Scientific Publications for Steven Erat

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Alanna Watt, Mark van Rossum, Sacha Nelson, Gina Turrigiano

Activity Coregulates Quantal AMPA and NMDA Currents at Neocortical Synapses.
Neuron, Vol. 26, 659-670, June, 2000

> AMPA and NMDA are coexpressed at many central synapses, but the factors that control the ratio of these two receptors are not well understood. We recorded mixed miniature or evoked synaptic currents arising from coactivation of AMPA and NMDAP receptors and found that the long-lasting changes in activity scaled both currents up and down proportianally through changes in the number of postsynaptic receptors. The ratio of AMPA and NMDA current was similar at different synapses onto the same neuron, and this relationship was preserved following activity-dependent synaptic scaling. These data show that AMPA and NMDA receptors are tightly corregulated by activity at synapses at which they are both expressed and suggest that a mechanism exists to actively maintain a constant receptor ratio across a neuron's synapses. We thank Steven Erat for the preparation of cultures.

Rabin BM, Joseph JA, Erat S.

Effects of exposure to different types of radiation on behaviors mediated by peripheral or central systems.
Advances in Space Research 1998;22(2):217-25. PMID: 11541399 [PubMed - indexed for MEDLINE]

> The effects of exposure to ionizing radiation on behavior may result from effects on peripheral or on central systems. For behavioral endpoints that are mediated by peripheral systems (e.g., radiation-induced conditioned taste aversion or vomiting), the behavioral effects of exposure to heavy particles (56Fe, 600MeV/n) are qualitatively similar to the effects of exposure to gamma radiation (60Co) and to fission spectrum neutrons. For these endpoints, the only differences between the different types of radiation are in terms of relative behavioral effectiveness. For behavioral endpoints that are mediated by central systems (e.g., amphetamine-induced taste aversion learning), the effects of exposure to 56Fe particles are not seen following exposure to lower LET gamma rays or fission spectrum neutrons. These results indicate that the effects of exposure to heavy particles on behavioral endpoints cannot necessarily be extrapolated from studies using gamma rays, but require the use of heavy particles.

Joseph JA, Erat S, Rabin BM.

CNS effects of heavy particle irradiation in space: behavioral implications.
Adv Space Res. 1998;22(2):209-16. PMID: 11541398 [PubMed - indexed for MEDLINE]

Research from several sources indicates that young (3mo) rats exposed to heavy particle irradiation (56Fe irradiation) produces changes in motor behavior as well as alterations in neuronal transmission similar to those seen in aged (22-24 mo) rats. These changes are specific to neuronal systems that are affected by aging. Since 56Fe particles make up approximately 1-2% of cosmic rays, these findings suggest that the neuronal effects of heavy particle irradiation on long-term space flights may be significant, and may even supercede subsequent mutagenic effects in their mission capabilities. It is suggested that among other methods, it may be possible to utilize nutritional modification procedures to offset the putative deleterious effects of these particles in space.

Shukitt-Hale B, Erat SA, Joseph JA.

Spatial learning and memory deficits induced by dopamine administration with decreased glutathione.
Free Radic Biol Med. 1998 May;24(7-8):1149-58. PMID: 9626569 [PubMed - indexed for MEDLINE]

Administration of buthionine sulfoximine (BSO) selectively inhibits glutathione (GSH) biosynthesis and induces a GSH deficiency. Decreased GSH levels in the brain may result in less oxidative stress (OS) protection, because GSH contributes substantially to intracellular antioxidant defense. Under these conditions, administration of the pro-oxidant, dopamine (DA), which rapidly oxidizes to form reactive oxygen species, may increase OS. To test the cognitive behavioral consequences of decreased GSH, BSO (3.2 mg in 30 microliters, intracerebroventricularly) was administered to male Fischer 344 rats every other day for 4 days. In addition, DA (15microliters of 500 microM) was administered every day [either 1 h after BSO (BSO + DA group) or 1 h before BSO (DA + BSO group), when given on the same day as BSO] and spatial learning and memory assessed (Morris water maze, six trials/day). BSO + DA rats, but not DA + BSO rats, demonstrated cognitive impairment compared to a vehicle group, as evidenced by increased latencies to find the hidden platform, particularly on the first trial each day. Also, the BSO + DA group utilized non-spatial strategies during the probe trials (swim with no platform): i.e., less time spent in the platform quadrant, fewer crossings and longer latencies to the previous platform location, and more time spent in the platform quadrant, fewer crossings and longer latencies to the previous platform location, and more time spent around the edge of the pool rather than in the platform zone. Therefore, the cognitive behavioral consequences of decreasing GSH brain levels with BSO in conjunction with DA administration depends on the order of

