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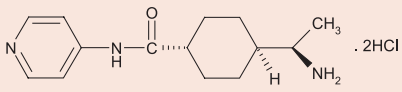

LIT: Calcium sensitization of smooth muscle mediated by a Rho-associated protein kinase in hypertension: M. Uehata, et al.; Nature **389,** 990 (1997) ▪ Molecular dissection of the Rho-associated protein kinase (p160ROCK)-regulated neurite remodeling in neuroblastoma N1E-115 cells: M. Hirose, et al.; J. Cell Biol. **141,** 1625 (1998) ▪ Signaling from Rho to the actin cytoskeleton through protein kinases ROCK and LIM-kinase: M. Maekawa, et al.; Science **285,** 895 (1999) ▪ Specificity and mechanism of action of some commonly used protein kinase inhibitors: S.P. Davies, et al.; Biochem. J. **351,** 95 (2000) ▪ Use and properties of ROCK-specific inhibitor Y-27632: S. Narumiya, et al.; Meth. Enzymol. **325,** 273 (2000) ▪ Pharmacological properties of Y-27632, a specific inhibitor of rho-associated kinases: T. Ishizaki, et al.; Mol. Pharmacol. **57,** 976 (2000) ▪ **For a comprehensive bibliography please visit our website.**

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Introduction

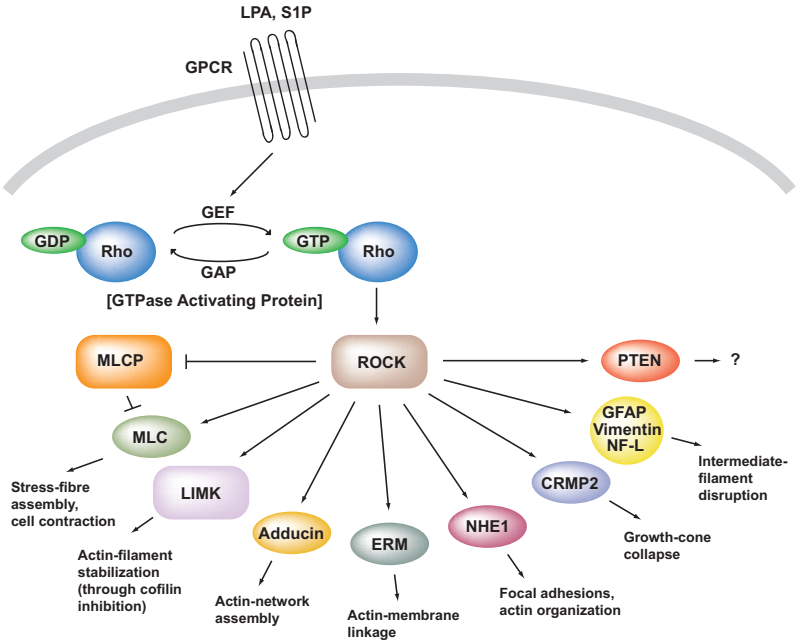

FIGURE: Targets of ROCK. Rho can be activated by guanine nucleotide exchange factors (GEFs) that are themselves activated, for example, in response to lysophosphatidic acid (LPA) or sphingosine-1-phosphate (S1P) binding to G-protein-coupled receptors (GPCRs). GTP-bound Rho subsequently activates ROCK to phosphorylate several substrates leading to various cellular responses. *Adapted from: Rocks: multifunctional kinases in cell behaviour: K. Riento & A. J. Ridley; Nat. Rev. Mol. Cell Biol. 4, 446 (2003)*

RhoGTPases constitute a subfamily of the Ras superfamily of GTPases. The three main classes of Rho GTPases are Rho, Rac and Cdc42, all of them are known to regulate actin cytoskeletal dynamics. Rho kinase (ROCK), a serine/threonine kinase, serves as a target protein for Rho (of which three isoforms RhoA, RhoB and RhoC exist) and has been initially characterized as a mediator of the formation of RhoA-induced stress fibers and focal adhesions [1, 2]. Two isoforms of ROCK have been described. ROCK1 (p160ROCK; ROKβ) and ROCK2 (ROKα) are comprised of a kinase domain at the N-terminus, followed by a coiled-coil domain containing a Rho-binding domain and a Pleckstrin-homology domain (PH). They are both important regulators of the cytoskeleton, mediating RhoA effects on stress fibre formation, smooth muscle contraction, cell adhesion, membrane ruffling, and cell motility.

ROCKs exert their biological activity by targeting downstream molecules (see Figure) such as myosin light chain (MLC) [3], MLC phosphatase (MLCP) [4] and the phosphatase and tensin homolog (PTEN) [5]. Adducin is a downstream substrate of ROCK2 [6] as well as of the collapsin response mediating protein-2 (CRMP2) [7, 8], ERM proteins

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(ezrin, radixin and moesin) [9], intermediate filament proteins such as vimentin, glial fibrillary acidic protein (GFAP) and neurofilament L protein (NF-L) [10-12]. ROCK1 targets the sodium-hydrogen exchanger NHE1 [13] and Ser/Thr kinases LIM kinases 1 and 2 (LIMK1 and LIMK2) [14, 15] which inhibit the action of cofilin [16].

