Current Trends in Endocrinology
Vol. 6, 2012

Review

Friedreich's ataxia: Disease progression and the case for estrogen therapy

Timothy E. Richardson and James W. Simpkins*

Institute for Aging and Alzheimer's Disease Research, Department of Pharmacology and Neuroscience
University of North Texas Health Science Center, 3500 Camp Bowie Blvd, Fort Worth, TX 76107, USA

ABSTRACT

First described in 1863, Friedreich's Ataxia (FRDA) is a progressive hereditary neurodegenerative disorder inherited in an autosomal recessive manner. Caused by a trinucleotide repeat expansion effectively preventing the production of frataxin protein, this disease is characterized by progressive mitochondrial damage, resulting in cell death in organ systems most dependent on the mitochondria for energy production, principally the nervous system and heart. While the exact role of frataxin is currently still unknown, its absence results in the depression of electron transport chain respiration, impairment of function of iron-sulfur containing proteins and impairment of the intrinsic intracellular antioxidant systems. Herein, we review the cellular events that initiate widespread organ dysfunction and discuss ongoing research in therapeutics aimed at inhibiting this damage and halting or slowing the progression of FRDA, including those on estrogen treatment from our laboratory.

KEYWORDS: Friedreich's ataxia, neuro-degeneration, antioxidant, estrogen, mitochondria

*Corresponding author
james.simpkins@unthsc.edu
Supported in part by NIH Grants P01 AG100485, P01 AG22550, and P01 AG027956 and NIA Grant T32 AG020494.

OUTLINE

1. INTRODUCTION

First described in a series of papers by Nikolaus Friedreich [1, 2, 3, 4, 5], Friedreich's ataxia (FRDA) affects 1 in 50,000 to 1 in 20,000 worldwide with a carrier rate of 1 in 120 to 1 in 60, making it the most common type of inherited ataxia worldwide [6, 7, 8, 9, 10, 11]. Although FRDA can be diagnosed with genetic tests before birth [12, 13, 14], FRDA usually presents clinically around puberty, although the onset can vary from infancy to the third decade of life [15, 16]. The presenting symptoms are usually related to gait and other motor symptoms, leading to progressive ataxia [8, 15, 17]. There is a degeneration of the dorsal root ganglia (DRG), followed by cranial nerve and ascending spinal cord tracts, including the spinocerebellar and corticospinal tracts and posterior columns, resulting in hearing and ocular abnormalities, tremor, ataxia, weakness and sensory abnormalities [8, 16, 18, 19]. Later, extra-neurological symptoms are common, including pes cavitis, lateral and kyphoscoliosis and an increased incidence of type 1 diabetes [8, 15, 17, 18, 19].

There is also a 66-91% incidence of cardiac symptoms, including hypertrophic cardiomyopathy with interstitial fibrosis, the most common cause of premature death in FRDA patients [8, 15, 18, 19, 20, 21].

2. Disease mechanism

FRDA is caused by a progressive GAA trinucleotide repeat expansion in the first intron of the FXN gene on chromosome 9q13-21, responsible for producing the frataxin [22, 23], causing a self-associating complex of triple helical DNA to form and inducing histone deacetylation during DNA transcription [24, 25, 26, 27, 28], preventing effective transcription and resulting in a loss of intracellular frataxin [6, 7, 8, 16, 29]. The exact function of frataxin is currently unclear, although it has been suggested that it is required for iron-sulfur (Fe-S) cluster assembly [30, 31, 32]. Its absence results in dysfunctional iron metabolism, with impaired function of Fe-S cluster proteins, including heme, electron transport chain (ETC) proteins and the Kreb's cycle protein, aconitase, as well as dysregulation of the cellular redox state [16, 33, 34], ultimately leading to widespread progressive oxidative damage to many components of the cell, specifically the mitochondria [35]. The inhibition of Fe-S containing protein function severely impairs cellular respiration [6, 36, 37], which is further complicated by simultaneous oxidative damage to these same mitochondrial proteins [18, 34, 36, 38]. This mitochondrial damage prevents the cell from being able to produce enough ATP to match its energetic needs, resulting in cell death [39, 40, 41], a disease mechanism common to many neurological and neurodegenerative diseases, including ischemic stroke, Alzheimer's disease and Parkinson's disease [42, 43, 44, 45, 46, 47, 48].