administration. These findings are similar to those seen previously on rod and plank walking performance, as well as to those seen in aged rats, suggesting that the oxidation of DA coupled with a reduced capacity to respond to oxidative stress may be responsible for the induction of age-related cognitive deficits.

Denisova NA, Erat SA, Kelly JF, Roth GS.

Differential effect of aging on cholesterol modulation of carbachol-stimulated low-K(m) GTPase in striatal synaptosomes.
Exp Gerontol. 1998 May;33(3):249-65. PMID: 9615923 [PubMed - indexed for MEDLINE]

Previous research has suggested that age-related decline in physiological functions may be the result of substantial alterations in membrane molecular structure. The purpose of the present experiments was to elucidate the role of cholesterol domains in the age-related decline in receptor-G-protein interactions in striatal synaptosomes. We observed a significant age-related deficit in muscarinic cholinergic stimulated Low-Km GTPase activity and its age-related susceptibility to cholesterol treatment in range of 10(-10)-10(-5) M. Treatment of synaptosomes from old rats with cholesterol in range of 10(-8)-10(-6) M restored the Low-Km GTPase activity up to the level seen in young animals and reached a maximum at 10(-7) M. In synaptosomes from young rats, however, cholesterol treatment did not have any effect on striatal Low-Km GTPase activity. We observed significant alterations in the membrane lipid composition of striatal synaptosomes as a function of age. Our results suggested a significant interaction of age and cholesterol treatment on physical properties of striatal synaptosomes. Thus, the present results of experiments in vitro support our previous results of experiments in vivo and suggested an interaction of cholesterol domains with muscarinic-cholinergic receptor G-protein alpha subunit coupling/uncoupling through regulation of physical properties of striatal synaptosomes.

Joseph JA, Erat S, Denisova N, Villalobos-Molina R.

Receptor- and age-selective effects of dopamine oxidation on receptor-G protein interactions in the striatum.
Free Radic Biol Med. 1998 Mar 15;24(5):827-34. PMID: 9586813 [PubMed - indexed for MEDLINE]

The striatum contains a high concentration of oxidizable dopamine (DA), and the aged organism shows a decreased ability to respond to oxidative stress (OS), making this area extremely vulnerable to free radical insult. To determine the receptor specificity of this putative increase in OS sensitivity,

striatal slices from 6- and 24-month-old animals were incubated (30min, 37degrees C) in a modified Krebs medium containing 0 to 500 microM DA with or without a preincubation (15min) in a nitrone trapping agent, 1or 5 mM alpha-phenyl-n-tert-butyl nitrone (PBN), and changes in low Km GTPase activity (an index of receptor-G protein coupling/uncoupling) assessed in muscarinic, 5-HT1A D1, and D2 receptors stimulated with carbachol, 8OH-DPAT-HBr, SKF 38393, or quinelorane, respectively. DA exposure induced selective decreases in the stimulated activity in all of these receptor systems, and an overall increase in conjugated dienes (56%) of the young. In the case of carbachol and 8 OH-DPAT-HBr, the DA-induced deficits in GTPase stimulation were seen primarily in the young (61and 32%, respectively), while DA-induced deficits in quinelorane (D2) stimulation were seen in both age groups. In the case of SKF 38393-stimulation (D1) the DA-induced deficits were higher in the striatal tissue from the old. The DA-induced decreases in carbachol stimulated GTPase activity in the tissue from the young could be prevented by pretreatment with PBN or the DA uptake inhibitor, nomifensin. No effect of nomifensin was seen in the old, because their DA uptake mechanisms were already compromised. These results suggest that although age-related declines in DA uptake may provide some protection against the OS effects in muscarinic or 5-HT1A receptors, other factors may increase the vulnerability of DA neurons to OS, even with reductions in DA uptake.

