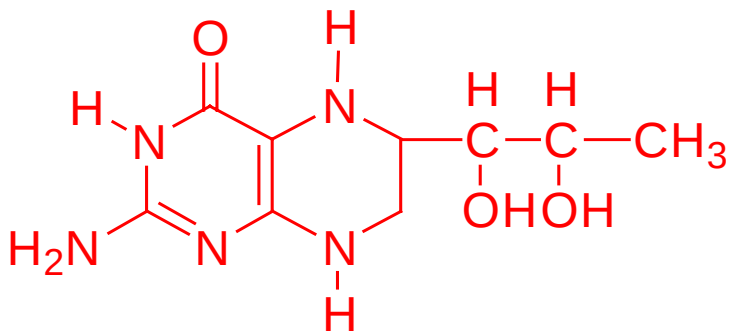
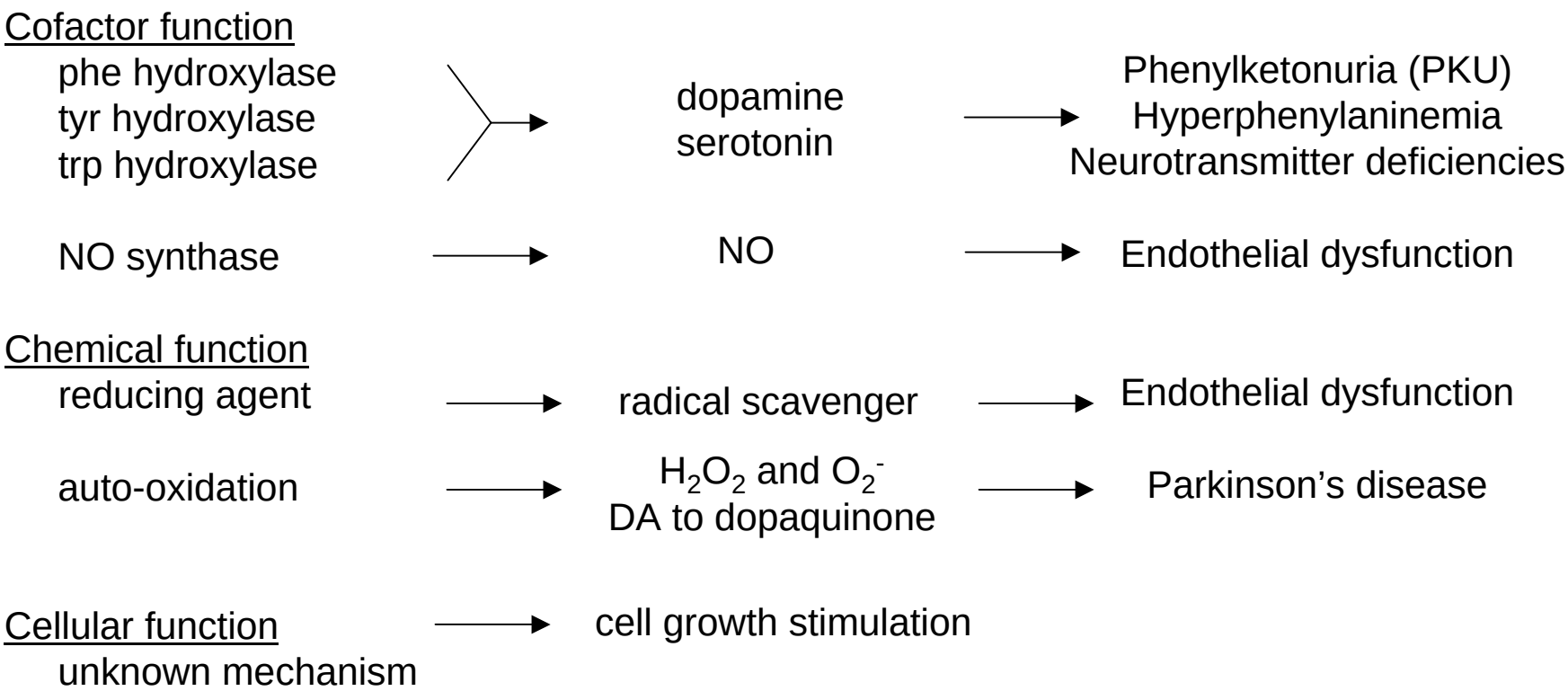
Cofactor in metabolism: Tetrahydrobiopterin (BH4)



