Supplemental Materials

Pharmacological Inhibitors

BQ-123 has been shown to be a selective ET_A receptor antagonist (Sakamoto *et al*, 1993) with an IC_{50} value of 0.4 μM (Maurice *et al*, 1997). A concentration of 1 μM of BQ-123 was shown to prevent the response to ET-1 in cerebral arteries and therefore we used this concentration in the present study (Lee *et al*, 2007).

BQ-788 has been shown to be a selective ET_B receptor antagonist (Ishikawa *et al*, 1994) with an EC_{50} value of 21±6 nM in cultured melanocytes (Sharif and Crider, 2011). In a previous study, 1 μM of BQ-788 was shown in the cerebrovasculature to inhibit ET_B receptor activation (Zuccarello *et al*, 1998), and therefore we used this dose in the present study.

Apocynin has been described as a potent NAD(P)H oxidase inhibitor (Van den Worm, 1996) with an EC_{50} value of 61.33 μM (Kalyanaraman *et al*, 2010). Because 100 μM of apocynin was shown to inhibit superoxide production in cerebral arteries (Mayhan *et al*, 2009), we used this concentration in the present study.

FeTMPyP has been shown to be an efficacious peroxynitrite decomposition catalyst with an EC_{50} value of 3.5 μM (Salvemini *et al*, 1998). In addition, according to the manufacture's catalog (Calbiochem), FeTMPyP can also catalytically decompose superoxide radicals. We used FeTMPyP at a concentration of 10 μM in vitro and a dose of 10 mg/kg in vivo as these concentrations have been previously shown to be efficacious under these conditions, respectively (Imam *et al*, 1999; Salvemini *et al*, 1998).

References

Imam SZ, Crow JP, Newport GD, Islam F, Slikker W, Jr., Ali SF (1999) Methamphetamine generates peroxynitrite and produces dopaminergic neurotoxicity in mice: protective effects of peroxynitrite decomposition catalyst. *Brain Res* 837:15-21

Kalyanaraman B, Joseph J, Kanthasamy A (2010) Neuroprotective compounds and their use. International Patent Application No. PCT/US2010/031296

Ishikawa K, Ihara M, Noguchi K, Mase T, Mino N, Saeki T, Fukuroda T, Fukami T, Ozaki S, Nagase T, et al. (1994) Biochemical and pharmacological profile of a potent and selective endothelin B-receptor antagonist, BQ-788. *Proc Natl Acad Sci U S A* 91:4892-6

Lee HA, Baek EB, Park KS, Jung HJ, Kim JI, Kim SJ, Earm YE (2007) Mechanosensitive nonselective cation channel facilitation by endothelin-1 is regulated by protein kinase C in arterial myocytes. *Cardiovasc Res* 76:224-35

Maurice MC, Gratton JP, D'Orleans-Juste P (1997) Pharmacology of two novel mixed ETA/ETB receptor antagonists, BQ-928 and 238, in the carotid and pulmonary arteries and the perfused kidney of the rabbit. *Br J Pharmacol* 120:319-25

Mayhan WG, Arrick DM, Sharpe GM, Sun H (2009) Nitric oxide synthase-dependent responses of the basilar artery during acute infusion of nicotine. *Nicotine Tob Res* 11:270-7

Sakamoto A, Yanagisawa M, Sawamura T, Enoki T, Ohtani T, Sakurai T, Nakao K, Toyo-oka T, Masaki T (1993) Distinct subdomains of human endothelin receptors determine their selectivity to endothelinA-selective antagonist and endothelinB-selective agonists. *J Biol Chem* 268:8547-53

Salvemini D, Wang ZQ, Stern MK, Currie MG, Misko TP (1998) Peroxynitrite decomposition catalysts: therapeutics for peroxynitrite-mediated pathology. *Proc Natl Acad Sci U S A* 95:2659-63

Sharif NA, Crider JY (2011) Intracellular signaling in human iridial fibroblasts and iridial melanocytes in response to prostaglandins, endothelin, isoproterenol, and other pharmacological agents. *Curr Eye Res* 36:310-20

Van den Worm E (1996) Investigation on apocynin, a potent NADPH oxidase inhibitor. Utrecht University. ISBN: 90-393-2702-5

Zuccarello M, Boccaletti R, Rapoport RM (1998) Endothelin ET(B1) receptor-mediated relaxation of rabbit basilar artery. *Eur J Pharmacol* 357:67-71