Joseph JA, Villalobos-Molinas R, Denisova NA, Erat S, Strain J.

Cholesterol: a two-edged sword in brain aging.
Free Radic Biol Med. 1997;22(3):455-62. PMID: 8981037 [PubMed - indexed for MEDLINE]

Previous research from several laboratories has indicated that cholesterol (CHO) accumulates in neuronal membranes and alters their structural and signal transduction (ST) properties during aging. The possible reasons for these increases in membrane CHO have not been specified. However, present findings suggest that such accumulation may actually serve to protect neuronal tissue from oxidative damage. Striatal slices (6, 24month rats) were preincubated in 1 mM CHO (30min) followed by incubation with H2O2 (10microM, 30min). The slices were then either superfused with 30 mM KCl in the presence or absence of 500 microM oxotremorine (Ox), and K(+)-evoked dopamine release (K(+)-ERDA) examined or assessed for carbachol-stimulated low K(m) GTPase activity. The results indicated that CHO incubation prior to H2O2 in either age group was effective in preventing H2O2 reductions in both non-Ox-enhanced K(+)-ERDA and Ox conditions, as well as sodium nitroprusside (SNP 150 microM)-induced decreases in K(+)-ERDA. In addition, H2O2-induced deficits in carbachol-stimulated low K(m) GTPase activity were reduced in the striatal tissue from the old animals pretreated with CHO. However, if the slices were incubated in H2O2 prior to CHO exposure, CHO enhanced the H2O2

effects in the tissue from the old animals. Thus, depending upon the order of exposure, CHO functioned to enhance or retard the effects of oxidative stress, in an age-dependent manner.

Joseph JA, Villalobos-Molina R, Denisova N, Erat S, Jimenez N, Strain J.

Increased sensitivity to oxidative stress and the loss of muscarinic receptor responsiveness in senescence.
Ann N Y Acad Sci. 1996 Jun 15;786:112-9. Review. PMID: 8687012 [PubMed - indexed for MEDLINE]

Although there are numerous findings which suggest that the pathogenesis of age-related neurodegenerative disorders (e.g., AD and PD) may involve oxidative stress (OS), relationships between functional age-related neuronal deficits, especially those with behavioral correlates, and OS have been difficult to establish. We have attempted to establish such relationships by determining the role of OS in the loss of muscarinic receptor (mAChR) sensitivity in aging. These decrements are expressed as age-related reductions in oxotremorine enhancement of K(+)-evoked dopamine release (K(+)-ERDA) from superfused striatal slices. Using this model we have found that: a) The reductions can be restored with in vivo administration of the free-radical trapping agent, N-tert-butyl-alpha-phenylnitrone (PBN); b) Striatal slices from old animals showed increased sensitivity (e.g., reduced DA release or oxo-enhancement of K(+)-ERDA) to the in vitro application of sodium nitroprusside, a potent NO generator or to H2O2 which treatment of striatal slices from young animals with these agents or exposure of young animals to low doses of whole-body 56Fe irradiation decreased mAChR sensitivity and signal transduction (ST). Protection from the NO- or H2O2-induced deficits could be prevented with Trolox, PBN or cholesterol pretreatment. Evidence derived from PC-12 cells suggests that OS may directly affect ST by decreasing Ca2+ flux and increasing the length of the recovery period (i.e., return to baseline Ca2+ levels) after KCl (30mM) depolarization.

Joseph JA, Denisova N, Villalobos-Molina R, Erat S, Strain J.

