

# From the Medicine of Radicals to a Radically New Medicine



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Oxidative stress, i.e. an increase in reactive oxygen species formation or imbalance with their formation and metabolism, is a hallmark of many cardiovascular and other diseases. In fact, there is hardly any disease where oxidative stress has not been suggested at one point of time to play a role as a pathomechanism. Yet after decades of research there is no therapeutic in the clinic that is based on an antioxidant mechanism. In fact, the non-targeted preventive application of vitamins and other supposedly antioxidant substances is associated with higher mortality. Is the oxidative stress theory wrong?

Probably not, but it needs a major amendment and an entirely different approach to exploiting it therapeutically. Data will be presented on delineating oxidative stress as a signalling network of ROS generators, ROS targets and ROS metabolisers, some of which inactivate, other toxify ROS. Each of these may play a specific role, or no role, in a given disease state. Identifying these pathomechanism will lead and has led to specific targets and highly specific therapies. Importantly these will leave essential physiological functions of ROS untouched. Targets and the ROS-relevant pathway also extends to NO-cGMP signalling. This entire network is clinically relevant and will open a new chapter of Radical Medicine.

Finally, when validating different indications, we came across non-expected disease states, which confused us as we set out working with what we thought were cardiovascular targets. However, the ROS-cGMP network is relevant to diverse disease phenotypes such diabetic end-organ damage, asthma, stroke, Alzheimer's disease, and pulmonary hypertension etc. This all made sense when we came across Barabasi's diseasome, the network of human diseases. All of these phenotypes clustered in one subnetwork. These clusters are likely formed by common mechanisms. Thus the ROS-cGMP network seems to define this cluster. Thus disease should no longer be defined by organs, symptoms or the first doctor who described the symptoms, but only by the molecular pathomechanism.

Fully validating this and expanding it to other clusters of the diseasome will introduce a Radically New Medicine, a Medicine that is fully digitalised and based on big data, Medicine 4.0. We are beginning to take first looks into this exciting future.

# CURRICULUM VITAE

## Executive Statement

Harald Schmidt is Professor & Chair of Pharmacology & Personalised Medicine at the Cardiovascular Research Institute Maastricht, co-leader of Maastricht University's Faculty of Health, Medicine and Life Sciences innovation platform, and Board Member of the Maastricht Institute of Advanced Studies at Maastricht University, Netherlands. He leads a research program as European Research Council Advanced Investigator, a EUROSTAR programme, and founded a European Science Foundation COST Action. Before he had worked in Australia, Germany and USA in different academic and business leadership positions. These include chair of Monash University's Centre for Vascular Health, Australia, different chairs in pharmacology and director of a drug discovery CRO at TransMIT, Giessen, Germany. He also co-founded and for two years led as CEO Vasopharm GmbH, a drug discovery company now entering into phase III clinical development. His research focuses on cardiovascular and neurological disease mechanisms, target validation, drug and biomarker discovery, personalised and network medicine. Professor Schmidt has published over 160 peer-reviewed papers, reviews, books and patents (Hirsch-index of 75,  $m=2.6$ ; Google-Scholar: [tinyurl.com/q4july7](https://tinyurl.com/q4july7)). He is a member of the European Society of Cardiology Working Group - Cardiovascular Pharmacology and Drug Therapy, Section Editor of the Public Library of Science. He has been awarded the Roche Molecular Biochemicals Research Prize for Cell Biology, the Phoenix Research Prize in Pharmacy, and the Pro Scientia Prize.

