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Role of Electrical Activity in Promoting Neural Repair

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Abstract

The nervous system communicates in a language of electrical activities. The motivation to replace function lost through injury or disease through electrical prostheses has gained traction through steady advances in basic and translational science addressing the interface between electrical prostheses and the nervous system. Recent experiments suggest that electrical activity, signaling through specific molecular pathways, promotes neuronal survival and regeneration. Such data suggests that electrical prostheses, in addition to replacing lost function, may slow underlying degenerative disease or induce regenerative response. Here we review these data with a focus on retinal neurons, and discuss current efforts to translate this effect of electrical activity into clinically applicable treatments.

Introduction

After injury or in neurodegenerative diseases in the mammalian central nervous system (CNS), there is a failure of regenerative response: severed axons do not grow back to their targets, and neurons that die do not get replaced from a pool of progenitor or stem cells. In the visual system, for example, retinal ganglion cell (RGC) axons injured in the optic nerve fail to regenerate back to the brain, and often die after injury [24]. Thus, optic nerve stroke, injury, or degeneration glaucoma and other diseases, all result in permanent loss of vision or blindness.

The CNS is replete with neuronal connections that collect and analyze information using a currency of electrical activity to communicate. Such coding of information by electrical activity has led to extensive research into artificial electronic prostheses to supplant nervous system functions damaged by trauma or disease. Generally, the goal for these prostheses is to replace the missing electrical signals — either translating environmental stimuli into sensory signals into the brain, or translating motor outputs from the brain into efferent signals to stimulate peripheral nerves or muscles. Of course, both require a reliable and predictable neuron-prosthesis interface. Significant steps forward have addressed the reliability of electrical transduction across the neuro-silicon interface, but less attention has focused on the molecular signaling in neurons induced by such exogenous electrical activity. Indeed, responses to electrical signals from prostheses elicit changes in the recipient neurons and in adjacent glial and immune cells [22]. Such changes may modulate neurons' responsiveness to exogenous stimulation and the neuronal survival signaling itself, both of which are

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necessary for the success of implanted devices. Emphasizing data derived from RGCs and visual prostheses, here I focus on the molecular mechanisms mediating neuronal responses to electrical activity, maintaining the neurosilico interface, enhancing neuronal survival, and stimulating axon regeneration [25].

Retinal prostheses provide electrical activity

Most retinal prostheses replace photoreceptor function and transduce light into electricity. Electrode microarrays may be subretinal, next to the photoreceptor cell layer [3, 7, 21] or epiretinal, close to RGCs and bypassing retinal interneurons [3, 32]. Electrodes can also be placed outside of the eye, stimulating retinal neurons across the sclera, although this would be expected to generate lower resolution stimuli [8, 60].

Although these approaches have shown some clinical efficacy in ongoing trials [4, 64, 65], challenges remain. Neurons differ in their electrophysiological thresholds [18], and electrodes may be too large or distant to stimulate individual neurons. Thus some prostheses only evoke phosphenes, or the sensation of spots of white light, across limited areas of the visual field [65]. After device implantation, inflammation and reactive gliosis may limit the prosthesis' ability to stimulate neurons, and could induce neuronal cell death [5]. Solutions may come in the form of smaller electrode microarrays, nanotechnology, better materials, and simultaneous pharmacological intervention to inhibit inflammatory responses. Feedback to the prostheses that allows threshold self-adjustment capabilities may also be useful.

Electrical activity enhances survival and neurite growth

Activity-dependent molecular mechanisms related to neuronal survival and growth may be simultaneously stimulated. What are the by-products of electrical stimulation on neurons' normal physiology, connectivity, survival and regenerative response? Could electrical stimulation be tailored to provide both neural prosthesis as well as optimal signaling for neuroprotection or neuroplasticity? Data from multiple models *in vivo* and *in vitro* support the hypothesis that a loss of electrical activity promotes neuronal degeneration, and that exogenous electrical activity promotes neuronal survival. *In vitro*, blocking electrical activity with tetrodotoxin increases RGC death [38]. A similar effect is seen in organotypic cortical cultures treated with tetrodotoxin or after blockade of a number of ion channel families; this death can be prevented at least partly by depolarizing the cultures in high extracellular potassium (25mM) [28]. Blocking endogenous retinal activity in retinal explants *in vitro* also prevents RGCs from extending neurites in response to brain-derived neurotrophic factor (BDNF) [25], supporting the hypothesis that activity is required to optimally promote axon growth [reviewed further in [23].

