Early Gene c-fos and Glial Cells

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The *c-fos* gene was first described as a proto-oncogene responsible for the induction of bone tumors. A few decades ago, activation of the protein product c-fos was reported in the brain after seizures and other noxious stimuli. Since then, multiple studies have used c-fos as a brain activity marker. Although it has been attributed to neurons, growing evidence demonstrates that c-fos expression in the brain may also include glial cells. Unlike neurons, whose expression changes used to be associated with depolarization, glial cells seem to express the c-fos proto-oncogene under the influence of proliferation, differentiation, growth, inflammation, repair, damage, plasticity, and other conditions. This glial cell may provide additional information related to the brain microenvironment that is difficult to obtain from the isolated neuron paradigm. Thus, detection techniques are improved in order to better differentiate the phenotypes expressing c-fos in the brain and to elucidate the specific roles of c-fos expression in glial cells.

Keywords: c-fos ; glial cell ; neurons

1. c-fos in the Brain

At the end of the past century, some immediate early gene (IEG) were associated with stimuli–transcription activity in the brain. The most commonly used reporter for this phenomenon was the *c-fos* gene, whose expression in neurons was described to be transient [1]. As a marker of cellular activity, c-fos was subsequently used to identify brain regions implicated in stimuli processing [2][3] or relationships between two or more brain areas [4]. Similar to electrophysiology, it was used to measure neuronal activity but also provided information about morphology and cell type both in vivo [5][6][7][8] and in vitro [9][10]. The most commonly used methods to reveal c-fos changes became immunohistochemistry and Western blotting (in situ hybridization). In addition, c-fos expression was also employed in transgenic models (i.e., fos-LacZ) to inactivate some genes in a quantitative manner [11][12][13][14]. More recently, optogenetic models used c-fos to mark and manipulate specific brain nuclei [15].

Former studies investigating the expression of c-fos in neuroblastic cells supported the use of this marker to evidence changes in brain activity. Neuroblastic cultures demonstrated that nerve growth factor (NGF) [11], phosphatidic acid [16], epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin, and potassium chloride (KCl) could induce the expression of c-fos in these cells [17]. Following experiments characterized the main cell pathways able to activate c-fos in neural cells [11][16][17]. It was demonstrated that growth factors, interferons, interleukins, calcium release, and G-protein ligands could initiate phosphorylation cascades, affecting c-fos expression. The phosphorylation proteins Jak 1-2, tyrosine kinase 2 (Tyk2), calmodulin kinases (CaMks), and protein kinase A (PKA) were described as key components of these pathways. The second messengers cAMP, GTP, and Ca^{2+} were evidenced as main mediators. Signaling complexes such as ras-raf, MEK-MAPK, or cAMP Response Element-Binding proteins (CREB) were also recognized in the c-fos signaling map. The list of transcription regulators affecting c-fos expression included the serum response element (SRE), cAMP response element (CRE), SIF-inducible element (SIE), interferon stimulation response element (ISRE), and IFN-γ-activated site (GAS) [18][19][20][21].

c-fos was initially used in brain research to measure the neural activity after seizures. In this area, it allowed researchers, for example, to map the neuronal pathways involved in different models/intensities of the seizure [22][23][24]; to estimate the effect of antiepileptic drugs [25]; or to analyze new-born cells and asymmetries after seizures [26][27]. c-fos has also been consolidated as a reliable marker for cell activation derived from learning [28] and memory [29][30]. The use of c-fos expression permitted researchers to predict cognitive worsening in Alzheimer's disease and other conditions [31][32]. The relevance of sleep for memory acquisition and synaptic plasticity was also investigated by measuring c-fos during REM sleep [33]. Furthermore, c-fos was crucial to elucidating the role of the amygdala, thalamus, and hypothalamus in conditioned fear processing [34] and the epigenetic regulation of neuroplasticity [35], and cognition [36].

Studies of psychiatric disorders and their therapeutics also benefited from the use of c-fos. Fos, Fos-B, Jun, and Egr1 were reported to be upregulated in patients suffering from schizophrenia [37]. The antidepressant effect of optogenetic

stimulation in the medial prefrontal cortex (mPFC) was assessed by mapping c-fos expression [38], and some antipsychotic drug effects in the brain were located through fos expression [39][40]. Stress studies, on the other hand, demonstrated activity changes in the frontal cortex and many limbic structures [41][42][43] that may predict susceptibility [44] or resilience to stress [45]. Moreover, it has been suggested that c-fos/Fos-B could be reliable markers for investigating the adaptive capabilities of the brain under stress conditions [46][47]. In addition, the study of endocrine responses demonstrated that suckling can modify the c-fos expression in the cerebral cortex [48], and that metabolic dysfunction produced by diabetes activates c-fos in the bed nucleus of stria terminalis (BNST) [49]. Research on circadian cycles and their alterations also evidenced c-fos changes in the suprachiasmatic nuclei (SCN), the main pacemaker in mammals [50] [51]. Hypothalamic changes in c-fos levels may be used to measure altered circadian rhythmicity [52], intraspecific alternative chronotypes [53], or differences between diurnal and nocturnal animals [54][55].