Physiological function of BH4

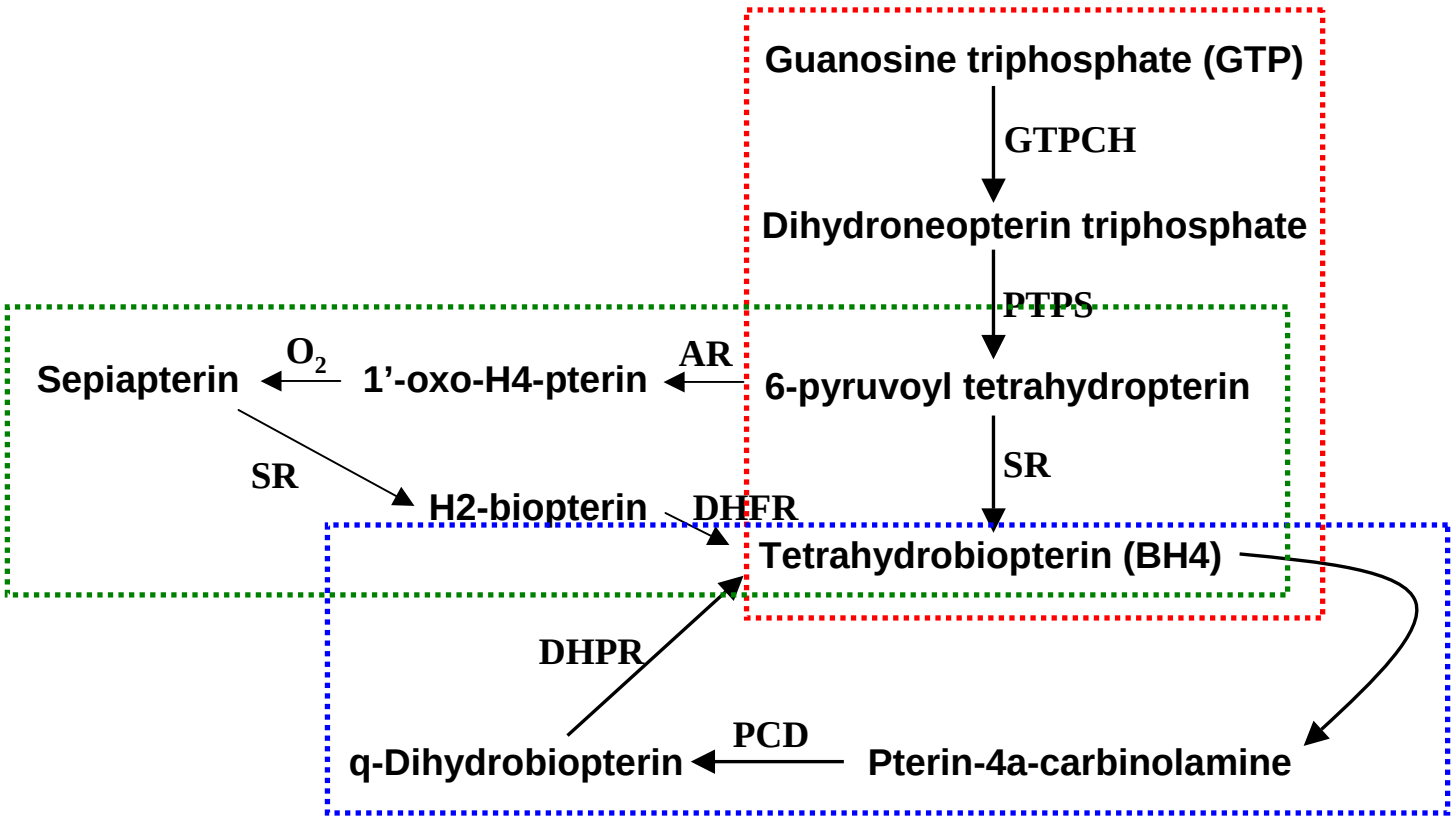


Biosynthesis of BH4

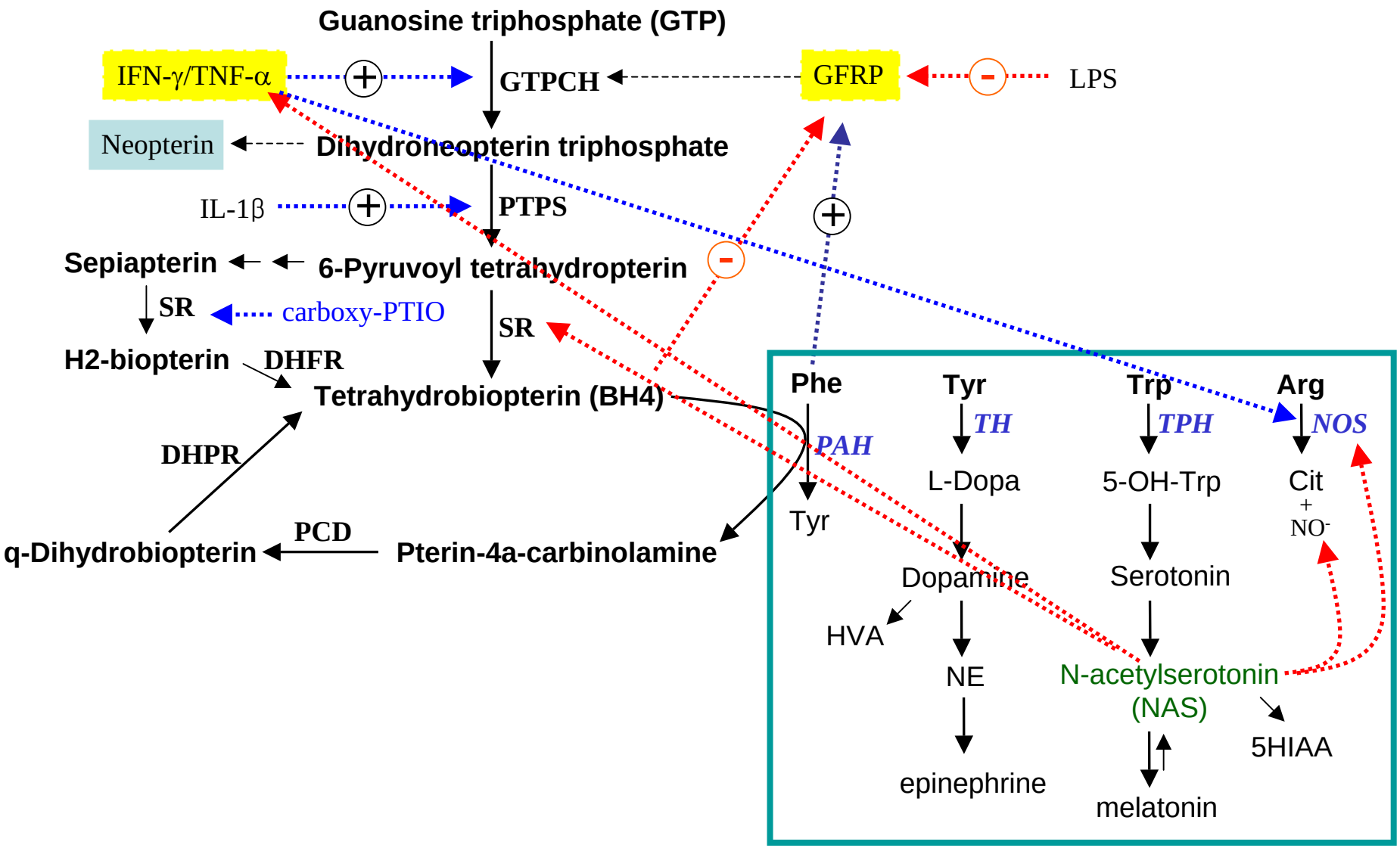
de novo synthesis from GTP: GTPCH, PTPS, SR

regeneration: PCD, DHPR

salvage pathway: AR, SR, DHFR



Regulation of BH4 synthesis



BH4 in brain disorders

Phenylketonuria (PKU): inborn error in phenylalanine hydroxylase

NCBI OMIM

BH4 deficiency: genetic defects in BH4 biosynthesis

BH4 website, type tetrahydrobiopterin at NCBI OMIM

BH4 implicated neuropsychiatric diseases

- Depression
- Parkinson's
- Schizophrenia
- Autism

BH4 distribution in mice

using [14C]BH4 in mice	
Liver	high
Kidney	high
Brain	low
Adrenal medulla	low
Bone marrow	low
Neonatal	similar to adult

J Pharmacol Exp Ther 1993, 267:971-8

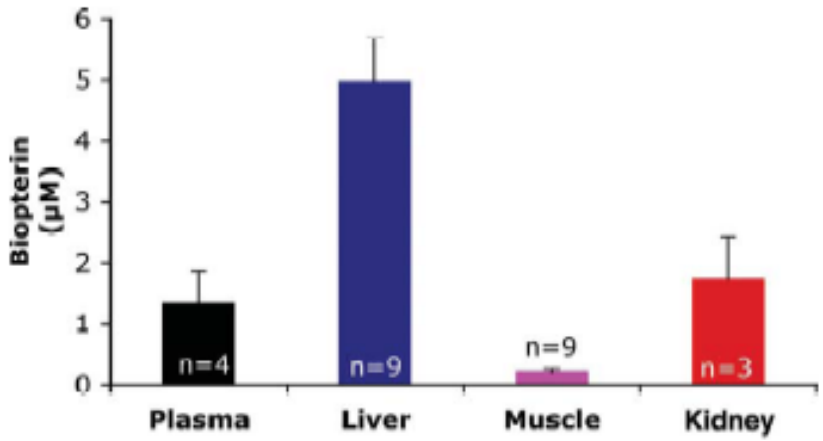
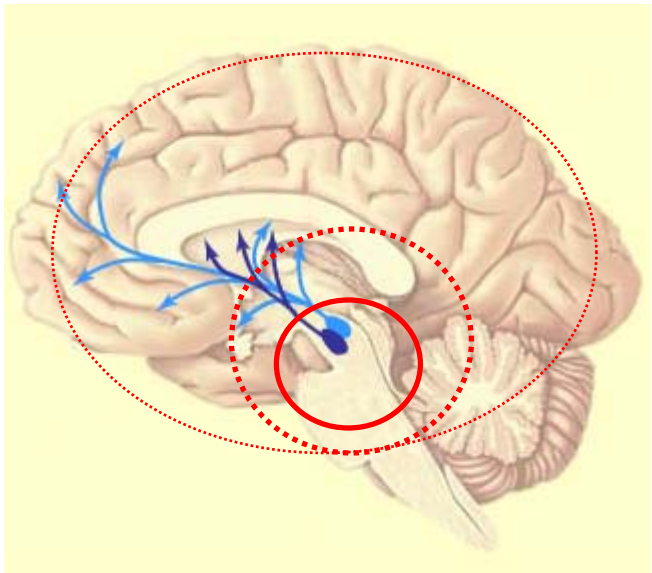


Fig. 2. Total biopterin concentration in select tissues of wild-type mice. Data represent the mean tissue biopterin concentration with the number of mice assayed for each tissue given in the figure. The error bars represent one standard error of the mean.