## Professional appointments

- 2010-        Professor of Pharmacology and Personalised Medicine, Maastricht University, The Netherlands
  
- 2009        Associate Dean International Research, Faculty of Medicine, Nursing and Health Sciences
  
- 2007-2009 Director, Centre for Vascular Health, Monash University, Australia
  
- 2005-2009 Professor and Head, Department of Pharmacology, Monash University, Australia
  
- 2000-2005 Professor and Head of the Rudolf-Buchheim-Institute for Pharmacology, Justus-Liebig-University, Gießen, Germany
  
- 1996-1999 Professor of Pharmacology and Toxicology, University of Würzburg, Germany  
              CEO of Vasopharm GmbH, Würzburg, Germany
  
- 1992-1996 Principal Research Fellow equivalent, Department of Medicine, Clinical Research Group, University Clinics, Würzburg, Germany
  
- 1990-1992 Adjunct Assistant Professor, Northwestern University Medical School, Department of Pharmacology, Chicago, USA  
              Senior Research Scientist, Abbott Laboratories, North Chicago, USA
  
- 1989-1990 German Research Council (DFG)-Postdoctoral-Fellow, Northwestern University Medical School, Department of Pharmacology, Chicago, USA
  
- 1987-1989 German Research Council (DFG) Postdoctoral Fellow, Free University Berlin, Institute of Pharmacology, West-Berlin, Germany

1986 Karl-Duisberg-Fellowship, Royal Melbourne Hospital, Department of Clinical Pharmacology, University of Melbourne, Australia

### Clinical experience

- ▶ 2007-2009: Clinical Pharmacologist in Southern Health Hospital, Vascular Medicine Outpatient Clinic
- ▶ 2006: Southern Health Therapeutics and Adverse Drug Reactions Committees
- ▶ 2004: Successful market launch of a clinical cardiovascular therapeutic monitoring kit
- ▶ 2007: One drug candidate (NOS inhibitor) entered clinical development
- ▶ 2006: Honorary Appointment at Monash Medical Centre
- ▶ 2000-2005: Ethics Committees (University Clinics, Gießen)
- ▶ 1999-2000: Clinical Pharmacology activity, participation in Quality Use of Medicine Committee (University Clinics, Würzburg and Gießen), Therapeutics Committee (Southern Health, Melbourne); ward rounds; Chair of Natural Compounds Forum (2001-2005, Germany)
- ▶ 1999, 2006: Active member of German and Australian Cardiology Societies
- ▶ 1989: Active member of German Society for Clinical Pharmacology

### Main clinical interests

1987-: Pharmacology, Hypertension, PAD, Stroke

2000-: ongoing: Clinical trial design and assessment

2007-: ongoing: Personalized medicine

### Teaching experience

1987-1989: Pharmacology for Medical Students, University of Berlin

1992-2000: Pharmacology for Medical, Pharmacy Students, University of Würzburg

2000-2005: Pharmacology for Medical, Dentistry and Science Students

2005-2009: Pharmacology for Science and Medicine Students, Monash University

2006-ongoing: Editor of a leading German Pharmacology text book (Estler-Schmidt)

2007-2009: Monash University, Medicine, Medical Course Management Committee

2010-: Curriculum committees, Faculty of Medicine and Life Sciences; Honours students committee

### Management positions

- ▶ Professor of Pharmacology for Pharmacists, Würzburg (1996-2000)
- ▶ Lehren lernen, Didactics program for lecturers, Würzburg (1995-1999)
- ▶ Member University Council, Würzburg (1996-1998)
- ▶ Head of Department of Pharmacology and Toxicology, Gießen (2000-2005)
- ▶ Member of Faculty Academic Board, Gießen, Germany (2002-2005)
- ▶ Director University Animal Facility, Gießen (2003-2005)
- ▶ Member of University Ethics Committee, Gießen, Germany (2002-2004)
- ▶ Director of Centre for Vascular Health, Melbourne (2006-2009)

- ▶ Head of Department of Pharmacology, Melbourne (2005-2009)
- ▶ Member of Faculty Board, ex officio, Melbourne (2005-2009)
- ▶ Member of Monash University Academic Board, Melbourne
- ▶ Member of Southern Health Therapeutics Committee, Melbourne
- ▶ Member of the Monash University Inclusive Practices Workplace Equity Committee (WEC) - Equal Opportunity Committee (2006-2007)
- ▶ Chair Faculty of Medicine Theme Committee, Melbourne (2007-2009)
- ▶ Monash Medical Course Managing Committee, Melbourne (2007-2009)
- ▶ Monash University Biomedical Imaging Initiative, Melbourne (2007-2009)
- ▶ Australian Chair Intl Core-2-Core Program, Melbourne (2008-2009)
- ▶ Head of Department, Maastricht University (2011-2013)
- ▶ Co-Chair Innovation Platform, Faculty of Medicine & Life Sciences (2013-)
- ▶ Board Member, Maastricht Institute of Advanced Studies (2014-)