Models inducing brain injury evidenced that c-fos increases 3 h after damage but also 3 days later. Thus, c-fos can accompany the immediate neuroprotective effects after brain edema, but also the delayed apoptosis in later stages of the lesion [56]. On the other hand, models inducing pain in the brain confirmed c-fos's ability to map the brain areas involved in nociception [57][58], and allowed researchers to elucidate the role of periaqueductal gray and adenylate-cyclase-activating polypeptide-38 (PACAP-38) [59] in nociception [60]. In addition, fos immunoreactivity permitted researchers to describe a non-canonical auditory nociceptive system evidencing that cochlear nuclei could be active in deaf mice exposed to noxious levels of noise (120 dB) [61]. Thus, it is clear that c-fos has a crucial role in signal transduction across the brain, but studies have prioritized neuronal cells. As mentioned before, c-fos could potentially be expressed in every cell type, and that could include the non-neuronal residents of the brain, the glial cells.

2. c-fos in Astrocytes

Initial studies investigating c-fos in this population explored implications in proliferation/maturation. Former in vitro experiments evaluated whether the mitogenic agents EGF, FGF, tetradecanoyl phorbol acetate (TPA), dbcAMP, or forskolin were able to induce c-fos in astrocytes. They found that these agents strongly induce c-fos and that major expression rates should be expected from 20 to 45 min after treatment [62]. In vitro stimulation of neurotransmitter systems also induced c-fos in astrocytes. Carbachol (cholinergic agonist), norepinephrine (NE), isoproterenol (ISO; β-adrenergic agonist), and phenylephrine (PHE; α-adrenergic agonist) were used to demonstrate that stimulation of c-fos through cholinergic or adrenergic pathways can modulate secondary genes or induce phenotypic changes [63]. The role of c-fos in astrocyte proliferation and differentiation was also explored by using mitogens (EGF, bFGF, db-cAMP, TPA) or depolarizing conditions (elevations in Ca^{2+} uptake or high concentrations of K^{+}). Results showing that mitogens but not depolarization enhanced the expression indicate that c-fos could be specifically involved in astrocyte proliferation/differentiation [64]. Additionally, serotonin induces c-fos in astrocytes through its receptor $5HT_{2B}R$, which in turn enhances calcium release, metalloproteinases, and EGF release [65]. The use of endothelins to stimulate astrocytes corroborated that c-fos might be implicated in NGF expression during brain development [66]. Later in the 1990s, it was evidenced that the calcitonin-gene-related peptide (CGRP), a molecule produced by damage, was able to induce dose–response expression of c-fos in astrocytes. Since forskolin (an adenylate cyclase activator) reduced its effect, it was supposed cAMP had a role in the induction of c-fos associated with transformation and reparation of the injured brain [67].

Immune system mediators are also implicated in the glial expression of IEGs. c-fos and c-jun have been reported to be increased in astrocytes exposed to IFN-γ in a dose–response manner [19]. The IFN-γ-induced expression of c-fos in astrocytes regulates the complement factor H, whose abnormal levels instead induce neuronal loss in pathologies such as Alzheimer's disease [68]. Other cytokines (TNF-α, IL-1β, and IFN-γ) and lipopolysaccharides (LPS) involved in inflammation modulate the expression of c-fos in astrocytes. LPS, LPS+ IL-1β, and IFN-γ induce c-fos in these cells. TNF-α, on the other hand, may enhance the LPS-induced increases in c-fos [69]. LPS induction of c-fos involves the p38 MAPK pathway, which activates Elk1, CREB/ATF-1, and later the SRE or CRE promoter [70]. Astrocytes infected with the adenovirus Ad.βGal expressed both c-fos and the apoptotic marker caspase-3, suggesting that c-fos can also indicate apoptosis [71]. Moreover, experimental autoimmune encephalitis allowed researchers to characterize a subpopulation of c-fos-expressing astrocytes named ieastrocytes. In this experimental model, the reporter system TetTag/green fluorescent protein was used to reveal the historical activity of c-fos in astrocytes. Promising results suggest astrocyte c-fos activity is a biomarker for autoimmune encephalitis [72].

Experimental models of damage also evidenced the activity of c-fos in astrocytes. In vitro models of heat shock and scratch wound showed not only that astrocytes express c-fos, but also that quercetin can inhibit the hypertrophy induced by scratches. That suggests that reactive astrogliosis could be associated with c-fos expression [73]. Experimental ocular hypertension models also demonstrated c-fos expression in astroglia. Monkeys with experimental glaucoma and astrocyte cultures of human glaucomatous optic nervous were found to overexpress c-fos [14]. Ischemia was also reported to induce

quick and transient expression of the *c-fos* gene in cultured astrocytes. Those experiments exhibited that astrocytes rapidly increase the expression of c-fos after 30 min, reach a maximal expression level after 60 min, and diminish their expression levels after 2 h [74]. Chemical hypoxia, in turn, reverted the enhancing effect of ATP on the expression of c-fos [75]. Mimicking excitotoxicity, it was found that glutamate stimulation of astrocytes can rapidly increase the expression of c-fos since peak levels were reached 1 h after exposure [76]. Glutamate enhancements of c-fos could be mediated by mGluR5 and calcium dynamics since the addition of BAPTA (a calcium chelator) inhibits this enhancement [77].

