Table S2 | A summary of neural functions that are regulated by purinergic signalling.

Function	Reference
Calcium signalling	
astrocytes	$1 - 10$
Schwann cells	$11 - 13$
terminal (perisynaptic) Schwann cells	$14 - 16$
oligodendrocytes	$17 - 18$
optic nerve glia	19
microglia	10, 20-24
Synaptic transmission	
sensory neurons	25, 26
motor neurons	27, 28
inhibitory interneurons	29
CNS	30
hippocampus	$31 - 33$
retina	34, 35
neuromuscular junction	36, 37
stimulate neurotransmitter release	$38 - 42$
inhibit neurotransmitter release	31, 33, 43, 44
Synaptic plasticity	
Long-term potentiation	40, 45 - 48
Long-term depression	45, 49
hypothalamic synapses	50
neuromuscular junction	14, 51
hippocampus	31, 33, 43, 44
Glial regulation of synaptic transmission	
hippocampus	45, 49
retina	34, 35
hypothalamus	50
neuromuscular junction	14, 51, 52
Muscle contraction	
heart and blood vessel	53
gut and bladder	54, 27
vas deferens	55
skeletal muscle	37
glial vascular interface	$56 - 58$
Release of bioactive substances from glia	
excitatory neurotransmitters	59
inhibitory neurotransmitters	60
cytokines	$61 - 65$
growth factors	66
ATP and adenosine	8, 40, 45, 67-73
Nervous system development	
cell proliferation	13, 18, 59, 74, 75
adult neural stem cells	76