### Main research themes

1. Molecular Pharmacology
2. Chemical Biology
3. Drug Discovery
4. Personalized/individualized medicine

### List of publications (H-index 75; m=2.7)

**Wi-1: Scientific publication in international journal mentioned in the Social Science Citation Index, Science Citation Index or Arts & Humanities Citation Index with Impact Factor**

1. Schmidt HHHW, Schurr C, Hedler L and Majewski H (1984) Local modulation of noradrenaline release in vivo: presynaptic  $\beta_2$ -adrenoceptors and endogenous adrenaline. *J Cardiovasc Pharmacol* 6 641-649 "IF=1.313" (66), part of PhD thesis
2. Schmidt HHHW, Klein MM, Niroomand F and Böhme E (1988) Is arginine a physiological precursor of endothelium-derived nitric oxide? *Eur J Pharmacol* 148: 293-295 "IF=2432" (78)
3. Schmidt HHHW, Nau H, Wittfoht W, Gerlach J, Prescher K-E, Klein MM, Niroomand F and Böhme E (1988) Arginine is a physiological precursor of endothelium-derived nitric oxide *Eur J Pharmacol* 154: 213-216 "IF=2432" (317)
4. Schmidt HHHW, Wilke P, Evers B and Böhme E (1989) Enzymatic formation of nitrogen oxides from L-arginine in bovine brain cytosol *Biochem Biophys Res Commun* 165: 284-291 "IF=3000" (111)
5. Schmidt HHHW, Seifert R and Böhme E (1990) Formation and release of nitric oxide from human neutrophils and HL-60 cells induced by a chemotactic peptide, platelet activating factor and leukotrien B4 *FEBS Lett* 244: 357-360 "IF=3.415" (235)
6. Förstermann U, Gorsky LD, Pollock JS, Schmidt, HHHW, Heller M and Murad F (1990) Regional distribution of EDRF/NO-synthesizing enzyme(s) in rat brain *Biochem Biophys Res Commun* 168: 727-732, 1990 "IF=2.836" (86)
7. Schmidt HHHW, Baeblich SE, Zernikow BC, Klein MM and Böhme E (1990) L-Arginine and arginine analogues: effects on isolated blood vessels and cultured endothelial cells *Br J Pharmacol* 101: 145-151 "IF=3.611" (30)
8. Förstermann U, Gorsky LD, Pollock JS, Schmidt HHHW, Ishii K, Heller M and Murad F (1990) Subcellular localization and regulation of the enzymes responsible for EDRF