Other conditions have been demonstrated to induce c-fos in astrocytes. Angiotensin II (AngII), for instance, can differentially regulate IEGs with lower increases in c-jun in contrast to c-fos. For some researchers, AngII dysregulation could lead to pathological responses through modulation of astrocytic c-fos expression [78]. The antidepressant fluoxetine was also evidenced to show a dual response varying with the effect of the dose; higher doses (5, 10 μM) enhance c-fos expression through ERK1/2, while lower doses (0.5, 1 μM) inhibit astrocyte expression of c-fos by the Akt pathway [79]. Conditions such as stress exposure or cognitive assessments have also evidenced c-fos induction in this population. It has been reported, for example, that learning activates c-fos in hippocampal astrocytes [80] and that restraint stress increases GFAP/c-fos+ in exposed subjects [81].

3. c-fos in Oligodendrocytes

Although astrocytes represent the vast majority of experiments investigating c-fos in glial cells, oligodendrocytes have also been the target of some experiments. Like astrocytes, growth factors (bFGF, EGF, PDGF, and IGF-1) were reported to stimulate proliferation or maturation in OPCs, also known as NG2-glia. It was then reported that PKC and c-fos were required for this effect since blocking with H-7 (a PKC inactivator) resulted in inhibited proliferation [82][83]. The idea of c-fos as a promoter of proliferation/maturation of oligodendroglia became strengthened when experiments demonstrated that maturation of NG2 cells was preceded by c-fos expression [84]. Moreover, reports showed that c-fos-expressing oligodendrocytes exhibited a dose-dependent decrease in proliferation [85]. Oligodendrocyte proliferation can also be induced by carbachol, a cholinergic analogous that acts as a growth factor and also activates PKC and c-fos [86]. Norepinephrine, on the other hand, was also proved to exert a c-fos proliferative effect on oligodendrocytes. Calcium dependence of this process was suggested since sensitive G proteins, inositol phosphate 3 kinase (IP3K), and PKC were also activated [87].

Some pathologic conditions also affect the expression of c-fos in oligodendroglia. It was demonstrated that oligodendrocytes can express c-fos under glutamate stimulation too. Maximal expression levels were reported 60 min after exposure, and returns to basal levels were observed 6 *h* later. Glutamate experiments demonstrated that c-fos induction is mediated by AMPA-R and KA-R but not NMDA-R since specific antagonist CNQX and DNQX inhibited the effect, but MK-801 (NMDA-specific antagonist) failed to inhibit c-fos expression. Hypoxic conditions are also able to induce c-fos in oligodendrocytes. Hypoxia models demonstrated that oligodendrocytes express c-fos as an event preceding myelin loss, axonal damage, and apoptotic death [88]. There is also evidence that c-fos expression is stimulated by the hallucinogen d-LSD in vivo, an action possibly linked to the modulation of neuronal impulses or growth factor production [89]. Finally, it was reported that c-fos expression diminished with maturation in oligodendrocytes, but ethanol consumption retarded this decrease as well as the myelin basic protein (MBP) production [90].

4. c-fos in Microglia

Given the mesodermal immune origin of microglia, it is highly expected that c-fos modulates some actions in this lineage. Even so, less research has explored this, with some pieces of evidence indicating that c-fos can be expressed by the immune residents of the brain. For instance, there are experiments showing that excitotoxic glutamate stimulation, through any of its ionotropic receptors or group I of metabotropic receptors, is able to induce c-fos expression and microglial activation [91]. In addition, it was reported that stimulation with kainic acid (KA) increases the expression of MHCII and class II transactivator (CIITA) in microglia, but coincidently, both are inhibited by pretreatment with triptolide, which actually decreases the phosphorylation of c-fos and c-jun and the consequent formation of AP1 [92].

Proinflammatory effects have been proposed for the expression of c-fos in microglia. It is known that microglial NOD-like receptor 3 (NLRP3) is associated with neuroinflammation and is also a therapeutic target in Alzheimer's disease. Thus, the anti-inflammatory effects of dexmedetomidine inhibit NLRP3-derived inflammasome, modulating the c-fos upregulated expression [93]. As in other glial types, there is also evidence showing that LPS can induce the expression of c-fos in microglia and the consequent inflammation in the brain [94]. Additionally, studies of paraquat, an herbicide that is associated with a higher incidence of Parkinson's disease, have evidenced that this substance can induce c-fos

expression, as well as HSP60 and TLR4, which then increases the proinflammatory cytokine production and accelerates inflammatory responses [95].

