollace, V. (2007). N-acetylcysteine prevents HIV gp 120-related damage of human cultured astrocytes: correlation with glutamine synthase dysfunction. BMC Neurosci 8, 106.

Vitkovic, L., Bockaert, J., and Jacque, C. (2000a). "Inflammatory" cytokines: neuromodulators in normal brain? J Neurochem 74, 457-471.

Vitkovic, L., Chatham, J.J., and da Cunha, A. (1995). Distinct expressions of three cytokines by IL-1-stimulated astrocytes in vitro and in AIDS brain. Brain Behav Immun 9, 378-388.

Vitkovic, L., Konsman, J.P., Bockaert, J., Dantzer, R., Homburger, V., and Jacque, C. (2000b). Cytokine signals propagate through the brain. Mol Psychiatry 5, 604-615.

Wang, T.F., Zhou, C., Tang, A.H., Wang, S.Q., and Chai, Z. (2006). Cellular mechanism for spontaneous calcium oscillations in astrocytes. Acta pharmacologica Sinica 27, 861-868.

Wang, Z., Pekarskaya, O., Bencheikh, M., Chao, W., Gelbard, H.A., Ghorpade, A., Rothstein, J.D., and Volsky, D.J. (2003). Reduced expression of glutamate transporter EAAT2 and impaired glutamate transport in human primary astrocytes exposed to HIV-1 or gp120. Virology 312, 60-73.

Wiley, C.A., and Achim, C. (1994). Human immunodeficiency virus encephalitis is the pathological correlate of dementia in acquired immunodeficiency syndrome. Ann Neurol 36, 673-676.

Woods, S.P., Moore, D.J., Weber, E., and Grant, I. (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. Neuropsychology review 19, 152-168.

Wu, V.W., and Schwartz, J.P. (1998). Cell culture models for reactive gliosis: new perspectives. J Neurosci Res 51, 675-681.

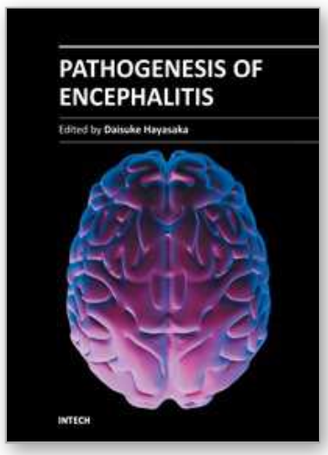
Yamada, M., Mizuguchi, M., Otsuka, N., Ikeda, K., and Takahashi, H. (1997). Ultrastructural localization of CD38 immunoreactivity in rat brain. Brain Res 756, 52-60.

Yi, Y., Lee, C., Liu, Q.H., Freedman, B.D., and Collman, R.G. (2004). Chemokine receptor utilization and macrophage signaling by human immunodeficiency virus type 1 gp120: Implications for neuropathogenesis. J Neurovirol 10 Suppl 1, 91-96.

Zhao, L., and Brinton, R.D. (2004). Suppression of proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha in astrocytes by a V1 vasopressin receptor

agonist: a cAMP response element-binding protein-dependent mechanism. The Journal of neuroscience : the official journal of the Society for Neuroscience 24, 2226-2235.

Zhao, M.L., Brosnan, C.F., and Lee, S.C. (2004). 15-deoxy-delta (12,14)-PGJ2 inhibits astrocyte IL-1 signaling: inhibition of NF-kappaB and MAP kinase pathways and suppression of cytokine and chemokine expression. J Neuroimmunol 153, 132-142.



Pathogenesis of Encephalitis
Edited by Dr. Daisuke Hayasaka

ISBN 978-953-307-741-3
Hard cover, 344 pages
Publisher InTech
Published online 09, December, 2011
Published in print edition December, 2011

Many infectious agents, such as viruses, bacteria, and parasites, can cause inflammation of the central nervous system (CNS). Encephalitis is an inflammation of the brain parenchyma, which may result in a more advanced and serious disease meningoencephalitis. To establish accurate diagnosis and develop effective vaccines and drugs to overcome this disease, it is important to understand and elucidate the mechanism of its pathogenesis. This book, which is divided into four sections, provides comprehensive commentaries on encephalitis. The first section (6 chapters) covers diagnosis and clinical symptoms of encephalitis with some neurological disorders. The second section (5 chapters) reviews some virus infections with the outlines of inflammatory and chemokine responses. The third section (7 chapters) deals with the non-viral causative agents of encephalitis. The last section (4 chapters) discusses the experimental model of encephalitis. The different chapters of this book provide valuable and important information not only to the researchers, but also to the physician and health care workers.

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