- synthesis in endothelial cells and N1E-115 neuroblastoma cells *Eur J Pharmacol* 183: 1625-1626 "IF=2.432" (13)
9. Schmidt, HHHW, Zernikow B, Baeblich S and Böhme E (1990) Basal and stimulated formation and release of L-arginine-derived nitrogen oxides from cultured endothelial cells *J Pharmacol Exp Ther* 254: 591-597 "IF=4098" (52)
  10. Förstermann U, Gorsky LD, Pollock JS, Ishii K, Schmidt HHHW, Heller M and Murad F (1990) Hormone-induced biosynthesis of endothelium-derived relaxing factor/nitric oxide-like material in N1E-115 neuroblastoma cells requires calcium and calmodulin *Molec Pharmacol* 38: 7-13 "IF=4.612" (87)
  11. Mitchell JA, Förstermann U, Warner TD, Pollock JS, Schmidt HHHW, Heller M and Murad F (1991) Endothelial cells have a particulate enzyme system responsible for EDRF formation: measurement by vascular relaxation *Biochem Biophys Res Commun* 176: 1417-1423 "IF=2836" (36)
  12. Schmidt HHHW and Murad F (1991) Purification and characterization of a human NO synthase *Biochem Biophys Res Commun* 181: 1372-1377 "IF=2836" (186)
  13. Förstermann U, Pollock JS Schmidt HHHW, Heller M and Murad F (1991) Calmodulin-dependent endothelium-derived relaxing factor/nitric oxide synthase activity is present in the particulate and cytosolic fractions of bovine aortic endothelial cells *Proc Natl Acad Sci USA* 88: 1788-1792 "IF=10231" (449)
  14. Pollock JS, Förstermann U, Mitchell JA, Warner TD, Schmidt HHHW, Nakane M and Murad, F (1991) Purification and characterization of particulate endothelium-derived relaxing factor synthase from cultured and native bovine aortic endothelial cells *Proc Natl Acad Sci USA* 88: 10480-10484 "IF=10231" (687)
  15. Schmidt HHHW, Pollock, JS, Nakane M, Gorsky LD, Förstermann U and Murad F (1991) Purification of a soluble isoform of guanylyl cyclase-activating-factor synthase *Proc Natl Acad Sci USA* 88: 365-369 "IF=10231" (397)
  16. Warner TD, Schmidt HHHW and Murad F (1991) Interactions of endothelin and EDRF in bovine native endothelial cell: presence of selective endothelin-3 receptors *Am J Physiol* 262: H1600-H1605 "IF=3942" (59)
  17. Schmidt HHHW, Smith RM, Nakane M and Murad F (1992) Ca<sup>2+</sup>/Calmodulin-dependent NO synthase Type I: a biopteroflavoprotein with Ca<sup>2+</sup>/calmodulin-independent diaphorase and reductase activities *Biochemistry* 31: 3243-3249 "IF=3848" (142)
  18. Matsumoto T, Mitchell JA, Schmidt HHHW, Kohlhaas KL, Warner TD, Förstermann U and Murad F (1992) Nitric oxide synthase in ferret brain: localization and characterization *Br J Pharmacol* 107: 849-852 "IF=3.611 (12)
  19. Sheng H, Schmidt HHHW, Nakane M, Mitchell JA, Pollock JS, Förstermann, U and Murad F (1992) Characterization and localization of nitric oxide synthase in non-adrenergic non-cholinergic nerves from bovine retractor penis muscles *Br J Pharmacol* 106: 768-773 "IF=3611" (62)
  20. Warner TD, Schmidt HHHW, Kuk J, Mitchell JA and Murad F (1992) Human brain contains a metalloprotease that converts big endothelin-1 to endothelin-1 and is inhibited by phosphoramidon and EDTA *Br J Pharmacol* 106: 505-506 "IF=3611" (17)