References

1. Hudson, A.E. Genetic Reporters of Neuronal Activity: C-Fos and G-CaMP6. Methods Enzymol. 2018, 603, 197–220.
2. Campeau, S.; Akil, H.; Watson, S.J. Lesions of the medial geniculate nuclei specifically block corticosterone release and induction of c-fos mRNA in the forebrain associated with audiogenic stress in rats. J. Neurosci. 1997, 17, 5979–5992.
3. Campeau, S.; Dolan, D.; Akil, H.; Watson, S.J. C-fos mRNA induction in acute and chronic audiogenic stress: Possible role of the orbitofrontal cortex in habituation. Stress 2002, 5, 121–130.
4. Rodriguez-Ortega, E.; Canadas, F.; Carvajal, F.; Cardona, D. In vivo stimulation of locus coeruleus: Effects on amygdala subnuclei. Acta Neurobiol. Exp. 2017, 77, 261–268.
5. Umezu, T.; Shibata, Y. Brain regions and monoaminergic neurotransmitters that are involved in mouse ambulatory activity promoted by bupropion. Toxicol. Rep. 2016, 3, 552–562.
6. Fetterly, T.L.; Basu, A.; Nabit, B.P.; Awad, E.; Williford, K.M.; Centanni, S.W.; Matthews, R.T.; Silberman, Y.; Winder, D.G. Alpha2A-Adrenergic Receptor Activation Decreases Parabrachial Nucleus Excitatory Drive onto BNST CRF Neurons and Reduces Their Activity In Vivo. J. Neurosci. 2019, 39, 472–484.
7. Mak, S.O.K.; Zhang, L.; Chow, B.K.C. In vivo actions of SCTR/AT1aR heteromer in controlling Vp expression and release via cFos/cAMP/CREB pathway in magnocellular neurons of PVN. FASEB J. 2019, 33, 5389–5398.
8. Schmidt, K.T.; Makhijani, V.H.; Boyt, K.M.; Cogan, E.S.; Pati, D.; Pina, M.M.; Bravo, I.M.; Locke, J.L.; Jones, S.R.; Besheer, J.; et al. Stress-Induced Alterations of Norepinephrine Release in the Bed Nucleus of the Stria Terminalis of Mice. ACS Chem. Neurosci. 2019, 10, 1908–1914.
9. Hashimoto, K.; Parker, A.; Malone, P.; Gabelt, B.T.; Rasmussen, C.; Kaufman, P.S.; Hernandez, M.R. Long-term activation of c-Fos and c-Jun in optic nerve head astrocytes in experimental ocular hypertension in monkeys and after exposure to elevated pressure in vitro. Brain Res. 2005, 1054, 103–115.
10. Prosser, R.A.; Macdonald, E.S.; Heller, H.C. C-fos mRNA in the suprachiasmatic nuclei in vitro shows a circadian rhythm and responds to a serotonergic agonist. Brain Res. Mol. Brain Res. 1994, 25, 151–156.
11. Curran, T.; Morgan, J.I. Fos: An immediate-early transcription factor in neurons. J. Neurobiol. 1995, 26, 403–412.
12. Koya, E.; Margetts-Smith, G.; Hope, B.T. Daun02 Inactivation of Behaviorally Activated Fos-Expressing Neuronal Ensembles. Curr. Protoc. Neurosci. 2016, 76, 8–36.
13. Warren, B.L.; Mendoza, M.P.; Cruz, F.C.; Leao, R.M.; Caprioli, D.; Rubio, F.J.; Whitaker, L.R.; McPherson, K.B.; Bossert, J.M.; Shaham, Y.; et al. Distinct Fos-Expressing Neuronal Ensembles in the Ventromedial Prefrontal Cortex Mediate Food Reward and Extinction Memories. J. Neurosci. 2016, 36, 6691–6703.
14. Whitaker, L.R.; Warren, B.L.; Venniro, M.; Harte, T.C.; McPherson, K.B.; Beidel, J.; Bossert, J.M.; Shaham, Y.; Bonci, A.; Hope, B.T. Bidirectional Modulation of Intrinsic Excitability in Rat Prelimbic Cortex Neuronal Ensembles and Non-Ensembles after Operant Learning. J. Neurosci. 2017, 37, 8845–8856.
15. Richter, F.; Bauer, A.; Perl, S.; Schulz, A.; Richter, A. Optogenetic augmentation of the hypercholinergic endophenotype in DYT1 knock-in mice induced erratic hyperactive movements but not dystonia. EBioMedicine 2019, 41, 649–658.
16. Moolenaar, W.H.; Kruijer, W.; Tilly, B.C.; Verlaan, I.; Bierman, A.J.; de Laat, S.W. Growth factor-like action of phosphatidic acid. Nature 1986, 323, 171–173.
17. Greenberg, M.E.; Greene, L.A.; Ziff, E.B. Nerve growth factor and epidermal growth factor induce rapid transient changes in proto-oncogene transcription in PC12 cells. J. Biol. Chem. 1985, 260, 14101–14110.
18. Piechaczyk, M.; Blanchard, J.M. C-fos proto-oncogene regulation and function. Crit. Rev. Oncol. Hematol. 1994, 17, 93–131.
19. Rubio, N. Interferon-gamma induces the expression of immediate early genes c-fos and c-jun in astrocytes. Immunology 1997, 91, 560–564.
20. Gauthier-Rouviere, C.; Fernandez, A.; Lamb, N.J. Ras-induced c-fos expression and proliferation in living rat fibroblasts involves C-kinase activation and the serum response element pathway. EMBO J. 1990, 9, 171–180.
21. Janknecht, R.; Cahill, M.A.; Nordheim, A. Signal integration at the c-fos promoter. Carcinogenesis 1995, 16, 443–450.

22. Andre, V.; Pineau, N.; Motte, J.E.; Marescaux, C.; Nehlig, A. Mapping of neuronal networks underlying generalized seizures induced by increasing doses of pentylenetetrazol in the immature and adult rat: A c-Fos immunohistochemical study. Eur. J. Neurosci. 1998, 10, 2094–2106.

23. Yang, H.; Shan, W.; Zhu, F.; Yu, T.; Fan, J.; Guo, A.; Li, F.; Yang, X.; Wang, Q. C-Fos mapping and EEG characteristics of multiple mice brain regions in pentylenetetrazol-induced seizure mice model. Neurol. Res. 2019, 41, 749–761.