Molecular Genetics and Metabolism 81 (2004) 52–57

Tissue distribution of BH4 generating enzymes (Adv Exp Med Biol 1993, 338:223-6)

BH4 in brain



Km values for BH4
0.02-0.03 uM for NOS
2-3 uM for PAH
30 uM for TH & TPH

TABLE 1. *Distribution of GFRP and GTPCH mRNA in various rat tissues*

Tissue	GFRP (amol/μg of RNA)	GTPCH (amol/μg of RNA)	GFRP/ GTPCH ratio
Brainstem			
Long form	1.83	0.99	2.85
Short form	1.00		
Ventral midbrain	1.08	2.45	0.44
Hypothalamus	0.99	0.65	1.52
Cerebellum	0.94	0.22	4.27
Cerebral cortex	0.21	ND	—
Adrenal gland	ND	0.76	—
Pineal gland	ND	720	—

Levels of mRNA were determined by nuclease protection assays as described in Materials and Methods. Results are the means of two or three experiments. ND, none detected. Refer to the text for a description of the long and short forms of GFRP mRNA found in the brainstem.

J Neurochem 1999, 72:669

Factors that may contribute to a reduction in nitric oxide bioavailability

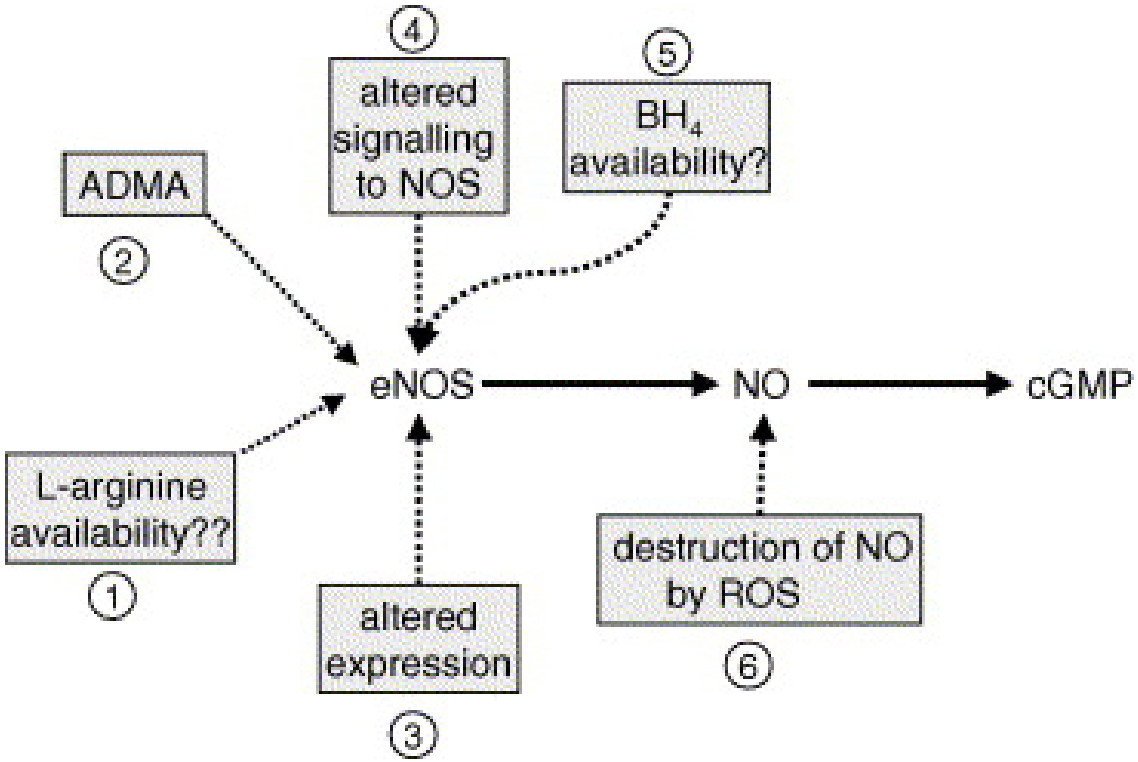
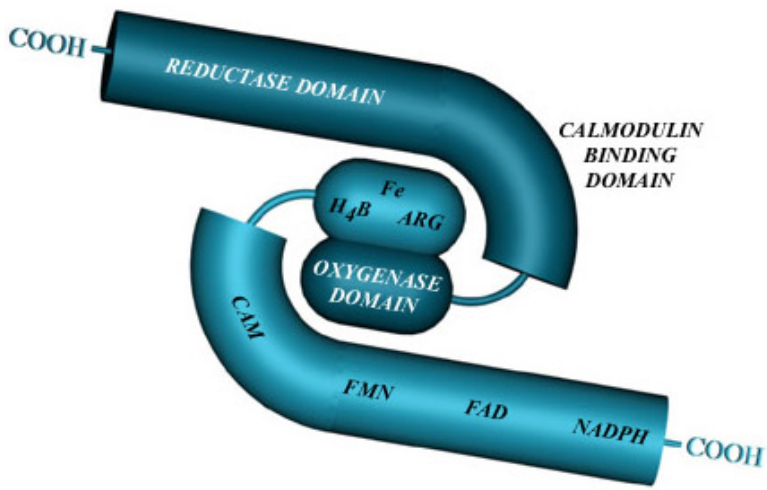


Fig. 5. Factors that may contribute to a reduction in nitric oxide bioavailability. One of the major contributing factors to the progression of cardiovascular diseases is a loss of NO-dependent actions. It is proposed that this is due to a reduction in the bioavailability of NO. There are a variety of factors which could reduce NO availability including (1) a reaction in the availability of the substrate l-arginine, (2) increased concentration of circulating inhibitors such as ADMA (asymmetric dimethylarginine), (3) altered levels of eNOS expression, (4) perturbed signal transduction reducing agonist-induced eNOS activation, (5) reduced availability of terahydrobiopterin (BH_4) an essential co-factor, or (6) the destruction of NO by other free radical species. Mol Aspects Med. 2005 Feb-Apr;26(1-2):33-65