Oxidative stress and age-related neuronal deficits.
Mol Chem Neuropathol. 1996 May-Aug;28(1-3):35-40. PMID: 8871939 [PubMed - indexed for MEDLINE]

Research from our laboratory has indicated that the loss of sensitivity that occurs in several receptor systems as a function of age may be an index of an increasing inability to respond to oxidative stress (OS). This loss occurs partially as a result of altered signal transduction (ST). Assessments have

involved determining the nature of age-related reductions in oxotremorine enhancement of K(+)-evoked dopamine release (K(+)-ERDA) from superfused striatal slices. Using this model, we have found that 1. Reductions can be restored with in vivo administration of the free-radical trapping agent, N-tert-butyl-alpha-phenylnitrone (PBN); 2. Decrements in DA release induced by NO or H2O2 from striatal slices from both young and old animals could be restored with alpha-tocopherol or PBN; 3. ST decrements, such as those seen in aging, could be induced with radiation exposure; and 4. Pre-incubation of the striatal slices with cholesterol decreased subsequent deleterious effects of NO or OH. on DA release. Thus, cholesterol, which increases in neuronal membranes as a function of age, may function as a potent antioxidant and protectant against neuronal damage. These results suggest that therapeutic efforts to restore cognitive deficits in aging and age-related disease might begin with antioxidant reversal of ST decrements.

Joseph JA, Villalobos-Molina R, Denisova N, Erat S, Cutler R, Strain J.

Age differences in sensitivity to H2O2- or NO-induced reductions in K(+)-evoked dopamine release from superfused striatal slices: reversals by PBN or Trolox. Free Radic Biol Med. 1996;20(6):821-30. PMID: 8728030 [PubMed - indexed for MEDLINE]

Previous research has indicated that many age-related functional alterations may be the result of a decreased ability of the organism to respond to oxidative stress (OS). However, this hypothesis is based on indirect indices of function (e.g., increased vulnerability of hepatocytes from senescent animals to H2O2-induced DNA damage, increases in lipofuscin accumulation). More direct tests of this hypothesis, especially as it relates to brain aging, have not been extensively undertaken. Present experiments were carried out to make such tests by examining age differences in the sensitivity to OS on reductions in striatal dopamine (DA) release. Thus, K(+)-evoked DA (K(+)-ERDA) release from superfused striatal slices from young (6-8 month) and old (24-25 month) animals was examined following either: (a) application of the NO-generator sodium nitroprusside or (b) preincubation with H2O2. In order to assess the specific effects of OS on muscarinic (mAChR) sensitivity, oxotremorine-enhancement of K(+) -ERDA was examined following incubation with H2O2. Results showed that the striatal tissue from the old animals showed greater sensitivity to both H2O2 and NO than young animals, and stimulated DA decreased at lower concentrations of these agents (e.g., NO--100 microM young, 30microM old). In addition, H2O2 was also effective in reducing oxo-enhanced K(+)-ERDA and was more effective as a function of age. If the striatal tissue was incubated in either Trolox (alpha-tocopherol) or alpha-phenyl-n-tert-butyl nitrone (PBN) prior to OS, the negative effects of NO. and H2O2 were reversed in both age groups. Results are discussed in terms of age-related membrane and endogenous antioxidant alterations that could induce increases in sensitivity to OS and the specificity of antioxidants in reducing

this sensitivity in key functional systems.

Kelly JF, Mason RP, Denisova NA, Joseph JA, Erat S, Roth GS.

Age-related impairment in striatal muscarinic cholinergic signal transduction is associated with reduced membrane bilayer width measured by small angle X-ray diffraction.
Biochem Biophys Res Commun. 1995 Aug 24;213(3):869-74. PMID: 7654249 [PubMed - indexed for MEDLINE]

In order to determine whether age-related changes in neuronal membrane structure contribute to previously reported changes in muscarinic cholinergic signal transduction, striata from 3, 13and 23 month old F344 male rats were examined for both carbachol-stimulated low Km GTPase activity and membrane one-dimensional electron density profile using small angle X-ray diffraction. Increasing age was associated with both a reduction in stimulated GTPase activity and a decrease in membrane bilayer width. These findings suggest the possibility that fundamental membrane structural changes may contribute to alterations in signal transduction seen with aging.