24. Krisztin-Peva, B.; Mihaly, A.; Toth, Z. Differential expression of the c-fos protein and synaptophysin in zebrin II positive and zebrin II negative cerebellar cortical areas in 4-aminopyridine seizures. Acta Neurobiol. Exp. 2019, 79, 238–250.

25. Wallengren, C.; Li, S.; Morris, M.J.; Jupp, B.; O'Brien, T.J. Aggravation of absence seizures by carbamazepine in a genetic rat model does not induce neuronal c-Fos activation. Clin. Neuropharmacol. 2005, 28, 60–65.

26. Kalinina, A.; Maletta, T.; Carr, J.; Lehmann, H.; Fournier, N.M. Spatial exploration induced expression of immediate early genes Fos and Zif268 in adult-born neurons Is reduced after pentylenetetrazole kindling. Brain Res. Bull. 2019, 152, 74–84.

27. Burnsed, J.; Skwarzynska, D.; Wagley, P.K.; Isbell, L.; Kapur, J. Neuronal Circuit Activity during Neonatal Hypoxic-Ischemic Seizures in Mice. Ann. Neurol. 2019, 86, 927–938.

28. Goelet, P.; Castellucci, V.F.; Schacher, S.; Kandel, E.R. The long and the short of long-term memory—A molecular framework. Nature 1986, 322, 419–422.

29. Hall, J.; Thomas, K.L.; Everitt, B.J. Fear memory retrieval induces CREB phosphorylation and Fos expression within the amygdala. Eur. J. Neurosci. 2001, 13, 1453–1458.

30. Vann, S.D.; Brown, M.W.; Erichsen, J.T.; Aggleton, J.P. Fos imaging reveals differential patterns of hippocampal and parahippocampal subfield activation in rats in response to different spatial memory tests. J. Neurosci. 2000, 20, 2711–2718.

31. Corbett, B.F.; You, J.C.; Zhang, X.; Pyfer, M.S.; Tosi, U.; Iascone, D.M.; Petrof, I.; Hazra, A.; Fu, C.H.; Stephens, G.S.; et al. DeltaFosB Regulates Gene Expression and Cognitive Dysfunction in a Mouse Model of Alzheimer's Disease. Cell Rep. 2017, 20, 344–355.

32. Calais, J.B.; Valvassori, S.S.; Resende, W.R.; Feier, G.; Athie, M.C.; Ribeiro, S.; Gattaz, W.F.; Quevedo, J.; Ojopi, E.B. Long-term decrease in immediate early gene expression after electroconvulsive seizures. J. Neural Transm. 2013, 120, 259–266.

33. Calais, J.B.; Ojopi, E.B.; Morya, E.; Sameshima, K.; Ribeiro, S. Experience-dependent upregulation of multiple plasticity factors in the hippocampus during early REM sleep. Neurobiol. Learn. Mem. 2015, 122, 19–27.

34. Nikolaev, E.; Kaczmarek, L.; Zhu, S.W.; Winblad, B.; Mohammed, A.H. Environmental manipulation differentially alters c-Fos expression in amygdaloid nuclei following aversive conditioning. Brain Res. 2002, 957, 91–98.

35. Su, Y.; Shin, J.; Zhong, C.; Wang, S.; Roychowdhury, P.; Lim, J.; Kim, D.; Ming, G.L.; Song, H. Neuronal activity modifies the chromatin accessibility landscape in the adult brain. Nat. Neurosci. 2017, 20, 476–483.

36. West, A.E.; Greenberg, M.E. Neuronal activity-regulated gene transcription in synapse development and cognitive function. Cold Spring Harb. Perspect. Biol. 2011, 3, a005744.

37. Cattane, N.; Minelli, A.; Milanesi, E.; Maj, C.; Bignotti, S.; Bortolomasi, M.; Chiavetto, L.B.; Gennarelli, M. Altered gene expression in schizophrenia: Findings from transcriptional signatures in fibroblasts and blood. PLoS ONE 2015, 10, e0116686.

38. Covington, H.E., 3rd; Lobo, M.K.; Maze, I.; Vialou, V.; Hyman, J.M.; Zaman, S.; LaPlant, Q.; Mouzon, E.; Ghose, S.; Tamminga, C.A.; et al. Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex. J. Neurosci. 2010, 30, 16082–16090.

39. MacGibbon, G.A.; Lawlor, P.A.; Bravo, R.; Dragunow, M. Clozapine and haloperidol produce a differential pattern of immediate early gene expression in rat caudate-putamen, nucleus accumbens, lateral septum and islands of Calleja. Brain Res. Mol. Brain Res. 1994, 23, 21–32.

40. Verma, V.; Rasmussen, K.; Dawe, G.S. Effects of short-term and chronic olanzapine treatment on immediate early gene protein and tyrosine hydroxylase immunoreactivity in the rat locus coeruleus and medial prefrontal cortex. Neuroscience 2006, 143, 573–585.

41. Quezada, D.F. Cambios Cognitivos, Expresión de C-Fos y Arborización Dendrítica Después de la Exposición a Ruido Ambiental Crónico en Ratas Macho Adultas; Universidad de Guadalajara: Guadalajara, México, 2020.