Indeed conversely, increasing electrical stimulation within certain limits has a neuroprotective effect and promotes axon growth. In rat RGCs *in vitro*, stimulation with pulses of depolarizing potassium, or with electrical activity from a silicon chip, enhances RGC survival and axon growth in response to BDNF [25]. On the silicon chip, a very low frequency train (stimulating RGCs for only 100 msec out of every 1 min) elicits a ten-fold enhancement in survival. Similarly, stimulating the retina with a trans-corneal electrode increases RGC survival [46] and preserves axons in a model of optic nerve crush *in vivo* when compared to unstimulated controls [44].

Similarly, in animal models of photoreceptor degeneration *in vivo*, subretinal prosthesis stimulation increases photoreceptor density and electrophysiological activity [10, 50]. This increased survival is associated with an activity-dependent increased expression of neurotrophic factors [10]. Electrical stimulation improves survival of inner retinal cells (e.g. amacrine and bipolar cells) after electrical stimulation of explanted retinas in a rat model of

photoreceptor degeneration [58]. Outside of the retina, similar effects are observed [36]. Thus throughout the nervous system in a number of neurodegenerations, electrical activity supports neuronal survival.

Even in human clinical trials, where assessment of neuronal survival is considerably more limited, implanted neural prostheses increase the survival and/or function of the remaining neurons, even in regions of the retina distant from the implant itself [7]. Similarly, measurement of ganglion cell and nerve fiber layer thickness in patients with photoreceptor degeneration suggests more RGC preservation in the central retina, where there are higher levels of activity [31, 54]. Together these data demonstrate that electrical stimulation improves survival of several types of neurons in the injured or degenerating retina.

Mechanisms of neuronal survival and growth response to electrical stimulation

Activity thus performs two roles in neurons: it codes information transferred from cell to cell, and it initiates molecular signaling of survival and neurite growth through protein synthesis or post-translational modifications, activation of signaling pathways, or regulation of gene expression [63]. Small sub-threshold local changes in membrane potential are able to activate signaling pathways locally or by gene transcription. Patterns of electrical stimulation, which could be even small, sub-threshold changes [15], may be critical to eliciting specific cellular signaling pathways [reviewed in [13]. Thus determining the optimal parameters for stimulation of each type of neuron may be required [30]. As optimal stimulation parameters for neuroprotection of RGCs or other neurons have not been definitively determined, the study of dose-response curves may help determine not only thresholds for stimulation [33, 45, 48], but also optimal stimuli for signaling survival.

How other cells like glia contribute to neuronal survival signaling is a complex question reviewed elsewhere [37], but both neurons and glia are able to respond directly to electrical stimulation. Glial cells participate in activity-dependent regulation of metabolism [6, 26, 29, 40] and survival signaling. For example, retinal Mueller glial cells, a specialized type of retinal astrocyte, upregulate expression of neurotrophic factors including BDNF [55] and insulin-like growth factor-1 (IGF-1) in response to electrical stimulation [56].

Activity also signals neurons to increase expression of neurotrophic factors [1, 41]. Electrical activity may also enhance neurons' sensitivity to these signals. For example, RGCs respond only poorly to BDNF and other peptide neurotrophic factors normally; depolarization or stimulation with electrical activity greatly enhances this trophic responsiveness [24, 25, 42]. Depolarization recruits the BDNF receptor TrkB to RGCs' surface [43]; a similar effect is seen in hippocampal neurons [34]. Increased TrkB expression is also observed in response to electrical activity in motor [2], hippocampal [17] and cortical neurons [27]. There may also be synergistic, bi-directional interactions between growth factors and electrical activity [53].

How does electrical activity lead to molecular changes in gene or protein expression, or cellular changes in survival or axon growth? Signaling pathways implicated in mediating the effect of electrical activity on neurons include PI3K/AKT, MEK/ERK, CaMKs, and NFkB [reviewed in [13].