Joseph JA, Algeri S, De-Cesare A, Comuzio M, Erat S, Kelly J, Cagnotto A, Mennini T.

A reduced calorie-high fiber diet retards age-associated decreases in muscarinic receptor sensitivity.
Neurobiol Aging. 1995 Jul-Aug;16(4):607-12. PMID: 8544911 [PubMed - indexed for MEDLINE]

The effects of a reduced calorie-high fiber diet (RCHF) were examined on three cholinergic signal transduction (ST) parameters: (a) oxotremorine enhancement of K(+)-evoked dopamine release and (b) carbachol-stimulated low KM GTPase activity [an indicator of muscarinic receptor (mAChR)-G protein coupling/uncoupling] , and (c) [3H] Quinuclidinyl benzilate (QNB) autoradiography. Comparisons were made among: young control (6months), old normal control, old reduced calorie high fiber [both 24 months)]. The results indicated that old reduced calorie high fiber rats (1900kcal/kg/day, 2.4%, lipids 2.4%, fiber 28%, carbohydrates 40.7%) as compared to the old normal control rats (3000kcal/kg/day, 4.8% lipids, 4.2% fiber, carbohydrates 61.5%) showed a retardation of age-related deficits in dopamine release (a above) and GTPase activity (b above). These parameters were 25% higher in the old reduced calorie high fiber rats as compared to old normal controls and did not differ from young controls, even though there was no increase in mAChR concentration in the restricted group. Thus, these results indicate that a reduced calorie high fiber diet as utilized in these experiments was effective in retarding the age-related decrements in two of three signal

transduction parameters. They are discussed in terms of the induction of membrane changes (e.g., fluidity) or related decreases in oxidative stress by the restricted diet that may be involved in these signal transduction effects.

Kelly JF, Joseph JA, Denisova NA, Erat S, Mason RP, Roth GS.

Dissociation of striatal GTPase and dopamine release responses to muscarinic cholinergic agonists in F344 rats: influence of age and dietary manipulation.
J Neurochem. 1995 Jun;64(6):2755-64. PMID: 7760056 [PubMed - indexed for MEDLINE]

There is evidence that dietary lipids and age both influence neuronal membrane composition and receptor G protein-linked signal transduction, but very little information is available on the interaction between these two factors. To investigate this, we obtained striata from 2, 12, and 22-month-old male F344 rats who were fed either a high-cholesterol, high-saturated fat or low-fat diet for 1 month. The striata were assayed for muscarinic agonist-stimulated low-Km GTPase activity using 10(-3) M carbachol and 10(-5) M oxotremorine and for KCl-evoked dopamine release enhancement by 10(-5) M oxotremorine. Membrane cholesterol and phospholipid content and phospholipid class composition were also determined. Mature animals showed significant but divergent changes in GTPase activity and dopamine release for high-cholesterol and low-fat diets: GTPase activity decreased, whereas dopamine release increased in these groups. Alterations in GTPase activity but not in dopamine release were inversely correlated with the cholesterol/phospholipid molar ratio. Old control animals showed reductions in both GTPase activity and oxotremorine-enhanced dopamine release compared with young animals. Whereas none of the experimental diets affected GTPase activity in old animals, the low-fat diet produced a marked decrease in dopamine release. In contrast to mature and old groups, young rats showed no significant change in either GTPase or dopamine release, suggesting a relative resistance to such dietary lipid modulation. The observed dissociation in GTPase and dopamine release responses to diet may reflect differing effects of these diets on discrete membrane lipid domains that preferentially influence different signal transduction components. The substantial age-related differences in striatal membrane response to dietary lipid modulation may represent the effects of underlying age differences in membrane lipid metabolism, structure, and/or dynamics. Our findings support the work of other groups that have shown that brain membranes are susceptible to modification by exogenous lipids. They also suggest the need for a more systematic examination of the influence of age on the response to other types of dietary lipid changes.