42. Fernández-Quezada, D.; Luquín, S.; Ruvalcaba-Delgadillo, Y.; García-Estrada, J.; Jauregui-Huerta, F. Sex Differences in the Expression of c-fos in a Rat Brain after Exposure to Environmental Noise. Sustainability 2022, 14, 2798.

43. Ons, S.; Rotllant, D.; Marin-Blasco, I.J.; Armario, A. Immediate-early gene response to repeated immobilization: Fos protein and arc mRNA levels appear to be less sensitive than c-fos mRNA to adaptation. Eur. J. Neurosci. 2010, 31, 2043–2052.

44. Vialou, V.; Robison, A.J.; Laplant, Q.C.; Covington, H.E., 3rd; Dietz, D.M.; Ohnishi, Y.N.; Mouzon, E.; Rush, A.J., 3rd; Watts, E.L.; Wallace, D.L.; et al. DeltaFosB in brain reward circuits mediates resilience to stress and antidepressant responses. Nat. Neurosci. 2010, 13, 745–752.

45. Vialou, V.; Bagot, R.C.; Cahill, M.E.; Ferguson, D.; Robison, A.J.; Dietz, D.M.; Fallon, B.; Mazei-Robison, M.; Ku, S.M.; Harrigan, E.; et al. Prefrontal cortical circuit for depression- and anxiety-related behaviors mediated by cholecystokinin: Role of DeltaFosB. J. Neurosci. 2014, 34, 3878–3887.

46. Perrotti, L.I.; Hadeishi, Y.; Ulery, P.G.; Barrot, M.; Monteggia, L.; Duman, R.S.; Nestler, E.J. Induction of deltaFosB in reward-related brain structures after chronic stress. J. Neurosci. 2004, 24, 10594–10602.

47. Machida, M.; Lonart, G.; Sanford, L.D. Effects of stressor controllability on transcriptional levels of c-fos, Arc, and brain-derived neurotrophic factor in mouse amygdala and medial prefrontal cortex. Neuroreport 2018, 29, 112–117.

48. Abbud, R.; Lee, W.S.; Hoffman, G.; Smith, M.S. Lactation inhibits hippocampal and cortical activation of cFos expression by nivida but not kainate receptor agonists. Mol. Cell. Neurosci. 1992, 3, 244–250.

49. Wosiski-Kuhn, M.; Bota, M.; Snider, C.A.; Wilson, S.P.; Venkataraju, K.U.; Osten, P.; Stranahan, A.M. Hippocampal brain-derived neurotrophic factor determines recruitment of anatomically connected networks after stress in diabetic mice. Hippocampus 2018, 28, 900–912.

50. Houben, T.; Coomans, C.P.; Meijer, J.H. Regulation of circadian and acute activity levels by the murine suprachiasmatic nuclei. PLoS ONE 2014, 9, e110172.

51. Caldelas, I.; Poirel, V.J.; Sicard, B.; Pevet, P.; Challet, E. Circadian profile and photic regulation of clock genes in the suprachiasmatic nucleus of a diurnal mammal Arvicanthis ansorgei. Neuroscience 2003, 116, 583–591.

52. Schwartz, M.D.; Nunez, A.A.; Smale, L. Rhythmic cFos expression in the ventral subparaventricular zone influences general activity rhythms in the Nile grass rat, Arvicanthis niloticus. Chronobiol. Int. 2009, 26, 1290–1306.

53. Langel, J.; Yan, L.; Nunez, A.A.; Smale, L. Behavioral Masking and cFos Responses to Light in Day- and Night-Active Grass Rats. J. Biol. Rhythm. 2014, 29, 192–202.

54. Shuboni-Mulligan, D.D.; Cavanaugh, B.L.; Tonson, A.; Shapiro, E.M.; Gall, A.J. Functional and anatomical variations in retinorecipient brain areas in Arvicanthis niloticus and Rattus norvegicus: Implications for the circadian and masking systems. Chronobiol. Int. 2019, 36, 1464–1481.

55. Schottner, K.; Vuillez, P.; Challet, E.; Pevet, P.; Weinert, D. Light-induced c-Fos expression in the SCN and behavioural phase shifts of Djungarian hamsters with a delayed activity onset. Chronobiol. Int. 2015, 32, 596–607.

56. Zheng, W.; Niu, L.; Zhang, C.; Zhu, C.; Xie, F.; Cao, C.; Li, G. Brain edema and protein expression of c-Fos and c-Jun in the brain after diffused brain injury. Int. J. Clin. Exp. Pathol. 2014, 7, 2809–2817.

57. Telford, S.; Wang, S.; Redgrave, P. Analysis of nociceptive neurones in the rat superior colliculus using c-fos immunohistochemistry. J. Comp. Neurol. 1996, 375, 601–617.

58. Pinto, M.; Lima, D.; Tavares, I. Correlation of noxious evoked c-fos expression in areas of the somatosensory system during chronic pain: Involvement of spino-medullary and intra-medullary connections. Neurosci. Lett. 2006, 409, 100–105.

59. Sandor, K.; Kormos, V.; Botz, B.; Imreh, A.; Bolcskei, K.; Gaszner, B.; Markovics, A.; Szolcsanyi, J.; Shintani, N.; Hashimoto, H.; et al. Impaired nocifensive behaviours and mechanical hyperalgesia, but enhanced thermal allodynia in pituitary adenylate cyclase-activating polypeptide deficient mice. Neuropeptides 2010, 44, 363–371.