BH4 & NOS

nNOS
eNOS
iNOS
mtNOS

uncoupling
dimerisation
ubiquitination



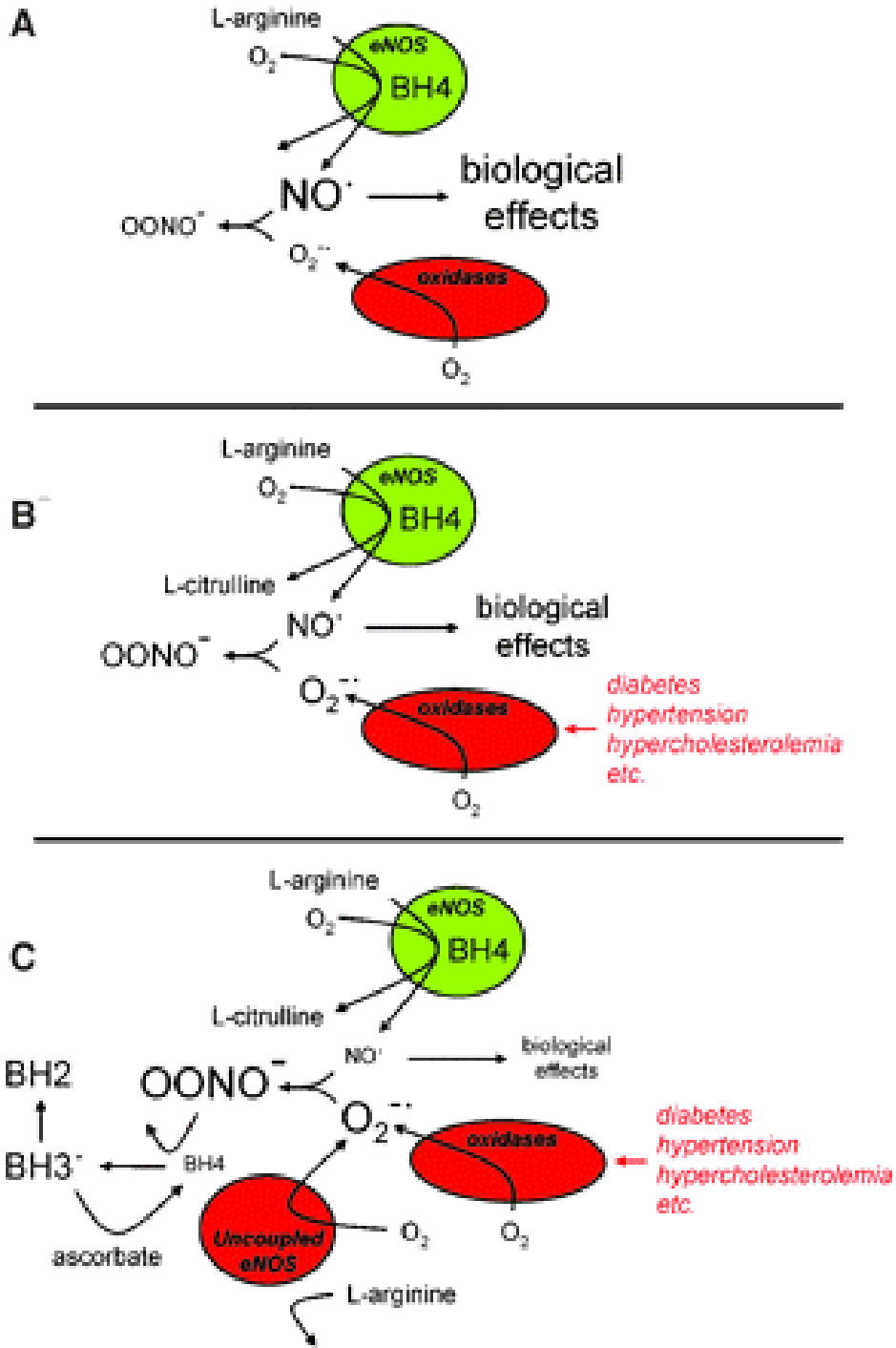
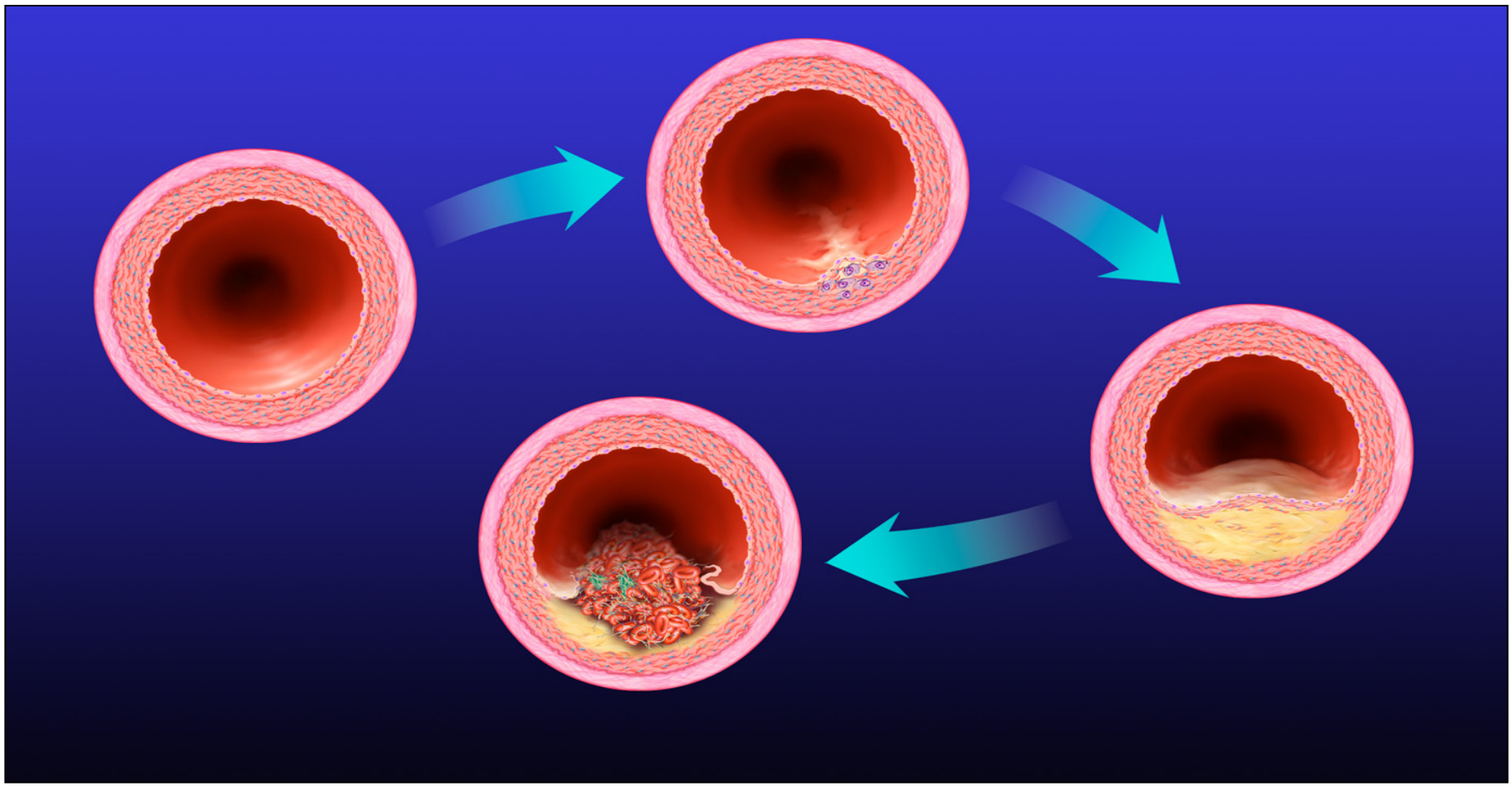