The length of the GAA triplet repeats, specifically the shorter of the two GAA repeat alleles, is inversely proportional to the level of frataxin protein present in the cell and the age of disease onset, and is directly proportional to the severity of clinical symptoms [15, 21, 49]. Studies in yeast have shown that the depletion of frataxin homologues is related to oxidative damage and results in progressive accumulation of mitochondrial damage [35]. Cells and tissues most dependent on aerobic respiration and oxidative phosphorylation for ATP production are the first to succumb to the oxidative damage, including neurons in the brain and spinal cord, cardiomyocytes and pancreatic beta cells. It is still unclear why there is variable cell death and dysfunction within these tissues, including why certain spinal cord tracts are affected and others are not. It should also be noted that there is a phenotypic contribution to the disease process of cells in these organ systems that are dysfunctional but still viable [41].

3. Treatment strategies

3.1. Iron chelators

Since there is a wealth of evidence detailing dysregulation of iron in FRDA patients and cellular models, drugs that have the potential for iron chelation have been investigated for use in FRDA [16, 41]. The accumulation of intracellular iron, specifically around the mitochondria, increases the levels of ROS and inhibits electron transport chain complexes in the heart [50], further inhibiting mitochondrial energy production [6, 36, 37]. One such drug, deferoxamine, is able to chelate iron in cell culture, attenuating the reduction of activity of mitochondrial complexes; however aconitase and frataxin mRNA and protein levels are reduced [51], making it a poor choice for FRDA treatment. Iron chelators that specifically target the mitochondria [16, 52] such as deferiprone are currently being evaluated *in vitro* [53, 54] and in clinical trials [55]. Trials with this compound have yielded conflicting results, with some studies showing that deferiprone reduces ROS-induced damage and protects the mitochondria [54], while others have suggested that it inhibited aconitase activity [53]. Clinical trials have shown that deferiprone reduces iron buildup in certain brain regions with possibly improved neurological function [55]. Compounds with phenol rings in their structure have long been known to act as iron chelators [56], and this property may prove to be partially responsible for their efficacy in protecting cell viability in FRDA fibroblast cultures [57, 58].

3.2. Antioxidants and electron transport chain modulators

For over a decade, much of the work in FRDA treatment that has been done has involved the

prevention of oxidative mitochondrial damage and the maintenance of mitochondrial oxidative phosphorylation function [41]. Studies have shown that in addition to the intracellular mechanism of FRDA, patients with the disease demonstrate impaired manganese superoxide dismutase [59], and have generally increased levels of lipid peroxidation [60], general oxidative stress and DNA damage [11]. Idebenone, currently the first drug to reach Phase III clinical trials for FRDA, is a CoQ_{10} equivalent that acts by both decreasing intracellular reactive oxygen species and by acting as an electron shuttle between the damaged complex I and III in the ETC, promoting oxidative phosphorylation in the face of impaired mitochondrial complexes [50, 61]. This strategy allows the cells to continue aerobically producing high levels of ATP even with reduced ETC complex activity. Clinical studies have found that idebenone is able to decrease lipid peroxidation and other markers of oxidative stress in the heart and decrease the extent of hypertrophic cardiomyoptahy [11, 50] and one study showed a small improvement in ataxia [62], although there was only a very modest increase in lifespan associated with this treatment. It is possible that the limited success on nervous function was due to the initiation of treatment too late in the disease course to prevent neuron death or lower CNS penetration relative to cardiac levels. In early 2011, idebenone failed its phase III clinical trial on the basis that it did not sufficiently improve cardiac outcomes in FRDA patients as measured by cardiac output or left ventricular hypertrophy [63].

A recent study has focused on methylene blue (MB) as a potential therapy for FRDA. Methylene blue, a drug used over the past century for cyanide and carbon monoxide poisoning, ifosfamide neurotoxicity, methemoglobinemia and malaria, has much the same neuroprotective mechanism of action as idebenone: it acts as both an antioxidant and promotes oxidative phosphorylation, serving as an electron carrier shuttling electrons from NADH to cytochrome c in the presence of complex I/III damage [64]. Studies in fibroblasts have shown that MB is effective in attenuating ROS, increasing intracellular ATP concentrations, enhancing oxidative phosphorylation function, and preventing cell death in an FRDA fibroblast cell model [65]. Other antioxidants have also been effective in the FRDA fibroblast model. Jauslin *et al.* have demonstrated that antioxidants, specifically those targeted to the mitochondria, are able to prevent cell death in FRDA fibroblasts [39, 40], and that a novel compound with the active groups of idebenone and vitamin E, Fe-Aox29, is more potent than either idebenone or vitamin E alone or in combination [66].