60. Araujo, P.; Coelho, C.A.; Oliveira, M.G.; Tufik, S.; Andersen, M.L. Neonatal Sleep Restriction Increases Nociceptive Sensitivity in Adolescent Mice. Pain Physician 2018, 21, E137–E148.

61. Flores, E.N.; Duggan, A.; Madathany, T.; Hogan, A.K.; Márquez, F.G.; Kumar, G.; Seal, R.P.; Edwards, R.H.; Liberman, M.C.; García-Añoveros, J. A Non-Canonical Pathway from Cochlea to Brain Signals Tissue-Damaging Noise. Curr. Biol. 2015, 25, 606–612.

62. Arenander, A.T.; Lim, R.W.; Varnum, B.C.; Cole, R.; de Vellis, J.; Herschman, H.R. TIS gene expression in cultured rat astrocytes: Multiple pathways of induction by mitogens. J. Neurosci. Res. 1989, 23, 257–265.

63. Arenander, A.T.; de Vellis, J.; Herschman, H.R. Induction of c-fos and TIS genes in cultured rat astrocytes by neurotransmitters. J. Neurosci. Res. 1989, 24, 107–114.

64. Hisanaga, K.; Sagar, S.M.; Hicks, K.J.; Swanson, R.A.; Sharp, F.R. c-fos proto-oncogene expression in astrocytes associated with differentiation or proliferation but not depolarization. Brain Res. Mol. Brain Res. 1990, 8, 69–75.

65. Peng, L.; Li, B.; Du, T.; Kong, E.K.; Hu, X.; Zhang, S.; Shan, X.; Zhang, M. Astrocytic transactivation by alpha2A-adrenergic and 5-HT2B serotonergic signaling. Neurochem. Int. 2010, 57, 421–431.

66. Ladenheim, R.G.; Lacroix, I.; Foignant-Chaverot, N.; Strosberg, A.D.; Couraud, P.O. Endothelins stimulate c-fos and nerve growth factor expression in astrocytes and astrocytoma. J. Neurochem. 1993, 60, 260–266.

67. Haas, C.A.; Reddington, M.; Kreutzberg, G.W. Calcitonin Gene-related Peptide Stimulates the Induction of c-fos Gene Expression in Rat Astrocyte Cultures. Eur. J. Neurosci. 1991, 3, 708–712.

68. Fraczek, L.A.; Martin, C.B.; Martin, B.K. C-Jun and c-Fos regulate the complement factor H promoter in murine astrocytes. Mol. Immunol. 2011, 49, 201–210.

69. Suh, H.W.; Choi, S.S.; Lee, J.K.; Lee, H.K.; Han, E.J.; Lee, J. Regulation of c-fos and c-jun gene expression by lipopolysaccharide and cytokines in primary cultured astrocytes: Effect of PKA and PKC pathways. Arch. Pharm. Res. 2004, 27, 396–401.

70. Simi, A.; Edling, Y.; Ingelman-Sundberg, M.; Tindberg, N. Activation of c-fos by lipopolysaccharide in glial cells via p38 mitogen-activated protein kinase-dependent activation of serum or cyclic AMP/calcium response element. J. Neurochem. 2005, 92, 915–924.

71. Rubio, N.; Martin-Clemente, B. Binding of adenovirus to its receptors in mouse astrocytes induces c-fos proto-oncogene and apoptosis. Virology 2002, 297, 211–219.

72. Groves, A.; Kihara, Y.; Jonnalagadda, D.; Rivera, R.; Kennedy, G.; Mayford, M.; Chun, J. A Functionally Defined In Vivo Astrocyte Population Identified by c-Fos Activation in a Mouse Model of Multiple Sclerosis Modulated by S1P Signaling: Immediate-Early Astrocytes (ieAstrocytes). eNeuro 2018, 5.

73. Wu, B.Y.; Yu, A.C. Quercetin inhibits c-fos, heat shock protein, and glial fibrillary acidic protein expression in injured astrocytes. J. Neurosci. Res. 2000, 62, 730–736.

74. Yu, A.C.; Lee, Y.L.; Fu, W.Y.; Eng, L.F. Gene expression in astrocytes during and after ischemia. Prog. Brain Res. 1995, 105, 245–253.

75. Hung, A.C.; Huang, H.M.; Tsay, H.J.; Lin, T.N.; Kuo, J.S.; Sun, S.H. ATP-stimulated c-fos and zif268 mRNA expression is inhibited by chemical hypoxia in a rat brain-derived type 2 astrocyte cell line, RBA-2. J. Cell. Biochem. 2000, 77, 323–332.

76. Pechan, P.A.; Chowdhury, K.; Gerdes, W.; Seifert, W. Glutamate induces the growth factors NGF, bFGF, the receptor FGF-R1 and c-fos mRNA expression in rat astrocyte culture. Neurosci. Lett. 1993, 153, 111–114.

77. Edling, Y.; Ingelman-Sundberg, M.; Simi, A. Glutamate activates c-fos in glial cells via a novel mechanism involving the glutamate receptor subtype mGlu5 and the transcriptional repressor DREAM. Glia 2007, 55, 328–340.