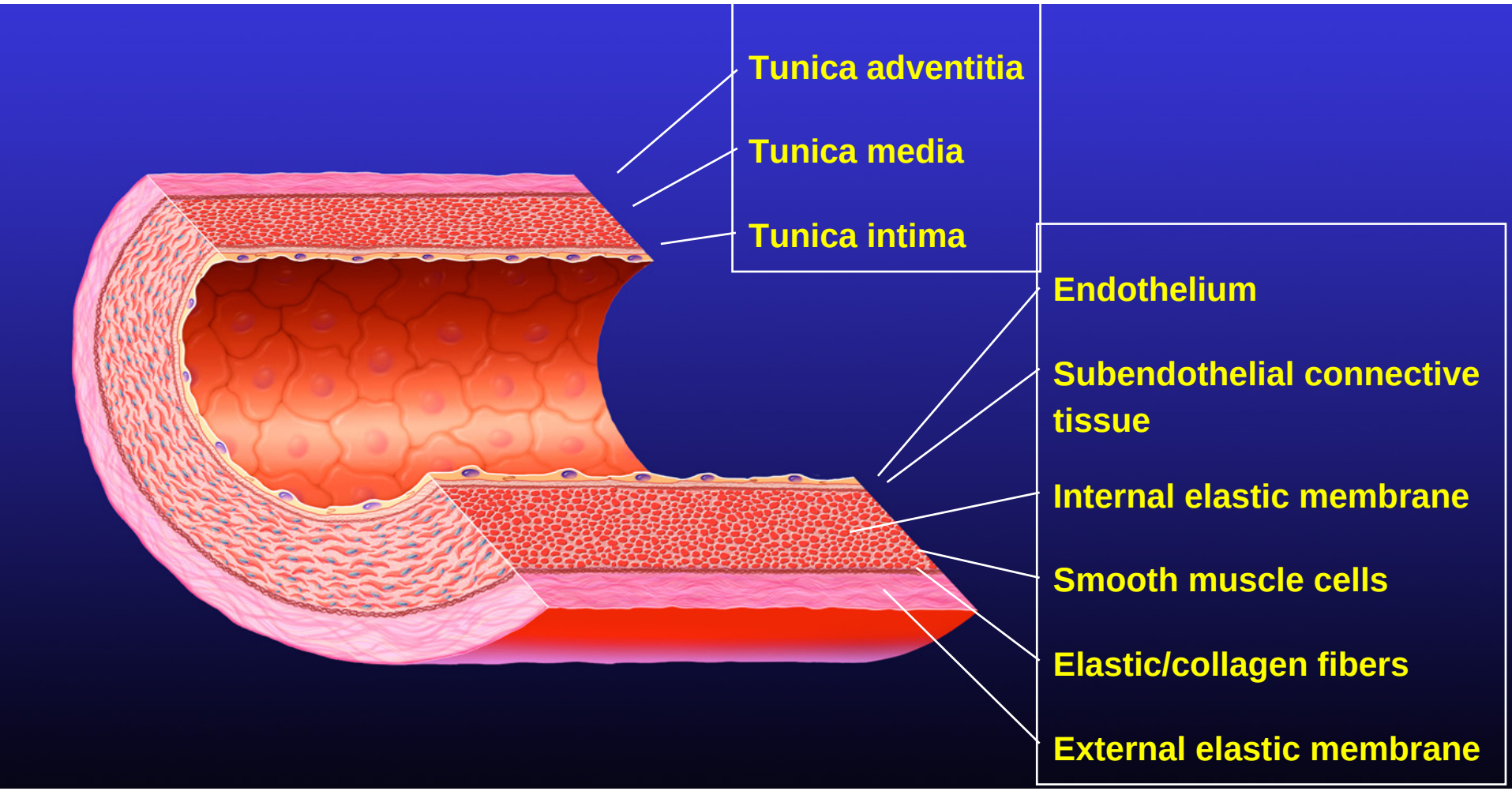
Figure 2. Schematic illustrating the role of BH4 in regulating eNOS activity in vascular disease. A, In healthy vascular endothelium, BH4 availability is not limiting. eNOS production of NO is appropriate for the regulation of multiple antiatherogenic biological effects. Superoxide production by various oxidases acts predominantly in a signaling capacity. Peroxynitrite formed by interaction between NO and superoxide is minimal. B, In vascular disease states such as diabetes, hypertension, or hypercholesterolemia, superoxide production by oxidases is markedly increased. NO production may remain unaffected initially, but NO bioavailability is reduced because of scavenging interactions with superoxide, forming increased peroxynitrite. C, Peroxynitrite and other reactive oxygen species oxidize BH4, via the BH3 radical to BH2 and biopterin, which reduces the bioavailability of BH4 and promotes eNOS uncoupling. eNOS now generates superoxide rather than NO, which contributes to vascular oxidative stress and further reduces NO bioavailability. Ascorbate may protect against oxidative degradation of BH4 by directly reducing the BH3 radical to BH4.