Our lab has focused on the antioxidant potential of phenolic estrogens in treating the ROS-mediated component of FRDA. We have shown that in FRDA fibroblasts, independent of any known estrogen receptor, estrogen and estrogen-like compounds, including several non-feminizing estrogens, are able to attenuate ROS and prevent cell death [57] through a phenol-quinol cycling antioxidant mechanism [67, 68]. The potency and efficacy of these compounds depended on having at least one phenol ring in the molecular structure, with potency being correlated to the number of phenol rings [57, 69, 70]. In addition, the EC_{50} values for this set of compounds were in the low nanomolar range [57], significantly lower than idebenone, vitamin E or tailor-made antioxidants such as Fe-Aox29 [66]. Further studies have shown that these phenol ring containing estrogens are able to prevent lipid peroxidation, maintain aconitase activity, mitochondrial function and ATP production in FRDA fibroblasts (Fig. 1) [58].

Newly developed non-feminizing estrogens are particularly good candidates for neuroprotection as they are ideally suited to penetrate the blood brain barrier and insert into lipid membranes preventing the sequence of oxidation to intracellular molecules and organelles [71, 72, 73, 74, 75, 76, 77, 78], without estrogen receptor binding ability or feminizing effects *in vivo* [77, 79]. Since FRDA can be detected genetically before birth in the offspring of known carriers [12, 13, 14], there is a window of opportunity for treatment before symptoms begin. During this time frame, beginning therapy with antioxidant molecules could potentially be very beneficial for preventing or delaying the disease process, rather than attempting to improve or suppress symptoms and recover from the neuronal damage and death later in life.

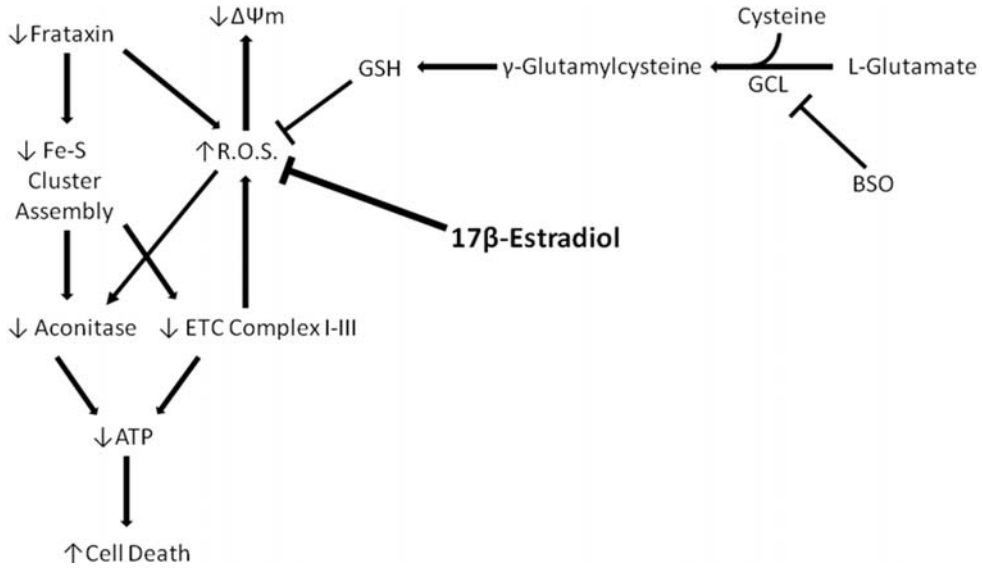

Fig. 1. Proposed mechanism of 17β-Estradiol in BSO-treated FRDA fibroblasts.