21. Förstermann U, Schmidt HHHW, Kohlhaas KL and Murad F (1992) Induced RAW 2647 macrophages express soluble and particulate nitric oxide synthase: Inhibition by transforming growth factor- $\beta$  Eur J Pharmacol 225: 161-165 "IF=2432" (66)
22. Schmidt HHHW, Gagne GD, Nakane M, Pollock JS, Miller MF and Murad, F (1992) Mapping of NO synthase in the rat suggests co-localization with NADPH diaphorase but not soluble guanylyl cyclase and novel paraneural functions for nitrinergic signal transduction J Histochem Cytochem 40: 1439-1456 "IF=2208" (549)
23. Mitchell JA, Kohlhaas KL, Matsumoto T, Pollock JS, Förstermann U, Warner TD, Schmidt HHHW and Murad F (1992) Induction of NADPH dependent diaphorase and NO synthase activity in aortic smooth muscle and cultured macrophages Mol Pharmacol 41: 1163-1168 "IF=4612" (50)
24. Schmidt HHHW, Warner TD, Nakane M, Förstermann U and Murad F (1992) Regulation and subcellular location of nitrogen oxide synthases in RAW2647 macrophages Mol Pharmacol 41: 615-624 "IF=4612" (204)
25. Saffrey MJ, Hassal CJS, Hoyle CHV, Belai A, Moss J, Schmidt HHHW, Förstermann U, Murad F and Burnstock, G (1992) Nitric oxide synthase and NADPH-diaphorase in cultured myenteric neurons Neuroreport 3: 333-336 "IF=2351" (99)
26. Valtschanoff JG, Weinberg RJ, Rustioni A and Schmidt HHHW (1992) Nitric oxide synthase and GABA colocalize in lamina II of rat spinal cord Neurosci Lett 148: 6-10 "IF=2019" (109)
27. Belai A, Schmidt HHHW, Hoyle CHV, Hassal CJS, Saffrey MJ, Moss J, Förstermann U, Murad F and Burnstock G (1992) Colocalization of nitric oxide synthase and NADPH-diaphorase in the myenteric plexus of the rat gut Neuroscience Lett 143: 60-64 "IF=2019" (182)
28. Hassal CJS, Saffrey MJ, Belai A, Hoyle CHV, Moules EW, Moss J, Schmidt HHHW, Murad F, Förstermann U and Burnstock G (1992) Nitric oxide synthase-immunoreactivity and NADPH-diaphorase activity in a subpopulation of intrinsic neurones of the guinea-pig heart Neuroscience Lett 143: 65-68 "IF=2019" (99)
29. Wilcox CS, Welch WJ, Murad F, Gross SS, Taylor G, Levi R and Schmidt HHHW (1992) Nitric oxide synthase in macula densa regulates glomerular capillary pressure Proc Natl Acad Sci USA 89: 11993-11997 "IF=10231"(384)
30. Schmidt HHHW, Warner TD, Ishii K, Sheng H and Murad F (1992) Insulin-secretion from pancreatic B-cells caused by L-arginine-derived nitrogen oxides Science 255: 721-723, 1992, Response ibid 258: 1376-1378 "IF=30927" (314)
31. Nakane M, Schmidt HHHW, Pollock JS, Förstermann U and Murad F (1993) Cloned human brain nitric oxide synthase is highly expressed in skeletal muscle FEBS Letters 316: 175-180 "IF=3415" (423)
32. Valtschanoff, J G, Weinberg, R J, Kharazia, V N, Nakane, M and Schmidt, HHHW (1993) Neurons in rat hippocampus that synthesize nitric oxide J Comp Neurol 331: 111-121 "IF=3855" (173)
33. Valtschanoff JG, Weinberg RJ, Kharazia VN, Schmidt HHHW, Nakane M, Rustioni A (1993) Neurons in rat cerebral cortex that synthesize nitric oxide: NADPH diaphorase