In RGCs, cyclic-AMP (cAMP) appears to be a critical player: neurotrophic factor responsiveness for survival or axon growth in response to depolarization is mimicked by elevating cAMP, and blocking cAMP elevation abolishes the effect of activity on RGC

survival and axon growth [25, 42]. Thus cAMP is a critical player in activity-induced survival and axon growth in RGCs.

How does cAMP mediate RGCs' response to electrical activity? cAMP activates protein kinase A (PKA), which is required for its effect on survival and axon growth, and also activates the Guanine Nucleotide Exchange Factor Activated by cAMP (Epac), which has demonstrated roles in neuronal proliferation, differentiation [35] and axon growth [9, 47]. cAMP elevation leads to an increase in the levels of neurotrophic factor receptors on the cell surface [43] and also increases receptor gene expression over a longer term [14]. Thus there are many pathways by which cAMP may mediate the relationship between electrical activity and neuronal survival and axon growth.

A critical area of research has involved understanding how electrical activity increases cAMP in neurons. In RGCs, activation of calcium sensitive adenylyl cyclases (ACs) is most likely [61], thereby establishing a link to activity. There are 3 calcium-dependent transmembrane ACs (TmACs): AC1 and -8 are activated by calcium, and AC6 is inhibited by calcium [51]. AC1 and AC8 are expressed by mammalian RGCs [49]. Interestingly, electrical stimulation of RGCs enhances survival *in vitro* even when simultaneously activating TmACs pharmacologically with forskolin [11, 12], raising the hypothesis that this electrical activity-mediated neuroprotection depends on pathways other than TmACs; this function could be served by the soluble AC (sAC), which is activated by both calcium and bicarbonate [39, 57]. We have characterized the expression of sAC in the cytoplasm and nucleus of RGCs, and found that sAC activity is required for electrical activity-dependent survival and axon growth of RGCs *in vitro*, and for RGC survival *in vivo* [11, 12]. These data suggest that sAC contributes to cAMP-dependent neuroprotective and regenerative effects of electrical activity in RGCs.

Translating electrical activity to treat human disease

Again, there are many applications for neuro-silicon interfaces to replace functional activity; progress in bringing these to human use has been reviewed elsewhere [examples in refs [52, 59, 62]. These data, however, suggest that providing exogenous electrical activity to neurons may also slow or reverse degenerative pathology or promote regeneration. With RGC neuroprotection as an example, a number of groups have been moving retinal stimulation towards human use. In a rat model of optic nerve injury, transcorneal electrical stimulation using a contact lens electrode increased RGC survival at one week [56]. Electrical stimulation using transcorneal contact lens electrodes or transorbital skin electrodes can stimulate human RGCs to produce visual phenomena such as phosphenes, as mentioned above [19, 45]. This approach has entered early clinical use for optic neuropathies including optic nerve stroke and glaucoma (e.g. clinicaltrials.gov identifiers NCT01270126, NCT01280877). For example, transorbital electrical stimulation for 10 days acutely enhanced visual function [20], either through enhancing local RGC function or by stimulating plasticity in the brain [16]. There is significant hope that these data will prove fruitful in clinical application.

Conclusions

Thus these data suggest a range of positive and negative effects of electrical activity in the nervous system, beyond simply coding information. Such effects are specific to patterns of electrical stimulation, and contribute to neuronal survival and regeneration both in the normal CNS, as well as after injury or as part of the pathogenesis of disease. Maintaining physiologic patterns of electrical activity may preserve remaining neurons by protecting them from activity deprivation-induced cell death, and prevent the aberrant dysfunctional

neural circuitry from forming, until regeneration is achieved or other interventions restore function. Accounting for these effects when designing electronic neural prostheses may add therapeutic advantages to functional benefits.