ROCK1 is known to be activated by caspase-3. In a recent study, ROCK1 dependent caspase-3 activation has been shown to be coupled with the activation of PTEN and subsequent inhibition of protein kinase B (Akt) survival pathway in myocytes [17].

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Selected Latest Review Articles

Rho-kinase inhibitors show promise in pulmonary hypertension: S. A. Doggrell; Expert. Opin. Investig. Drugs **14,** 1157 (2005)

Therapeutic potential of rho-kinase inhibitors in cardiovascular diseases: Y. Hirooka & H. Shimokawa; Am. J. Cardiovasc. Drugs **5,** 31 (2005)

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Rho-kinase is an important therapeutic target in cardiovascular medicine: H. Shimokawa & A. Takeshita; Arterioscler. Thromb. Vasc. Biol. **25,** 1767 (2005)

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Rho-kinase as a drug target for the treatment of airway hyperresponsiveness in asthma: R. Gosens, et al.; Mini Rev. Med. Chem. **6,** 339 (2006)

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LIT: The effects of an intracellular calcium antagonist HA 1077 on delayed cerebral vasospasm in dogs: O. Shibuya, et al.; Acta Neurochir. **90,** 53 (1988) ▪ Vasodilator actions of HA1077 in vitro and in vivo putatively mediated by the inhibition of protein kinase: T. Asano, et al.; Br. J. Pharmacol. **98,** 1091 (1989) ▪ **For a comprehensive bibliography please visit our website.**

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LIT: Rho-kinase-mediated pathway induces enhanced myosin light chain phosphorylations in a swine model of coronary artery spasm: H. Shimokawa, et al.; Cardiovasc. Res. **43,** 1029 (1999) ▪ Hydroxyfasudil, an active metabolite of fasudil hydrochloride, relaxes the rabbit basilar artery by disinhibition of myosin light chain phosphatase: K. Nakamura, et al.; J. Cereb. Blood Flow Metab. **21,** 876 (2001) ▪ Pitavastatin enhanced BMP-2 and osteocalcin expression by inhibition of Rho-associated kinase in human osteoblasts: K. Ohnaka, et al.; BBRC **287,** 337 (2001) ▪ Antianginal effects of hydroxyfasudil, a Rho-kinase inhibitor, in a canine model of effort angina: T. Utsunomiya, et al.; Br. J. Pharmacol. **134,** 1724 (2001) ▪ **For a comprehensive bibliography please visit our website.**

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LIT: Screening for cell migration inhibitors via automated microscopy reveals a Rho-kinase inhibitor: J.C. Yarrow, et al.; Chem. Biol. **12,** 385 (2005) ▪ Scratch n'screen for inhibitors of cell migration: J. Soderholm & R. Heald; Chem. Biol. **12,** 263 (2005)

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LIT: Inhibition of rho-kinase-induced myristoylated alanine-rich C kinase substrate (MARCKS) phosphorylation in human neuronal cells by H-1152, a novel and specific Rho-kinase inhibitor: M. Ikenoya, et al.; J. Neurochem. **81,** 9 (2002) ▪ The novel and specific Rho-kinase inhibitor (S)-(+)-2-methyl-1-[(4-methyl-5-isoquinoline)sulfonyl]-homopiperazine as a probing molecule for Rho-kinase-involved pathway: Y. Sasaki, et al.; Pharmacol. Ther. **93,** 225 (2002) ▪ New aspects of neurotransmitter release and exocytosis: Rho-kinase-dependent myristoylated alanine-rich C-kinase substrate phosphorylation and regulation of neurofilament structure in neuronal cells: Y. Sasaki; J. Pharmacol. Sci. **93,** 35 (2003) ▪ Protein kinase A in complex with Rho-kinase inhibitors Y-27632, Fasudil, and H-1152P: structural basis of selectivity: C. Breitenlechner, et al.; Structure **11,** 1595 (2003) ▪ Involvement of Rho-kinase in inflammatory and neuropathic pain through phosphorylation of myristoylated alanine-rich C-kinase substrate (MARCKS): S. Tatsumi, et al.; Neuroscience **131,** 491 (2005) ▪ Rho-kinase mediates spinal nitric oxide formation by prostaglandin E2 via EP3 subtype: S. Matsumura, et al.; BBRC **338,** 550 (2005) ▪ **For a comprehensive bibliography please visit our website.**

N-(4-Pyridyl)-N′-(2,4,6-trichlorophenyl) urea

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LIT: Design and synthesis of Rho kinase inhibitors (I): A. Takami, et al.; Bioorg. Med. Chem. **12,** 2115 (2004)

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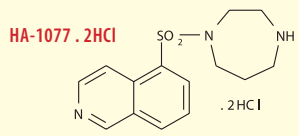

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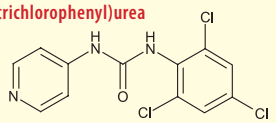

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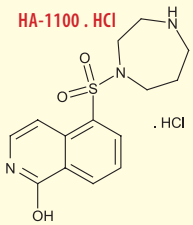

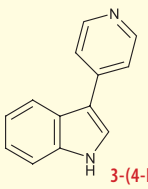

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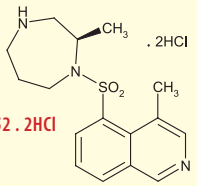

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