- histochemistry, NOS histochemistry, and colocalization with GABA *Neurosc Lett* 157, 157-161 "IF=2019" (153)
34. Dun NJ, Dun SL, Wu SY, Förstermann U, Schmidt HHHW and Tseng LF (1993) Nitric oxide synthase immunoreactivity in the rat, mouse, cat and squirrel monkey spinal cord *Neuroscience* 54: 845-857 "IF=3456" (189)
  35. Blottner D, Schmidt HHHW, Baumgarten HG (1993) Nitroergic autonomic neurones in rat spinal cord *Neuroreport* 4, 923-926 "IF=1995" (20)
  36. Tojo A, Gross SS, Zhang L, Tisher CC, Schmidt HHHW, Madsen KM, Wilcox CS (1994) Immunocytochemical localization of distinct forms of nitric oxide synthase in juxtaglomerular apparatus of normal rat-kidney *J Am Soc Nephrol* 4: 1438-1447 "IF=7240" (147)
  37. Schilling K, Schmidt HHHW and Baader SL (1994) Nitric oxide synthase expression reveals compartments of cerebellar granule cells and suggests a role for mossy fibers in their development *Neuroscience* 59: 893-903 "IF=3456" (60)
  38. Koch K-W, Lambrecht H-G, Haberecht M, Redburn D and Schmidt HHHW (1994) Functional coupling of a Ca<sup>2+</sup>/calmodulin dependent nitric oxide synthase and a soluble guanylyl cyclase in vertebrate photoreceptor cells *EMBO J* 13: 3312-3320 "IF=10051" (102)
  39. Graf R, Langer J-U, Schönfelder G, Öney T, Hartel-Schenk S, Reutter W and Schmidt HHHW (1994) The extravascular contractile system in the human placenta: Morphology and co-localization with different autacoid generating systems *Anatomy and Embryology*: 190, 541-548 "IF=1255" (18)
  40. Laing I, Todd AJ, Heizmann CW and Schmidt HHHW (1994) Subpopulations of GABAergic neurons in laminae I-III of rat spinal dorsal horn defined by coexistence with classical transmitters, peptides, nitric oxide synthase or parvalbumin *Neuroscience*:61, 123-132 "IF=3456" (61)
  41. Bernardi PS, Valtschanoff JG, Weinberg RJ, Schmidt HHHW and Rustioni A (1994) Synaptic interactions between primary afferent terminals and GABA and nitric oxide-synthesizing neurons in superficial laminae of the rat spinal cord *J Neuroscience*: 15, 1363-71 "IF=7907" (57)
  42. Peng Z-C, Chen S, Bertini G, Schmidt HHHW and Bentivoglio M (1994) Co-localization of nitric oxide synthase and NGF receptor in neurons in the medial septal and diagonal band nuclei of the rat *Neuroscience Letters* 166: 153-156 "IF=2.019" (17)
  43. Soyguder Z, Schmidt HHHW, Morris R (1994) Postnatal development of nitric oxide synthase type 1 expression in the lumbar spinal cord of the rat: a comparison with the induction of c-fos in response to peripheral application of mustard oil *Neuroscience Letters* 180: 118-192 "IF=2019" (21)
  44. Kharazia VN, Schmidt HHHW, Weinberg RJ (1994) Type I nitric oxide synthase fully accounts for NADPH-diaphorase in rat striatum, but not cortex *Neuroscience* 62: 983-987 "IF=3456" (72)
  45. Zhang ZG, Chopp M, Gautam S, Zaloga C, Zhang RL, Schmidt HHHW, Pollock JS, Förstermann U (1994) Upregulation of neuronal nitric-oxide synthase and mRNA, and selective sparing of nitric oxide synthase-containing neurons after focal cerebral ischemia in rat *Brain Research* 654: 85-95 "IF=2389" (148)