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References

1. Al-Majed AA, Brushart TM, Gordon T. Electrical stimulation accelerates and increases expression of BDNF and trkB mRNA in regenerating rat femoral motoneurons. *Eur J Neurosci.* 2000; 12:4381–4390. [PubMed: 11122348]
2. Al-Majed AA, Tam SL, Gordon T. Electrical stimulation accelerates and enhances expression of regeneration-associated genes in regenerating rat femoral motoneurons. *Cell Mol Neurobiol.* 2004; 24:379–402. [PubMed: 15206821]
3. Bertschinger DR, Beknazar E, Simonutti M, Safran AB, Sahel JA, Rosolen SG, Picaud S, Salzmann J. A review of in vivo animal studies in retinal prosthesis research. *Graefes Arch Clin Exp Ophthalmol.* 2008; 246:1505–1517. [PubMed: 18709385]
4. Besch D, Sachs H, Szurman P, Gulicher D, Wilke R, Reinert S, Zrenner E, Bartz-Schmidt KU, Gekeler F. Extraocular surgery for implantation of an active subretinal visual prosthesis with external connections: feasibility and outcome in seven patients. *Br J Ophthalmol.* 2008; 92:1361–1368. [PubMed: 18662916]
5. Butterwick A, Huie P, Jones BW, Marc RE, Marmor M, Palanker D. Effect of shape and coating of a subretinal prosthesis on its integration with the retina. *Exp Eye Res.* 2009; 88:22–29. [PubMed: 18955050]
6. Charles A. Reaching out beyond the synapse: glial intercellular waves coordinate metabolism. *Sci STKE.* 2005; 2005:pe6. [PubMed: 15701894]
7. Chow AY, Chow VY, Packo KH, Pollack JS, Peyman GA, Schuchard R. The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa. *Arch Ophthalmol.* 2004; 122:460–469. [PubMed: 15078662]
8. Chowdhury V, Morley JW, Coroneo MT. Development of an extraocular retinal prosthesis: evaluation of stimulation parameters in the cat. *J Clin Neurosci.* 2008; 15:900–906. [PubMed: 18586497]
9. Christensen AE, Selheim F, de Rooij J, Dremier S, Schwede F, Dao KK, Martinez A, Maenhaut C, Bos JL, Genieser HG, Døskeland SO. cAMP analog mapping of Epac1 and cAMP kinase. Discriminating analogs demonstrate that Epac and cAMP kinase act synergistically to promote PC-12 cell neurite extension. *J Biol Chem.* 2003; 278:35394–35402. [PubMed: 12819211]
10. Ciavatta VT, Kim M, Wong PW, Nickerson JM, Shuler RK, McLean GY, Pardue MT. Subretinal implantation of a microphotodiode array induces retinal expression of Fgf2 in RCS rats. *Invest Ophthalmol Vis Sci.* 2009
11. Corredor, R.; Goldberg, JL. Electrical activity enhances retinal ganglion cell survival and axon growth: role of cyclic-AMP and soluble adenylyl cyclase. Society for Neuroscience; Washington, D.C: 2008. p. 818.818
12. Corredor, R.; Goldberg, JL. Role of Electrical Activity in Retinal Ganglion Cell Survival and Axon Growth. Neural Interfaces Conference; Cleveland, OH. 2008.
13. Corredor RG, Goldberg JL. Electrical activity enhances neuronal survival and regeneration. *J Neural Eng.* 2009; 6:055001. [PubMed: 19721179]
14. Deogracias R, Espliguero G, Iglesias T, Rodriguez-Pena A. Expression of the neurotrophin receptor trkB is regulated by the cAMP/CREB pathway in neurons. *Mol Cell Neurosci.* 2004; 26:470–480. [PubMed: 15234351]
15. Dudek SM, Fields RD. Somatic action potentials are sufficient for late-phase LTP-related cell signaling. *Proc Natl Acad Sci U S A.* 2002; 99:3962–3967. [PubMed: 11891337]