3.3. Frataxin level modifiers

Another strategy in treating FRDA has been to correct the frataxin deficiency underlying the molecular disorder of FRDA. The disorder is caused by the lack of frataxin, caused by the GAA trinucleotide repeat section in the first intron of the gene on chromosome 9q13-21 [22, 23], resulting in a self-associating complex of triple helical DNA to form preventing effective DNA transcription [6, 7, 8, 16, 24, 26, 27, 28, 29]. This strategy is particularly appealing since murine models indicate that a compound may only have to increase intracellular frataxin concentration to ~25% of normal levels to prevent cellular abnormalities and neuropathological findings [80]. Several compounds have been tested to increase frataxin levels. Histone deacetylase inhibitors such as BML-210 have been found to increase frataxin levels in FRDA carriers and mice [81, 82]. Recombinant erythropoietin (EPO) has also been found to significantly increase frataxin protein levels in FRDA fibroblasts [83], although no increase in mRNA levels was observed indicating that this effect is due primarily to post-transcriptional effects [84]. In our lab, estradiol was not observed to increase the levels of frataxin protein in the FRDA fibroblast cell model [Richardson and Simpkins, unpublished observations], although the estrogen effect in these cells is ER-independent. In neural or cardiac tissue containing ERα or ERβ, there is a possibility that in addition to the observed antioxidant effects of estrogen [57], there may also be ER-dependent effects, including a transcriptional effect involving the production of extra frataxin or other protective proteins.

4. CONCLUSIONS

FRDA is a mitochondrial disease that affects tissues that are most dependent on aerobic respiration, principally the CNS and heart [15, 18, 20]. The root cause of the disease is the absence of functional frataxin, resulting in iron dysregulation and oxidative damage to lipids and proteins, ultimately disrupting mitochondrial function [10, 35, 59], similar to other neurodegenerative disorders such as Alzheimer's and Parkinson's diseases [42, 43, 44, 45, 46, 47, 48]. Antioxidant and mitochondrial treatment of FRDA has been met with modest success, with idebenone decreasing cardiac complications and slightly prolonging life [50, 62, 85]. Since FRDA can be diagnosed before birth [12, 13, 14], drugs designed to penetrate the blood brain barrier, increase frataxin levels, attenuate ROS or support oxidative phosphorylation could be applied in this brief symptom-free time window to prevent or delay the devastating effects of FRDA and neuronal death, rather than try to control symptoms or reverse the disease process at a later date.