Arterioscler Thromb Vasc Biol. 2004 Mar;24(3):413-20

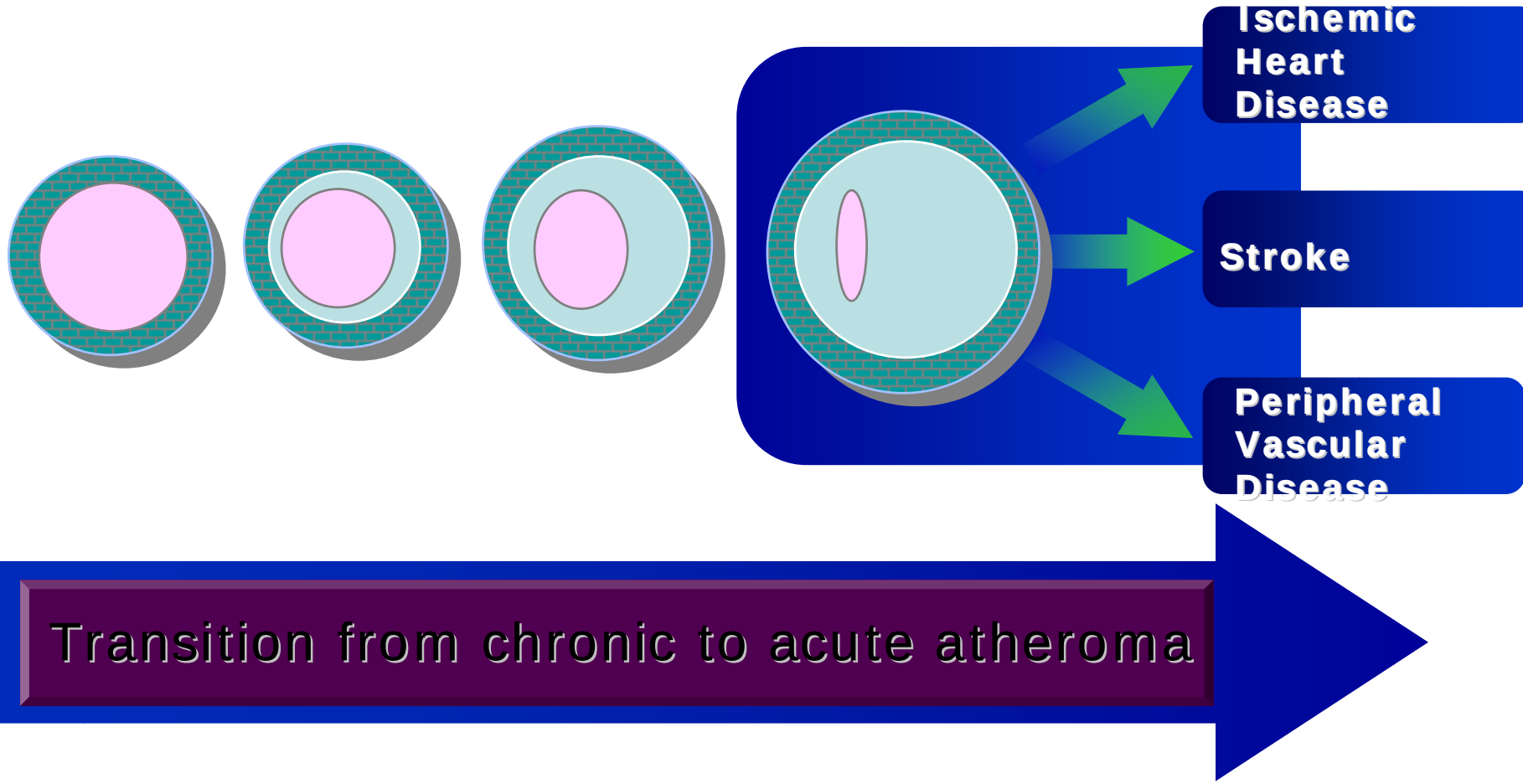
Development of Atherosclerotic Plaques



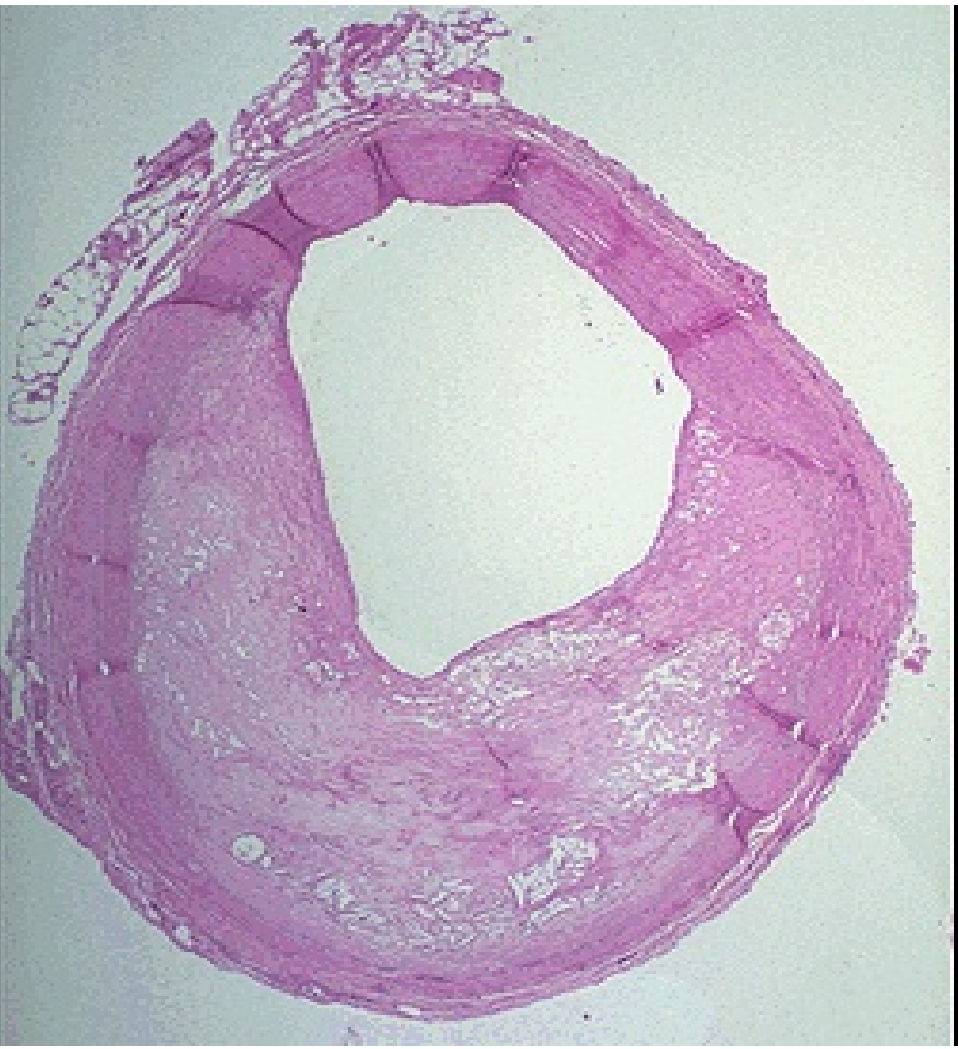
Normal Arterial Wall

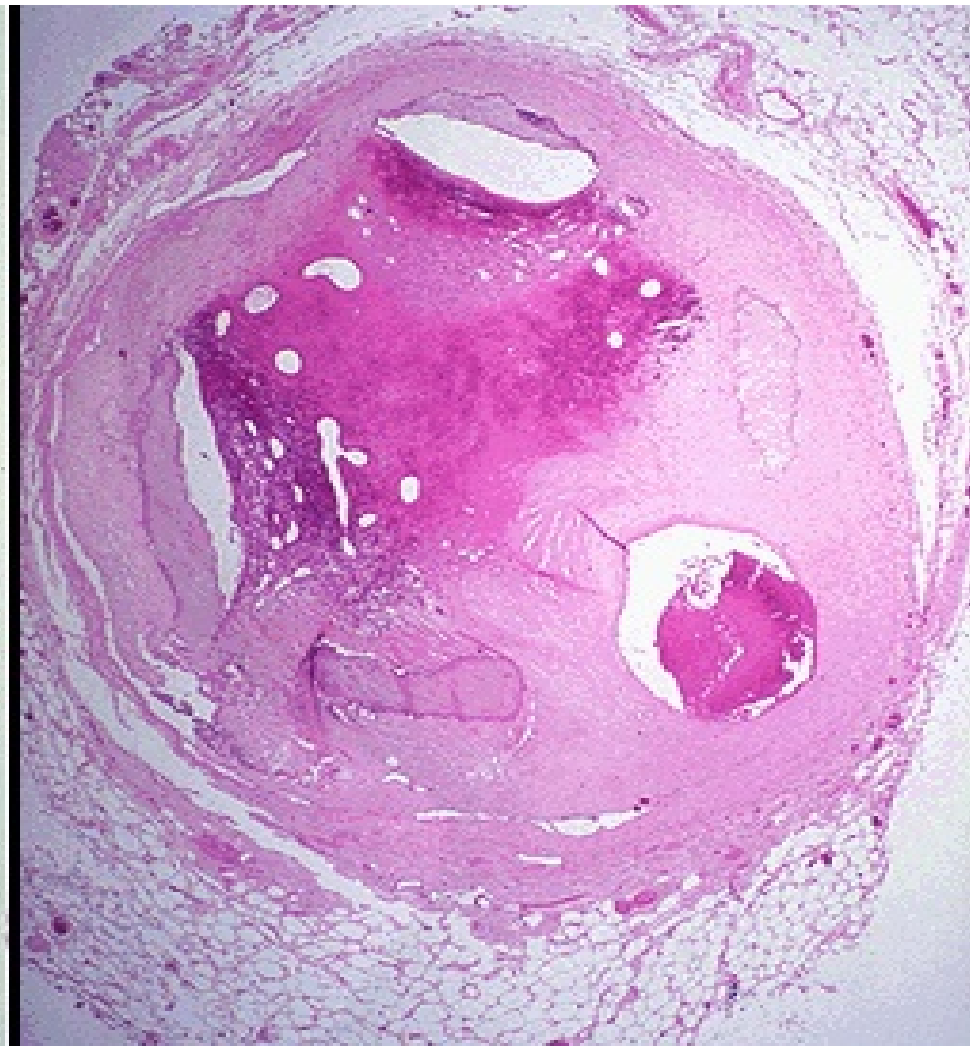


Schematic Time Course of Human Atherogenesis



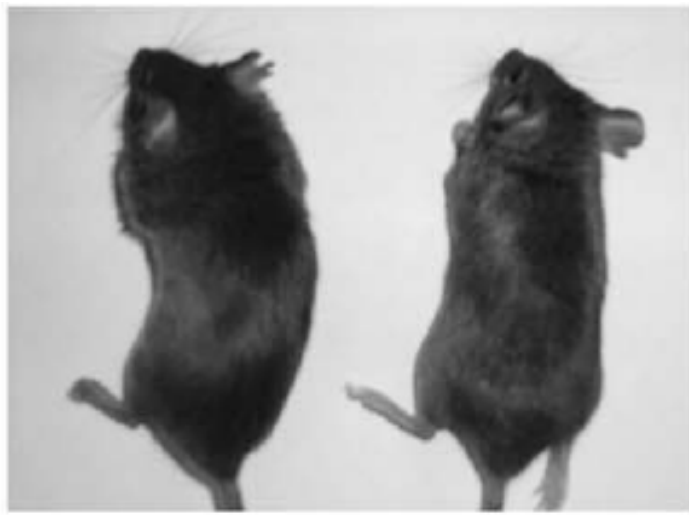
Coronary Atherosclerosis



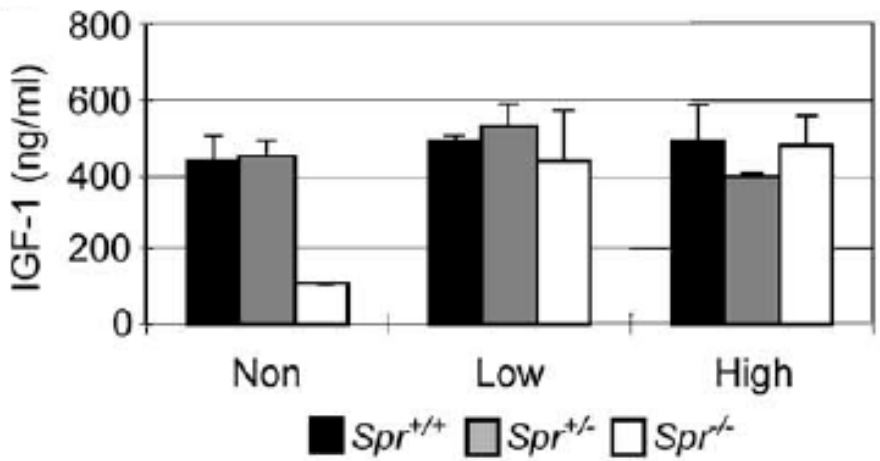


Knockout mouse

$Spr^{+/+}$ $Spr^{-/-}$



$Spr^{+/+}$ $Spr^{-/-}$



Salvage pathway of BH4 synthesis

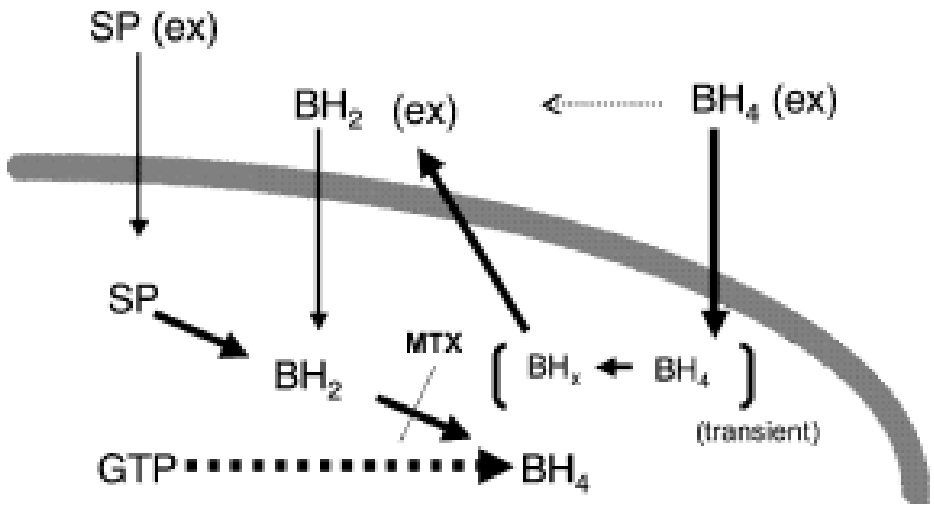


Fig. 4. Model for cellular accumulation of BH_4 caused by extracellular supplementation with sepiapterin, $7,8BH_2$ or $6RBH_4$: sepiapterin and $7,8BH_2$ can be taken up by the cell and converted into BH_4 via the salvage pathway. BH_4 production by this pathway is effectively inhibited by methotrexate (MTX). Supplementation with extracellular