78. Delaney, J.; Chiarello, R.; Villar, D.; Kandalam, U.; Castejon, A.M.; Clark, M.A. Regulation of c-fos, c-jun and c-myc gene expression by angiotensin II in primary cultured rat astrocytes: Role of ERK1/2 MAP kinases. Neurochem. Res. 2008, 33, 545–550.

79. Li, B.; Jia, S.; Yue, T.; Yang, L.; Huang, C.; Verkhratsky, A.; Peng, L. Biphasic Regulation of Caveolin-1 Gene Expression by Fluoxetine in Astrocytes: Opposite Effects of PI3K/AKT and MAPK/ERK Signaling Pathways on c-fos. Front. Cell. Neurosci. 2017, 11, 335.

80. Adamsky, A.; Kol, A.; Kreisel, T.; Doron, A.; Ozeri-Engelhard, N.; Melcer, T.; Refaeli, R.; Horn, H.; Regev, L.; Groysman, M.; et al. Astrocytic Activation Generates De Novo Neuronal Potentiation and Memory Enhancement. Cell 2018, 174, 59–71.e14.

81. Fan, F.; Li, L.; Liu, W.; Yang, M.; Ma, X.; Sun, H. Astrocytes and neurons in locus coeruleus mediate restraint water immersion stress-induced gastric mucosal damage through the ERK1/2 signaling pathway. Neurosci. Lett. 2018, 675, 95–102.

82. Bhat, N.R.; Hauser, K.F.; Kindy, M.S. Cell proliferation and protooncogene induction in oligodendroglial progenitors. J. Neurosci. Res. 1992, 32, 340–349.

83. Radhakrishna, M.; Almazan, G. Protein kinases mediate basic fibroblast growth factor's stimulation of proliferation and c-fos induction in oligodendrocyte progenitors. Brain Res. Mol. Brain Res. 1994, 24, 118–128.

84. Prasad, A.; Teh, D.B.L.; Blasiak, A.; Chai, C.; Wu, Y.; Gharibani, P.M.; Yang, I.H.; Phan, T.T.; Lim, K.L.; Yang, H.; et al. Static Magnetic Field Stimulation Enhances Oligodendrocyte Differentiation and Secretion of Neurotrophic Factors. Sci. Rep. 2017, 7, 6743.

85. Liu, H.N.; Almazan, G. Glutamate induces c-fos proto-oncogene expression and inhibits proliferation in oligodendrocyte progenitors: Receptor characterization. Eur. J. Neurosci. 1995, 7, 2355–2363.

86. Cohen, R.I.; Molina-Holgado, E.; Almazan, G. Carbachol stimulates c-fos expression and proliferation in oligodendrocyte progenitors. Brain Res. Mol. Brain Res. 1996, 43, 193–201.
87. Khorchid, A.; Larocca, J.N.; Almazan, G. Characterization of the signal transduction pathways mediating noradrenaline-stimulated MAPK activation and c-fos expression in oligodendrocyte progenitors. J. Neurosci. Res. 1999, 58, 765–778.
88. Goldenberg-Cohen, N.; Guo, Y.; Margolis, F.; Cohen, Y.; Miller, N.R.; Bernstein, S.L. Oligodendrocyte dysfunction after induction of experimental anterior optic nerve ischemia. Investig. Ophthalmol. Vis. Sci. 2005, 46, 2716–2725.
89. Reissig, C.J.; Rabin, R.A.; Winter, J.C.; Dlugos, C.A. D-LSD-induced c-Fos expression occurs in a population of oligodendrocytes in rat prefrontal cortex. Eur. J. Pharmacol. 2008, 583, 40–47.
90. Bichenkov, E.; Ellingson, J.S. Ethanol alters the expressions of c-Fos and myelin basic protein in differentiating oligodendrocytes. Alcohol 2009, 43, 627–634.
91. Eun, S.Y.; Hong, Y.H.; Kim, E.H.; Jeon, H.; Suh, Y.H.; Lee, J.E.; Jo, C.; Jo, S.A.; Kim, J. Glutamate receptor-mediated regulation of c-fos expression in cultured microglia. Biochem. Biophys. Res. Commun. 2004, 325, 320–327.
92. Sun, Z.; Du, M.; Lu, Y.; Zeng, C.Q. Effects of triptolide on the expression of MHC II in microglia in kainic acidinduced epilepsy. Mol. Med. Rep. 2018, 17, 8357–8362.
93. Li, H.; Zhang, X.; Chen, M.; Chen, J.; Gao, T.; Yao, S. Dexmedetomidine inhibits inflammation in microglia cells under stimulation of LPS and ATP by c-Fos/NLRP3/caspase-1 cascades. EXCLI J. 2018, 17, 302–311.
94. Rigillo, G.; Vilella, A.; Benatti, C.; Schaeffer, L.; Brunello, N.; Blom, J.M.C.; Zoli, M.; Tascedda, F. LPS-induced histone H3 phospho(Ser10)-acetylation(Lys14) regulates neuronal and microglial neuroinflammatory response. Brain Behav. Immun. 2018, 74, 277–290.
95. Sun, Y.; Zheng, J.; Xu, Y.; Zhang, X. Paraquat-induced inflammatory response of microglia through HSP60/TLR4 signaling. Hum. Exp. Toxicol. 2018, 37, 1161–1168.