46. Xue C, Pollock JS, Schmidt HHHW, Ward SM, Sanders KM (1994) Expression of nitric oxide synthase immunoreactivity by interstitial cells of the canine proximal colon *J Auton Nerv System* 49: 1-14 "IF=1389" (74)
47. Ogilvie P, Schilling K, Billingsley ML, Schmidt HHHW (1995) Induction and variants of neuronal nitric oxide synthase type I during synaptogenesis *FASEB J* 9, 799-806 IF=6.820" (65)
48. Valtschanoff JG, Weinberg RJ, Rustioni A, Schmidt HHHW (1995) Colocalization of neuronal nitric oxide synthase with GABA in rat cuneate nucleus *J Neurocytology* 24, 237-245 IF=1.838" (15)
49. Akaike T, Weihe E, Schaefer M, Fu ZF, Zheng YM, Vogel W, Schmidt H, Koprowsky H, Dietzschold B (1995) Effect of neurotropic virus infection on neuronal and inducible nitric oxide synthase activity in rat brain *J Neurovirology* 1, 118-125 "IF=3.290" (60)
50. Schmidt W, Wolf G, Calka J, Schmidt HHHW (1995) Evidence for bidirectional changes in nitric oxide synthase activity in the rat striatum after excitotoxically (quinolinic acid) induced degeneration *Neuroscience* 67, 345-356 "IF=3456" (37)
51. Papka RE, McNeill DL, Thompson D, Schmidt HHHW (1995) Nitric oxide nerves in the uterus are parasympathetic, sensory, and contain neuropeptides *Cell Tissue Res* 279, 339-349 "IF=2.383" (42)
52. Hofmann H, Schmidt HHHW (1995) Thiol-dependence of nitric oxide synthase *Biochemistry* 34, 13443-13452 "IF=3848" (63)
53. Schmidt HHHW, Hofmann H, Schindler U, Shutenko Z, Cunningham, D, Feelisch M (1996) No NO from NO synthase *Proc Natl Acad Sci USA* 93, 13712-13717 "IF=10231" (196)
54. Papka RE, Thompson BD, Schmidt HHHW (1996) Identification of uterine-related sympathetic neurons in rat inferior mesenteric ganglion: neurotransmitter content and afferent input *J Auton Nerv Syst* 59, 51-59 "IF=1389" (20)
55. Bertini G, Savio T, Zaccheo D, Schmidt HHHW, Bentivoglio M (1996) NADPH-Diaphorase activity in brain macrophages during postnatal development in the rat *Neuroscience* 70, 287-293 "IF=3456" (10)
56. Buwalda B, Nykas C, Gast J, Luiten PG, Schmidt HHHW (1996) Aldehyde fixation differentially affects distribution of diaphorase activity but not of nitric oxide synthase immunoreactivity in rat brain *Brain Res Bull* 38, 467-473 "IF=2841" (33)
57. Kuin A, Aalders M, van der Valk MA, Frey A, Schmidt HHHW, Smets LA (1998) Renal toxicity of the neuron-blocking and mitochondriotropic agent m-iodobenzylguanidine *Cancer Chemother Pharmacol* 42, 37-45 "IF=2235" (6)
58. Zabel U, Weeger M, La M, Schmidt HHHW (1998) Human soluble guanylyl cyclase: functional expression and revised isozyme family *Biochem J* 335, 51-57 "IF=4224" (63)
59. De Vente J, Hopkins DA, Markerink-Van Ittersum M, Emson PC, Schmidt HHHW, Steinbusch HWM (1998) Distribution of nitric oxide synthase and nitric oxide-receptive, cyclic GMP-producing structures in the rat brain *Neuroscience* 87, 207-241 "IF=3456" (85)
60. Bömmel HM, Reif AJ, Fröhlich LG, Frey A, Hofmann H, Marecak DM, Groehn V, Kotsonis P, La M, Köster S, Meinecke M, Bernhardt M, Weeger M, Klingler O, Ghisla S, Prestwich GD,