16. Fedorov A, Chibisova Y, Szymaszek A, Alexandrov M, Gall C, Sabel BA. Non-invasive alternating current stimulation induces recovery from stroke. *Restor Neurol Neurosci*. 2011; 28:825–833. [PubMed: 21209497]
17. Fields RD, Eshete F, Stevens B, Itoh K. Action potential-dependent regulation of gene expression: temporal specificity in Ca^{2+} , cAMP-responsive element binding proteins, and mitogen-activated protein kinase signaling. *J Neurosci*. 1997; 17:7252–7266. [PubMed: 9295372]
18. Fried SI, Lasker AC, Desai NJ, Eddington DK, Rizzo JF 3rd. Axonal sodium-channel bands shape the response to electric stimulation in retinal ganglion cells. *J Neurophysiol*. 2009; 101:1972–1987. [PubMed: 19193771]
19. Fujikado T, Morimoto T, Matsushita K, Shimojo H, Okawa Y, Tano Y. Effect of transcorneal electrical stimulation in patients with nonarteritic ischemic optic neuropathy or traumatic optic neuropathy. *Jpn J Ophthalmol*. 2006; 50:266–273. [PubMed: 16767383]
20. Gall C, Fedorov AB, Ernst L, Bormann A, Sabel BA. Repetitive transorbital alternating current stimulation in optic neuropathy. *NeuroRehabilitation*. 2010; 27:335–341. [PubMed: 21160123]
21. Gekeler F, Szurman P, Grisanti S, Weiler U, Claus R, Greiner TO, Volker M, Kohler K, Zrenner E, Bartz-Schmidt KU. Compound subretinal prostheses with extra-ocular parts designed for human trials: successful long-term implantation in pigs. *Graefes Arch Clin Exp Ophthalmol*. 2007; 245:230–241. [PubMed: 16645861]
22. Gerding H. A new approach towards a minimal invasive retina implant. *J Neural Eng*. 2007; 4:S30–37. [PubMed: 17325414]
23. Goldberg JL. How does an axon grow? *Genes Dev*. 2003; 17:941–958. [PubMed: 12704078]
24. Goldberg JL, Barres BA. The relationship between neuronal survival and regeneration. *Annu Rev Neurosci*. 2000; 23:579–612. [PubMed: 10845076]
25. Goldberg JL, Espinosa JS, Xu Y, Davidson N, Kovacs GT, Barres BA. Retinal ganglion cells do not extend axons by default: promotion by neurotrophic signaling and electrical activity. *Neuron*. 2002; 33:689–702. [PubMed: 11879647]
26. Haas B, Schipke CG, Peters O, Sohl G, Willecke K, Kettenmann H. Activity-dependent ATP-waves in the mouse neocortex are independent from astrocytic calcium waves. *Cereb Cortex*. 2006; 16:237–246. [PubMed: 15930372]
27. Hartmann M, Heumann R, Lessmann V. Synaptic secretion of BDNF after high-frequency stimulation of glutamatergic synapses. *EMBO J*. 2001; 20:5887–5897. [PubMed: 11689429]
28. Heck N, Golbs A, Riedemann T, Sun JJ, Lessmann V, Luhmann HJ. Activity-dependent regulation of neuronal apoptosis in neonatal mouse cerebral cortex. *Cereb Cortex*. 2008; 18:1335–1349. [PubMed: 17965127]
29. Hoogland TM, Kuhn B, Gobel W, Huang W, Nakai J, Helmchen F, Flint J, Wang SS. Radially expanding transglial calcium waves in the intact cerebellum. *Proc Natl Acad Sci U S A*. 2009; 106:3496–3501. [PubMed: 19211787]
30. Humayun MS, de Juan E Jr, Weiland JD, Dagnelie G, Katona S, Greenberg R, Suzuki S. Pattern electrical stimulation of the human retina. *Vision Res*. 1999; 39:2569–2576. [PubMed: 10396625]
31. Humayun MS, Prince M, de Juan E Jr, Barron Y, Moskowitz M, Klock IB, Milam AH. Morphometric analysis of the extramacular retina from postmortem eyes with retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 1999; 40:143–148. [PubMed: 9888437]
32. Javaheri M, Hahn DS, Lakhapal RR, Weiland JD, Humayun MS. Retinal prostheses for the blind. *Ann Acad Med Singapore*. 2006; 35:137–144. [PubMed: 16625261]
33. Jensen RJ, Rizzo JF 3rd. Thresholds for activation of rabbit retinal ganglion cells with a subretinal electrode. *Exp Eye Res*. 2006; 83:367–373. [PubMed: 16616739]
34. Ji Y, Pang PT, Feng L, Lu B. Cyclic AMP controls BDNF-induced TrkB phosphorylation and dendritic spine formation in mature hippocampal neurons. *Nat Neurosci*. 2005; 8:164–172. [PubMed: 15665879]
35. Kiermayer S, Biondi RM, Imig J, Plotz G, Haupenthal J, Zeuzem S, Piiper A. Epac activation converts cAMP from a proliferative into a differentiation signal in PC12 cells. *Mol Biol Cell*. 2005; 16:5639–5648. [PubMed: 16207818]