REFERENCES

1. Friedreich, N. 1863, Arch. Pathol. Anat. Phys. Klin. Med., 26, 391-419.
2. Friedreich, N. 1863, Arch. Pathol. Anat. Phys. Klin. Med., 26, 433-459.
3. Friedreich, N. 1963, Arch. Pathol. Anat. Phys. Klin. Med., 27, 1-26.
4. Friedreich, N. 1876, Virchow's Arch. Pathol. Anat., 68, 145-245.
5. Friedreich, N. 1877, Virchow's Arch. Pathol. Anat., 70, 140-142.
6. Bradley, J. L., Blake, J. C., Chamberlain, S., Thomas, P. K., Cooper, J. M., and Schapira, A. H. 2000, Hum. Mol. Genet., 9, 275-282.
7. Campuzano, V., Montermini, L., Moltò, M. D., Pianese, L., Cossee, M., Cavalcanti, F., Monros, E., Rodius, F., Duclos, F., Monticelli, A., Zara, F., Cañizares, J., Koutnikova, H., Bidichandani, S. I., Gellera, C., Brice, A., Patel, P. I., Di Donato, S., Mandel, J. L., Cocozza, S., Koenig, M., and Pandolfo, M. 1996, Science, 271, 1423-1427.
8. Harding, A. E. 1983, Lancet, 1, 1151-1155.
9. Leone, M., Brignolio, F., Rosso, M. G., Curtoni, E. S., Moroni, A., Tribolo, A., and Schiffer, D. 1990, Clin. Genet., 38, 161-169.
10. Pandolfo, M. 1998, Neuromucul. Disord., 8, 409-415.
11. Schulz, J. B., Boesch, S., Bürk, K., Dürr, A., Giunti, P., Mariotti, C., Pousset, F., Schöls, L., Vankan, P., and Pandolfo, M. 2009, Nat. Rev. Neurol., 5, 222-234.
12. Monros, E., Smeyers, P., Ramos, M. A., Prieto, F., and Paulo, F. 1995, Prenat. Diagn., 15, 551-554.
13. Pandolfo, M. and Montermini, L. 1998, Prenat. Diagn., 18, 831-833.
14. Wallis, J., Shaw, J., Wilkes, D., Farrall, M., Williamson, R., Chamberlain, S., Skare, J. C., and Milunsky, A. 1989, Am. J. Med. Genet., 34, 458-461.
15. Dürr, A., Cossee, M., Agid, Y., Campuzano, V., Mignard, C., Penet, C., Mandel, J. L., Brice, A., and Koenig, M. 1996, N. Engl. J. Med., 335, 1169-1175.
16. Lodi, A., Tonon, C., Calabrese, V., and Schapira, A. H. V. 2006, Antiox. Redox Signal., 8, 438-443.
17. Harding, A. E. 1981, Brain, 104, 589-620.
18. Al-Mahdawi, S., Pinto, R. M., Varshney, D., Lawrence, L., Lowrie, M. B., Hughes, S., Webster, Z., Blake, J., Cooper, J. M., King, R., and Pook, M. A. 2006, Genomics, 88, 580-90.
19. Geoffroy, G., Barbeau, A., Breton, G., Lemieux, B., Aube, M., Leger, C., and Bouchard, J. P. 1976, Can. J. Neurol. Sci., 3, 279-286.
20. Dutka, D. P., Donnelly, J. E., Palka, P., Lange, A., Nuñez, D. J., and Nihoyannopoulous, P. 2000, Circulation, 102, 1276-1282.
21. Isnard, R., Kalotka, H., Dürr, A., Cossèe, M., Schmitt, M., Pousset, F., Thomas, D., Brice, A., Koenig, M., and Komajda, M. 1997, Circulation, 95, 2247-9.
22. Fujita, R., Agid, Y., Trouillas, P., Seck, A., Tommasi-Davenas, C., Driesel, A. J., Olek, K., Grzeschik, K. H., Nakamura, Y., Mandel, J. L., and Hanauer, A. 1989, Genomics, 4, 110-111.
23. Hanauer, A., Chery, M., Fujita, R., Driesel, A. J., Gilgenkrantz, S., and Mandel, J. L. 1990, Am. J. Hum. Genet., 46, 133-137.
24. Grabczyk, E. and Usdin, K. 2000, Nucl. Acids Res., 28, 2815-2822.
25. Heidenfelder, B. L., Makhov, A. M., and Topal, M. D. 2003, J. Biol. Chem., 278, 2425-2431.
26. Sakamoto, N., Chastain, P. D., Parniewski, P., Ohshima, K., Pandolfo, M., Griffith, J. D., and Wells, R. D. 1999, Mol. Cell., 3, 465-475.
27. Sakamoto, N., Ohshima, K., Montermini, L., Pandolfo, M., and Wells, R. D. 2001, J. Biol. Chem., 276, 27171-27177.
28. Wells, R. D. 2008, FASEB J., 22, 1625-1634.
29. Montermini, L., Andermann, E., Labuda, M., Richter, A., Pandolfo, M., Cavalcanti, F., Pianese, L., Iodice, L., Farina, G., Monticelli, A., Turano, M., Filla, A., De Michele, G., and Cocozza, S. 1997, Hum. Mol. Genet., 6, 1261-6.
30. Adinolfi, S., Iannuzzi, C., Prischi, F., Pastore, C., Iametti, S., Martin, S. R., Bonomi, F., and Pastore, A. 2009, Nat. Struct. Mol. Biol., 16, 390-396.
31. Prischi, F., Konarey, P. V., Iannuzzi, C., Pastore, C., Adinolfi, S., Martin, S. R., Svergun, D. I., and Pastore, A. 2010, Nat. Commun., 1, 95.