BH_4 resulted in a "transient" accumulation, which does not mix with the endogenous pool of BH_4 and is excreted, but causes an accumulation of extracellular $7,8BH_2$. SP, sepiapterin; BH_2, 7,8-dihydrobiopterin. The suffix "ex" denotes extracellular and is mostly applied to the administered pterin compounds. BHx, unidentified intermediate of BH_4 oxidation.

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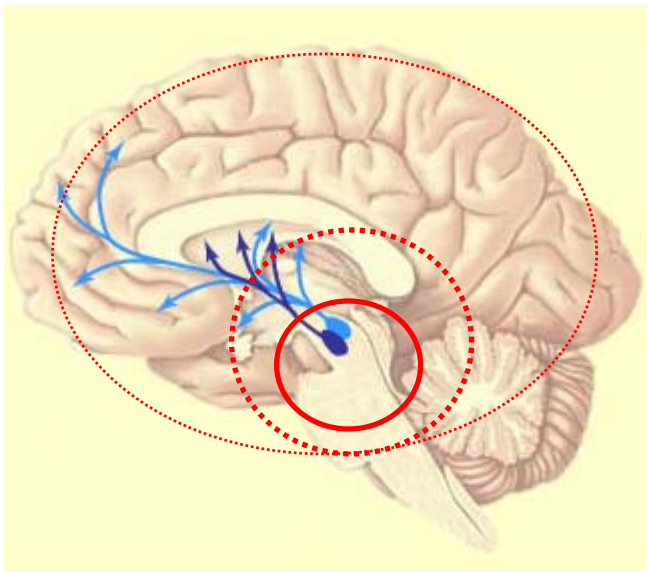
Activities of SPR and GCH in the human brain regions

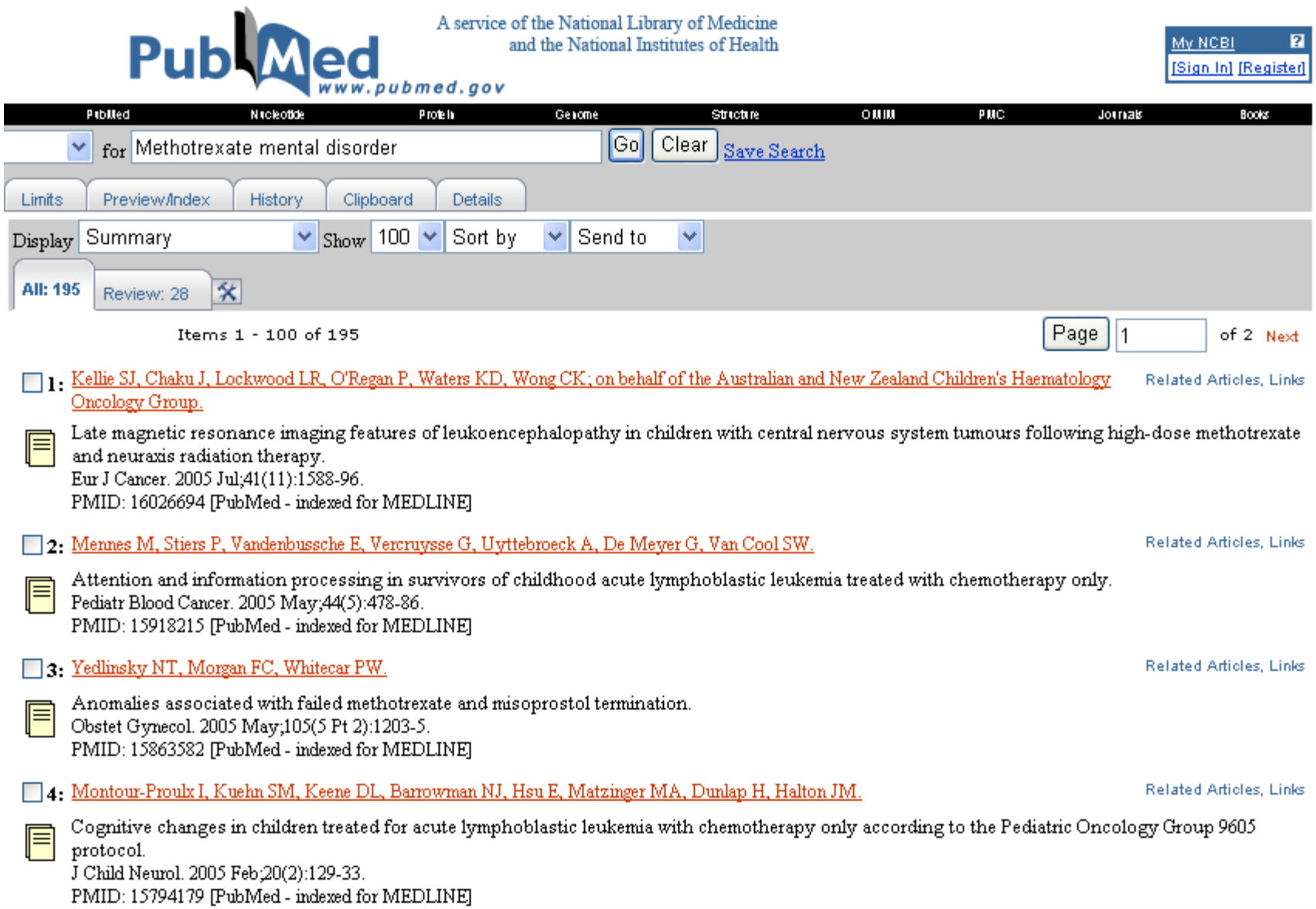
	Sepiapterin reductase activity (nmol/h per mg protein)	GTP cyclohydrolase I activity (pmol/h per mg protein)
Substantia nigra	44.5±2.8	3.82±0.25
Caudate nucleus	22.5±2.3	1.82±0.26
Cerebral cortex:		
Gray matter	23.7±0.2	N. D.
White matter	26.8±1.6	N. D.
Medulla oblongata:		
Dorsal part	26.5±0.6	4.15±0.64
Ventral part	42.0±1.1	2.54±0.28