36. Leake PA, Hradek GT, Snyder RL. Chronic electrical stimulation by a cochlear implant promotes survival of spiral ganglion neurons after neonatal deafness. *J Comp Neurol.* 1999; 412:543–562. [PubMed: 10464355]
37. Lemke G. Glial control of neuronal development. *Annu Rev Neurosci.* 2001; 24:87–105. [PubMed: 11283306]
38. Lipton SA. Blockade of electrical activity promotes the death of mammalian retinal ganglion cells in culture. *Proc Natl Acad Sci U S A.* 1986; 83:9774–9778. [PubMed: 3025849]
39. Litvin TN, Kamenetsky M, Zarifyan A, Buck J, Levin LR. Kinetic properties of "soluble" adenylyl cyclase. Synergism between calcium and bicarbonate. *J Biol Chem.* 2003; 278:15922–15926. [PubMed: 12609998]
40. Liu Y, Teige I, Birnir B, Issazadeh-Navikas S. Neuron-mediated generation of regulatory T cells from encephalitogenic T cells suppresses EAE. *Nat Med.* 2006; 12:518–525. [PubMed: 16633347]
41. Mao Z, Bonni A, Xia F, Nadal-Vicens M, Greenberg ME. Neuronal activity-dependent cell survival mediated by transcription factor MEF2. *Science.* 1999; 286:785–790. [PubMed: 10531066]
42. Meyer-Franke A, Kaplan MR, Pfrieger FW, Barres BA. Characterization of the signaling interactions that promote the survival and growth of developing retinal ganglion cells in culture. *Neuron.* 1995; 15:805–819. [PubMed: 7576630]
43. Meyer-Franke A, Wilkinson GA, Kruttgen A, Hu M, Munro E, Hanson MG Jr, Reichardt LF, Barres BA. Depolarization and cAMP elevation rapidly recruit TrkB to the plasma membrane of CNS neurons. *Neuron.* 1998; 21:681–693. [PubMed: 9808456]
44. Miyake K, Yoshida M, Inoue Y, Hata Y. Neuroprotective effect of transcorneal electrical stimulation on the acute phase of optic nerve injury. *Invest Ophthalmol Vis Sci.* 2007; 48:2356–2361. [PubMed: 17460302]
45. Morimoto T, Fukui T, Matsushita K, Okawa Y, Shimojyo H, Kusaka S, Tano Y, Fujikado T. Evaluation of residual retinal function by pupillary constrictions and phosphenes using transcorneal electrical stimulation in patients with retinal degeneration. *Graefes Arch Clin Exp Ophthalmol.* 2006; 244:1283–1292. [PubMed: 16550408]
46. Morimoto T, Miyoshi T, Matsuda S, Tano Y, Fujikado T, Fukuda Y. Transcorneal electrical stimulation rescues axotomized retinal ganglion cells by activating endogenous retinal IGF-1 system. *Invest Ophthalmol Vis Sci.* 2005; 46:2147–2155. [PubMed: 15914636]
47. Murray AJ, Shewan DA. Epac mediates cyclic AMP-dependent axon growth, guidance and regeneration. *Mol Cell Neurosci.* 2008; 38:578–588. [PubMed: 18583150]
48. Nakauchi K, Fujikado T, Kanda H, Kusaka S, Ozawa M, Sakaguchi H, Ikuno Y, Kamei M, Tano Y. Threshold suprachoroidal-transretinal stimulation current resulting in retinal damage in rabbits. *J Neural Eng.* 2007; 4:S50–57. [PubMed: 17325416]
49. Nicol X, Bennis M, Ishikawa Y, Chan GC, Reperant J, Storm DR, Gaspar P. Role of the calcium modulated cyclases in the development of the retinal projections. *Eur J Neurosci.* 2006; 24:3401–3414. [PubMed: 17229090]
50. Pardue MT, Phillips MJ, Yin H, Sippy BD, Webb-Wood S, Chow AY, Ball SL. Neuroprotective effect of subretinal implants in the RCS rat. *Invest Ophthalmol Vis Sci.* 2005; 46:674–682. [PubMed: 15671299]
51. Pinto C, Papa D, Hubner M, Mou TC, Lushington GH, Seifert R. Activation and inhibition of adenylyl cyclase isoforms by forskolin analogs. *J Pharmacol Exp Ther.* 2008; 325:27–36. [PubMed: 18184830]
52. Popovic DB, Popovic MB. Advances in the use of electrical stimulation for the recovery of motor function. *Prog Brain Res.* 194:215–225. [PubMed: 21867806]
53. Pozzo-Miller L. BDNF enhances dendritic Ca²⁺ signals evoked by coincident EPSPs and back-propagating action potentials in CA1 pyramidal neurons. *Brain Res.* 2006; 1104:45–54. [PubMed: 16797499]
54. Santos A, Humayun MS, de Juan E Jr, Greenburg RJ, Marsh MJ, Klock IB, Milam AH. Preservation of the inner retina in retinitis pigmentosa. A morphometric analysis. *Arch Ophthalmol.* 1997; 115:511–515. [PubMed: 9109761]