32. Tsai, C. L. and Barondeau, D. P. 2010 Biochemistry, 49, 9132-9139.
33. Delatycki, M. B., Williamson, R., and Forrest, S. M. 2000, J. Med. Genet., 37, 1-8.
34. Gakh, O., Park, S., Liu, G., Macomber, L., Imlay, J. A., Ferreira, G. C., and Isaya, G. 2006, Hum. Mol. Genet., 15, 467-479.
35. Karthikeyan, G., Santos, J. H., Graziewicz, M. A., Copeland, W. C., Isaya, G., Van Houten, B., and Resnick, M. A. 2003, Hum. Mol. Genet., 12, 3331-3342.
36. Bulteau, A. L., O'Neill, H. A., Kennedy, M. C., Ikeda-Saito, M., Isaya, G., and Szweda, L. I. 2004, Science, 305, 242-245.
37. Rötig, A., De Lonlay, P., Chretien, D., Foury, F., Koenig, M., Sidi, D., Munnich, A., and Rustin, P. 1997, Nat. Genet., 17, 215-217.
38. Chantrel-Groussard, K., Geromel, V., Puccio, H., Koenig, M., Munnich, A., Rotig, A., and Rustin, P. 2001, Hum. Mol. Genet., 10, 2061-2067.
39. Jauslin, M. L., Wirth, T., Meier, T., and Shoumacher, F. 2002, Hum. Mol. Genet., 11, 3055-3063.
40. Jauslin, M. L., Meier, T., Smith, R. A., and Murphy, M. P. 2003, FASEB J., 17, 1972-1974.
41. Santos, R., Lefevre, S., Silwa, D., Seguin, A., Camadro, J. M., and Lesuisse, E. 2010, Antiox. Redox Signal., 13, 651-690.
42. Beal, M. F. 2000, Trends. Neurosci., 23, 298-304.
43. Gibson, G. E., Sheu, K. F., and Blass, J. P. 1998, J. Neural Transm., 105, 855-70.
44. Lenaz, G., Baracca, A., Fato, R., Genova, M. L., and Solaini, G. 2006, Ital. J. Biochem., 55, 232-53.
45. Lenaz, G., Baracca, A., Barbero, G., Bergamini, C., Dalmonte, M. E., Del Sole, M., Faccioli, M., Falasca, A., Fato, R., Genova, M. L., Sgarbi, G., and Solaini, G. 2010, Biochim. Biophys. Acta., 1797, 633-640.
46. Mizuno, Y., Ohta, S., Tanaka, M., Takamiva, S., Suzuki, K., Sato, T., Oya, H., Ozawa, T., and Kagawa, Y. 1989, Biochem. Biophys. Res. Commun., 163, 1450-5.
47. Parker, W. D. Jr., Boyson, S. J., and Parks, J. K. 1989, Ann. Neurol., 26, 719-23.
48. Simpkins, J. W. and Dykens, J. A. 2008, Brain. Res. Rev., 57, 421-430.
49. Campuzano, V., Montermini, L., Lutz, Y., Cova, L., Hindelang, C., Jiralerspong, S., Trottier, Y., Kish, S. J., Faucheux, B., Trouillas, P., Authier, F. J., Dürr, A., Mandel, J. L., Vescovi, A., Pandolfo, M., and Koenig, M. 1997, Hum. Mol. Genet., 6, 1771-1780.
50. Rustin, P., von Kleist-Retzow, J. C., Chantrel-Groussard, K., Sidi, D., Munnich, A., and Rotic, A. 1999, Lancet, 354, 477-479.
51. Li, K., Besse, E. K., Ha, D., Kovtunovych, G., and Rouault, T. A. 2008, Hum. Mol. Genet., 17, 2265-2273.
52. Richardson, D. R. 2003, Expert Opin. Invest. Drugs, 12, 235-245.
53. Goncalves, S., Paupe, V., Dassa, E. P., and Rustin, P. 2008, BMC Neurol., 8, 20.
54. Kakhlon, O., Manning, H., Breuer, W., Melamed-Book, N., Lu, C., Cortopassi, G., Munnich, A., and Cabantchik, Z. I. 2008, Blood, 112, 5219-5227.
55. Boddaert, N., Le Quan Sang, K. H., Rötig, A., Leroy-Willig, A., Gallet, S., Brunelle, F., Sidi, D., Thalabard, J. C., Munnich, A., and Cabantchik, Z. I. 2007, Blood, 110, 521-524.
56. Moeller, T. and Shellman, R. W. 1953, Science, 118, 327-328.
57. Richardson, T. E., Yang, S. H., Wen, Y., and Simpkins, J. W. 2011, Endocrinology, 152, 2742-2749.
58. Richardson, T. E., Yu, A. E., Wen, Y., Yang, S. H., and Simpkins, J. W. 2012, PLoS One, 7, e36400.
59. Pandolfo, M. 2002, Mitochondrion, 2, 87-93.
60. Emond, M., Lepage, G., Vanasse, M., and Pandolfo, M. 2000, Neurology, 55, 1752-1753.
61. Meier, T. and Buyse, G. 2009, J. Neurol., 256, 25-30.
62. Di Prospero, N. A., Baker, A., Jeffries, N., and Fishbeck, K. H. 2007, Lancet Neurol., 6, 878-886.
63. Lagedrost, S. J., Sutton, M. S., Cohen, M. S., Satou, G. M., Kaufman, B. D., Perlman, S. L., Rummey, C., Meier, T., and Lynch, D. R. 2011, Am. Heart J., 161, 639-645.
64. Wen, Y., Li, W., Poteet, E. C., Xie, L., Tan, C., Yan, L. J., Ju, X., Liu, R., Qian, H., Marvin, M. A., Goldberg, M. S., She, H., Mao, Z., Simpkins, J. W., and Yang, S. H. 2011, J. Biol. Chem., 286, 16504-16515.