- Pfleiderer W, Schmidt HHHW (1998) Anti-pterins as tools to characterize the function tetrahydrobiopterin in NO synthase J Biol Chem 273, 33142-33149 "IF=25854" (30)
61. Haberecht MF, Schmidt HHHW, Mills SL, Massey SC, Nakane M, Redburn-Johnson DA (1998) Localization of nitric oxide synthase, NADPHdiaphorase and soluble guanylyl cyclase in adult rabbit retina Visual neuroscience 15, 881-890 "IF=1566" (23)
  62. Hügel S, Neubauer S, Lie S, Ernst R, Horn M, Schmidt HHHW, Allolio B, Reincke M (1999) Multiple mechanisms are involved in the acute vasodilatory effect of 17 $\beta$ -estradiol in the isolated perfused rat heart J Cardiovascular Pharmacology 33, 852-858 "IF=1313" (9)
  63. Galle J, Zabel U, Hübner U, Hatzelmann A, Wagner B, Wanner C, Schmidt HHHW (1999) Effects of the soluble guanylyl cyclase activator, YC-1, on vascular tone, cGMP levels and phosphodiesterase activity Br J Pharmacol 127, 195-203 "IF=3611" (79)
  64. Stopper H, Möller M, Bömmel HM, Schmidt HHHW (1999) Cytotoxic versus genotoxic effects of NO Toxicology Letters 106, 59-67 "IF=2430" (8)
  65. Seeber F, Beuerle B, Schmidt HHHW (1999) Cloning and functional expression of the calmodulin gene from *Toxoplasma gondii* Mol Bioch Parasitol 99, 295-299 "IF=2733" (2)
  66. Feelisch M, Kotsonis P, Siebe J, Clement B, Schmidt HHHW (1999) The soluble guanylyl cyclase inhibitor, ODQ, is a non-selective heme protein inhibitor of NO synthase and other cytochrome P450 enzymes involved in NO donor bioactivation Molecular Pharmacology 56, 243-253 "IF=4612" (58)
  67. Zabel U, Häusler C, Weeger M, Schmidt HHHW (1999) Homodimerization of soluble guanylyl cyclase subunits J Biol Chem 274, 18149-18152 "IF=5854" (40)
  68. Hügel S, Reincke M, Strömer H, Winning J, Horn M, Dienesch C, Mora P, Schmidt HHHW, Allolio B, Neubauer S (1999) Evidence against a role of physiological concentrations of estrogen in post-myocardial infarction remodeling J Amer Coll Cardiol 34:1427-1434 "IF=3059" (8)
  69. Fröhlich LG, Kotsonis P, Traub H, Taghavi-Moghadam S, Almasoudi N, Hofman H, Strobel H, Matter H, Pfleiderer W, Schmidt HHHW (1999) Inhibition of neuronal nitric oxide synthase by 4-amino pteridine derivatives: Structure-activity relationship of antagonists of (6R)-5,6,7,8-tetrahydrobiopterin cofactor J Med Chem 42:4108-4121 "IF=4926" (18)
  70. Kotsonis P, Frey A, Fröhlich LG, Hofmann H, Reif A, Wink D, Feelisch M, Schmidt HHHW (1999) Autoinhibition of neuronal nitric oxide synthase: Distinct effects of reactive nitrogen and oxygen species on enzyme activity Biochem J 340:745-752 "IF=4224" (19)
  71. Reif A, Fröhlich LG, Kotsonis P, Frey A, Bömmel H, Wink DA, Pfleiderer W, Schmidt HHHW (1999) Tetrahydrobiopterin inhibits monomerization and is consumed during catalysis in neuronal NO synthase J Biol Chem 274, 24921-24929 "IF=5854" (51)
  72. Ruetten H, Zabel U, Schmidt HHHW (1999) Down-regulation of soluble guanylyl cyclase in young and ageing spontaneously hypertensive rats Circulation Research 85, 534-541 "IF=9.408" (77)
  73. Usunoff KG, Kharazia VN, Valtschanoff JG, Schmidt HHHW, Weinberg RJ (1999) Nitric oxide synthase-containing projections to the ventrobasal thalamus in the rat Anat Embryol 200:265-281 IF=1255 (16)

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75. Komarov A, Wink D, Feelisch, Schmidt HHHW (2000) Electron-paramagnetic resonance spectroscopy using N-methyl-D-glucosamine dithiocarbamate cannot discriminate between nitric oxide and nitroxyl: Implications for the detection of reaction products from NO synthase *Free Rad Biol Med* 28, 739-742 "IF=4971" (21)
76. Butt E, Bernhardt M, Smolenski A, Kotsonis P, Fröhlich LG, Lohmann SM, Schmidt HHHW (1999) Endothelial nitric oxide synthase (Type III) is activated and becomes calcium-independent upon phosphorylation by cyclic nucleotide-dependent protein kinases *J Biol Chem* 275, 5179-5187 "IF=5.824" (126)
77. Kotsonis P, Fröhlich LG, Shutenko ZV, Horejsi R, Pfeleiderer W, Schmidt HHHW (2000) Allosteric regulation of neuronal nitric-oxide synthase by tetrahydrobiopterin and suppression of auto-damaging superoxide *Bioch J* 346, 767-776 "IF=4224" (22)
78. Groehn V, Fröhlich L, Schmidt HHHW, Pfeleiderer W (2000) Pteridine-based photoaffinity probes for nitric oxide synthase and aromatic amino acid hydroxylases *Helv Chim Acta* 83, 2738-2750 "IF=1.650" (4)
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