55. Sato T, Fujikado T, Lee TS, Tano Y. Direct effect of electrical stimulation on induction of brain-derived neurotrophic factor from cultured retinal Muller cells. *Invest Ophthalmol Vis Sci*. 2008; 49:4641–4646. [PubMed: 18539944]
56. Sato T, Fujikado T, Morimoto T, Matsushita K, Harada T, Tano Y. Effect of electrical stimulation on IGF-1 transcription by L-type calcium channels in cultured retinal Muller cells. *Jpn J Ophthalmol*. 2008; 52:217–223. [PubMed: 18661273]
57. Schlicker C, Rauch A, Hess KC, Kachholz B, Levin LR, Buck J, Steegborn C. Structure-based development of novel adenylyl cyclase inhibitors. *J Med Chem*. 2008; 51:4456–4464. [PubMed: 18630896]
58. Schmid H, Herrmann T, Kohler K, Stett A. Neuroprotective effect of transretinal electrical stimulation on neurons in the inner nuclear layer of the degenerated retina. *Brain Res Bull*. 2009; 79:15–25. [PubMed: 19150490]
59. Shannon RV. Advances in auditory prostheses. *Curr Opin Neurol*.
60. Siu TL, Morley JW. In vivo evaluation of an episcleral multielectrode array for stimulation of the retina with reduced retinal ganglion cell mass. *J Clin Neurosci*. 2008; 15:552–558. [PubMed: 18342512]
61. Soto I, Rosenthal JJ, Blagburn JM, Blanco RE. Fibroblast growth factor 2 applied to the optic nerve after axotomy up-regulates BDNF and TrkB in ganglion cells by activating the ERK and PKA signaling pathways. *J Neurochem*. 2006; 96:82–96. [PubMed: 16269011]
62. Weiland JD, Cho AK, Humayun MS. Retinal prostheses: current clinical results and future needs. *Ophthalmology*. 118:2227–2237. [PubMed: 22047893]
63. Xiang G, Pan L, Xing W, Zhang L, Huang L, Yu J, Zhang R, Wu J, Cheng J, Zhou Y. Identification of activity-dependent gene expression profiles reveals specific subsets of genes induced by different routes of Ca(2+) entry in cultured rat cortical neurons. *J Cell Physiol*. 2007; 212:126–136. [PubMed: 17443680]
64. Zrenner E. Initial success in retinitis pigmentosa patients. Retinal chip brings hope to the blind (interview by Dr. med. Thomas Meissner). *MMW Fortschr Med*. 2007; 149:16. [PubMed: 17672001]
65. Zrenner, E. Visual sensations mediated by subretinal microelectrode arrays implanted into blind retinitis pigmentosa patients. Proceedings of the 13th annual conference of the IFESS; Freiburg, Germany. 2008.

Highlights

- Neural prostheses code information in electrical impulses
- Electrical activity also promotes neuronal survival and regeneration
- Our understanding of mechanisms activity-induced survival and growth is increasing
- Use of electrical activity as a therapeutic is moving into human trials