65. Yu, A. E., Poteet, E., Ryou, M. G., Li, W., Wen, Y., Simpkins, J. W., and Yang, S. H. 2011, Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience, Program No. 361.23, Online.
66. Jauslin, M. L., Vertuani, S., Durini, E., Buzzoni, L., Ciliberti, N., Verdecchia, S., Palozza, P., Meier. T., and Manfredini, S. 2007, Mol. Cell. Biochem., 302, 79-85.
67. Prokai, L., Prokai-Tatrai, K., Perjesi, P., Zharikova, A. D., Perez, E. J., Liu, R., and Simpkins, J. W. 2003, Proc. Natl. Acad. Sci. USA, 100, 11741-11746.
68. Prokai-Tatrai, K., Perjesi, P., Rivera-Portalatin, N. M., Simpkins, J. W., and Prokai, L. 2008, Steroids, 73, 280-288.
69. Behl, C., Skutella, T., Lezoualc'h, F., Post, A., Widmann, M., Newton, C. J., and Holsboer, F. 1997, Mol. Pharmacol., 51, 535-541.
70. Moosmann, B. and Behl, C. 1999, Proc. Natl. Acad. Sci. USA, 96, 8867-8872.
71. Behl, C. 2002, Nat. Rev. Neurosci., 3, 433-442.
72. Behl, C. and Manthey, D. 2000, J. Neurocytol., 29, 351-358.
73. Behl, C. and Moosmann, B. 2002, Free Radic. Biol. Med., 33, 182-191.
74. Behl, C., Widmann, M., Trapp, T., and Holsboer, F. 1995, Biochem. Biophys. Res. Commun., 216, 473-482.
75. Rupprecht, R. and Holsboer, F. 1999, Trends Neurosci., 22, 410-416.
76. Simpkins, J. W., Yi, K. D., Yang, S. H., and Dykens, J. A. 2010, Biochim. Biophys. Acta., 1800, 1113-1120.
77. Simpkins, J. W., Yang, S. H., Sarkar, S. N., and Pearce, V. 2008, Mol. Cell Endocrinol., 290, 51-59.
78. Walf, A. A., Paris, J. J., Rhodes, M. E., Simpkins, J. W., and Frye, C. A. 2011, Brain Res., 1379, 119-136.
79. Yi, K. D., Perez, E., Yang, S., Liu, R., Covey, D. F., and Simpkins, J. W. 2011, Brain Res., 1379, 61-70.
80. Miranda, C. J., Santos, M. M., Ohshima, K., Smith, J., Li, L., Bunting, M., Cossée, M., Koenig, M., Sequeiros, J., Kaplan, J., and Pandolfo, M. 2002, FEBS Lett., 512, 291-297.
81. Herman, D., Jenssen, K., Burnett, R., Soragni, E., Perlman, S. L., and Gottesfeld, J. M. 2006, Nat. Chem. Biol., 2, 551-558.
82. Rai, M., Soragni, E., Jenssen, K., Burnett, R., Herman, D., Coppola, G., Geschwind, D. H., Gottesfeld, J. M., and Pandolfo, M. 2008, PLoS One, 3, e1958.
83. Sturm, B., Stupphann, D., Kaun, C., Boesch, S., Schranzhofer, M., Wojta, J., Goldenberg, H., and Scheiber-Mojdehkar, B. 2005, Eur. J. Clin. Invest., 35, 711-717.
84. Acquaviva, F., Castaldo, I., Filla, A., Giacchetti, M., Marmolino, D., Monticelli, A., Pinelli, M., Saccà, F., and Cocozza, S. 2008, Cerebellum, 7, 360-365.
85. Schulz, J. B., Dehmer, T., Schöls, L., Mende, H., Hardt, C., Vorgerd, M., Bürk, K., Matson, W., Dichgans, J., Beal, M. F., and Bogdanov, M. B. 2000, Neurology, 55, 1719-1721.