Results represent the mean (S.D. from three independent experiments. N.D., not detectable (<0.1 pmol/h per mg protein).

Brain Research 954 (2002) 237–246



MTX and mental disorder



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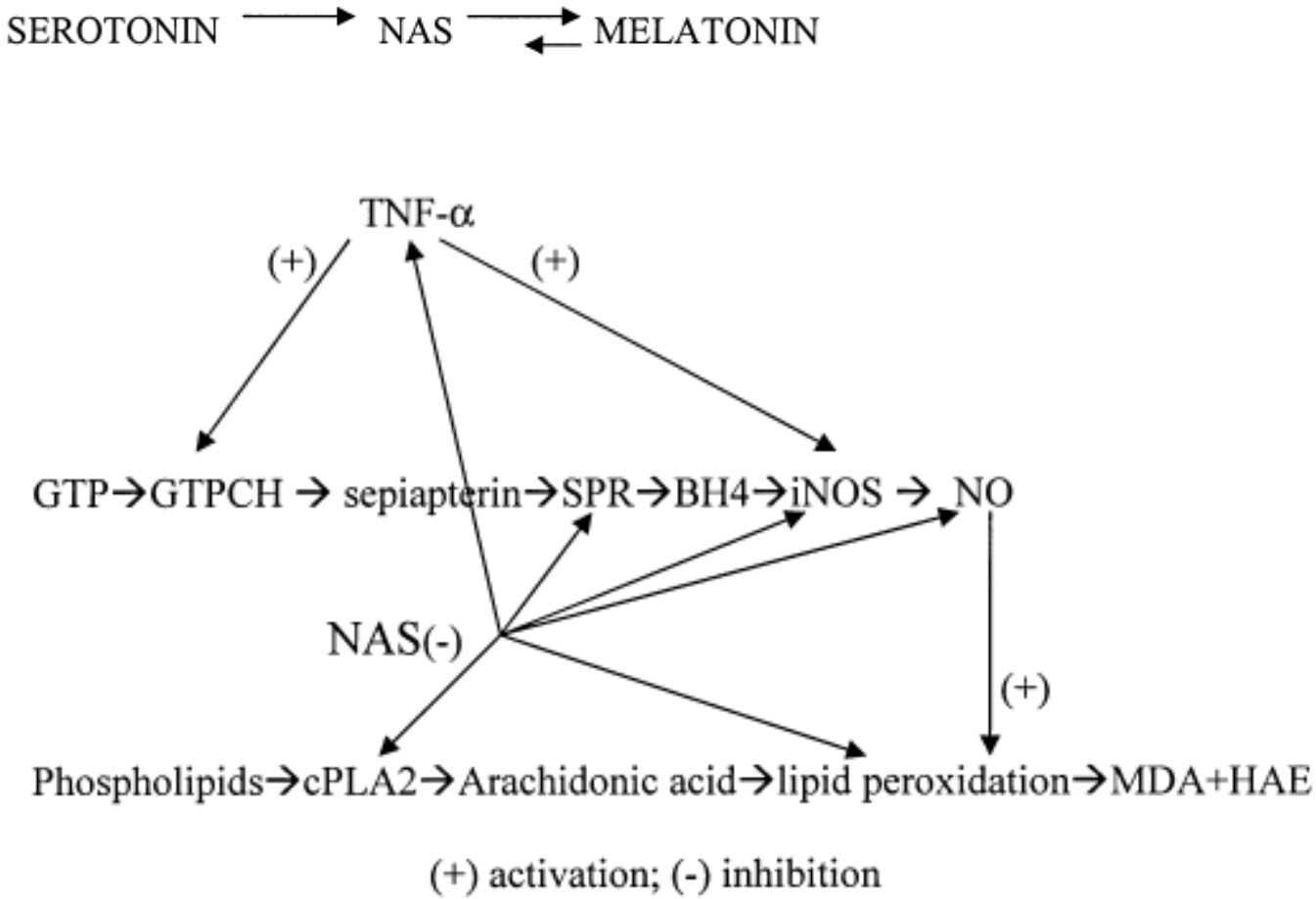
1: Kellie SJ, Chaku J, Lockwood LR, O'Regan P, Waters KD, Wong CK; on behalf of the Australian and New Zealand Children's Haematology Oncology Group. Related Articles, Links
Late magnetic resonance imaging features of leukoencephalopathy in children with central nervous system tumours following high-dose methotrexate and neuraxis radiation therapy.
Eur J Cancer. 2005 Jul;41(11):1588-96.
PMID: 16026694 [PubMed - indexed for MEDLINE]

2: Mennes M, Stiers P, Vandenbussche E, Vercruysse G, Uyttebroeck A, De Meyer G, Van Cool SW. Related Articles, Links
Attention and information processing in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only.
Pediatr Blood Cancer. 2005 May;44(5):478-86.
PMID: 15918215 [PubMed - indexed for MEDLINE]

3: Yedlinsky NT, Morgan FC, Whitecar PW. Related Articles, Links
Anomalies associated with failed methotrexate and misoprostol termination.
Obstet Gynecol. 2005 May;105(5 Pt 2):1203-5.
PMID: 15863582 [PubMed - indexed for MEDLINE]

4: Montour-Proulx I, Kuehn SM, Keene DL, Barrowman NJ, Hsu E, Matzinger MA, Dunlap H, Halton JM. Related Articles, Links
Cognitive changes in children treated for acute lymphoblastic leukemia with chemotherapy only according to the Pediatric Oncology Group 9605 protocol.
J Child Neurol. 2005 Feb;20(2):129-33.
PMID: 15794179 [PubMed - indexed for MEDLINE]

N-acetylserotonin and BH4



Ann. N.Y. Acad. Sci. 1053: 334–347 (2005).