References

- 1. Porter, J. T. & McCarthy, K. D. Hippocampal astrocytes *in situ* respond to glutamate released from synaptic terminals. *J. Neurosci.* **16**, 5073–5081 (1996).
- 2. Neary, J. T., van Breemen, C., Forster, E., Norenberg, L. O. & Norenberg, M. D. ATP stimulates calcium influx in primary astrocyte cultures. *Biochem. Biophys. Res. Commun.* **157**, 1410–1416 (1988).
- 3. Pearce, B., Murphy, S., Jeremy, J., Morrow, C. & Dandona, P. ATP-evoked Ca²⁺ mobilisation and prostanoid release from astrocytes: P_2 -purinergic receptors linked to phosphoinositide hydrolysis. *J. Neurochem.* **52**, 971–977 (1989).
- 4. Kirischuk, S., Moller, T., Voitenko, N., Kettenmann, H. & Verkhratsky, A. ATP-induced cytoplasmic calcium mobilization in Bergmann glial cells. *J. Neurosci.* **15**, 7861–7871 (1995).
- 5. Guthrie, P. B. *et al.* ATP release from astrocytes mediates glial calcium waves. *J. Neurosci.* **19**, 520–528 (1999).
- 6. Cotrina, M. L. *et al.* Connexins regulate calcium signaling by controlling ATP release. *Proc. Natl Acad. Sci. USA* **95**, 15735–15740 (1998).
- 7. Hassinger, T. D. *et al.* An extracellular signaling component in propagation of astrocytic calcium waves. *Proc. Natl Acad. Sci. USA* **93**, 13268–13273 (1996).
- 8. Wang, Z., Haydon, P. G. & Yeung, E. S. Direct observation of calcium-independent intercellular ATP signaling in astrocytes. *Anal. Chem.* **72**, 2001–2007 (2000).
- 9. Newman, E. A. Propagation of intercellular calcium waves in retinal astrocytes and Müller cells. *J. Neurosci.* **21**, 1–13 (2001).
- 10. Schipke, C. G., Boucsein, C., Ohlemeyer, C., Kirchhoff, F. & Kettenmann, H. Astrocyte Ca2+ waves trigger responses in microglial cells in brain slices. *FASEB J.* **16**, 255–257 (2002).
- 11. Lyons, S. A., Morell, P. & McCarthy, K. D. Schwann cells exhibit P2Y purinergic receptors that regulate intracellular calcium and are up-regulated by cyclic AMP analogs. *J. Neurochem.* **63**, 552–560 (1994).
- 12. Mayer, C., Quasthoff, S. & Grafe, P. Differences in the sensitivity to purinergic stimulation of myelinating and non-myelinating Schwann cells in peripheral human and rat nerve. *Glia* **23**, 374–382 (1998).
- 13. Stevens, B. & Fields, R. D. Action potentials regulate Schwann cell proliferation and development. *Science* **287**, 2267–2271 (2000).
- 14. Robitaille, R. Purinergic receptors and their activation by endogenous purines at perisynaptic glial cells of the frog neuromuscular junction. *J. Neurosci.* **15**, 7121–7131 (1995).
- 15. Jahromi, B. S., Robitaille, R. & Charlton, M. P. Transmitter release increases intracellular calcium in perisynaptic Schwann cells *in situ. Neuron* **8**, 1069–1077 (1992).
- 16. Reist, N. E. & Smith, S. J. Neurally evoked calcium transients in terminal Schwann cells at the neuromuscular junction. *Proc. Natl Acad. Sci. USA* **89**, 7625–7629 (1992).
- 17. Kastritsis, C. H. & McCarthy, K. D. Oligodendroglial lineage cells express neuroligand receptors. *Glia* **8**, 106–113 (1993).
- 18. Stevens, B. *et al.* Adenosine: a neuron–glial transmitter promoting myelination in the CNS in response to action potentials. *Neuron* **36**, 855–868 (2002).
- 19. Kriegler, S. & Chiu, S. Y. Calcium signaling of glial cells along mammalian axons. *J. Neurosci.* **13**, 4229–4245 (1993).
- 20. Toescu, E. C., Moller, T., Kettenmann, H. & Verkhratsky, A. Long-term activation of capacitive Ca2+ entry in mouse microglial cells. *Neuroscience* **86**, 925–935 (1998).
- 21. Boucsein, C. *et al.* Purinergic receptors on microglia cells: functional expression in acute brain slices and modulation of microglial activation *in vitro*. *Eur. J. Neurosci.* **17**, 2267– 2276 (2003).
- 22. Light, A. R., Wu, Y., Hughen, R. W. & Guthrie, P. B. Purinergic receptors activating rapid intracellular Ca2+ increases in microglia. *Neuron Glia Biol.* **2**, 125–138 (2006).
- 23. Davalos, D. *et al.* ATP mediates rapid microglial response to local brain injury *in vivo*. *Nature Neurosci.* **8**, 752–758 (2005).
- 24. McLaron, J. G. Purinergic mediated changes in $Ca²⁺$ mobilization and functional responses in microglia; effects of low levels of ATP. *J. Neurosci. Res.* **81**, 349–356 (2005).
- 25. Holton, F. A. & Holton, P. The capillary dilator substances in dry powders of spinal roots; a possible role of adenosine triphosphate in chemical transmission from nerve endings. *J. Physiol.* **126**, 124–140 (1954).
- 26. Sawynok, J. *et al.* ATP release from dorsal spinal cord synaptosomes: characterization and neuronal origin. *Brain Res.* **610**, 32–38 (1993).
- 27. Burnstock, G., Campbell, G., Satchell, D. & Smythe, A. Evidence that adenosine triphosphate or a related nucleotide is the transmitter substance released by non-adrenergic inhibitory nerves in the gut. *Br. J. Pharmacol.* **40**, 668–688 (1970).
- 28. Burnstock, G. Do some nerve cells release more than one transmitter? *Neuroscience* **1**, 239–248 (1976).
- 29. Bowser, D. N. & Khakh, B. S. ATP excites interneurons and astrocytes to increase synaptic inhibition in neuronal networks. *J. Neurosci*. **24**, 8606–8620 (2004).
- 30. Edwards, F. A., Gibb, A. J. & Colquhoun, D. ATP receptor-mediated synaptic currents in the central nervous system. *Nature* **369**, 144–147 (1992).
- 31. Lopes, L. V., Cunha, R. A., Kull, B., Fredholm, B. B. & Ribeiro, J. A. Adenosine A_{2A} receptor facilitation of hippocampal synaptic transmission is dependent on tonic A_1 receptor inhibition. *Neuroscience* **112**, 319–329 (2002).
- 32. Rebola, N. *et al.* Adenosine A_1 and A_{2A} receptors are co-expressed in pyramidal neurons and co-localized in glutamatergic nerve terminals of the rat hippocampus. *Neuroscience* **133**, 79–83 (2005).
- 33. Duner-Engstrom, M. & Fredholm, B. B. Evidence that prejunctional adenosine receptors regulating acetylcholine release from rat hippocampal slices are linked to an N-ethylmaleimide-sensitive G-protein, but not to adenylate cyclase or dihydropyridinesensitive Ca2+ channels. *Acta Physiol. Scand.* **134**, 119–126 (1988).
- 34. Newman, E. A. Calcium increases in retinal glial cells evoked by light-induced neuronal activity. *J. Neurosci.* **25**, 5502–5510 (2005).
- 35. Newman, E. A. Glial cell inhibition of neurons by release of ATP. *J. Neurosci.* **23**, 1659– 1666 (2003).
- 36. Redman, R. S. & Silinsky, E. M. ATP release together with acetylcholine as the mediator of neuromuscular depression at frog motor nerve endings. *J. Physiol. (Lond.)* **477**, 117–127 (1994).
- 37. Kolb, H. A. & Wakelam, M. J. Transmitter-like action of ATP on patched membranes of cultured myoblasts and myotubes. *Nature* **303**, 621–623 (1983).
- 38. Choi, R. C. *et al.* ATP acts via P2Y1 receptors to stimulate acetylcholinesterase and acetylcholine receptor expression: transduction and transcription control. *J. Neurosci.* **23**, 4445–4456 (2003).
- 39. Rodrigues, R. J., Almeida, T., Richardson, P. J., Oliveira, C. R. & Cunha, R. A. Dual presynaptic control by ATP of glutamate release via facilitatory P_2X_1 , $P_2X_{2/3}$, and P_2X_3 and inhibitory P_2Y_1 , P_2Y_2 , and/or P_2Y_4 receptors in the rat hippocampus. *J. Neurosci.* **25**, 6286– 6295 (2005).
- 40. Almeida, T., Rodrigues, R. J., de Mendonca, A., Ribeiro, J. A. & Cunha, R. A. Purinergic P_2 receptors trigger adenosine release leading to adenosine A_{2A} receptor activation and facilitation of long-term potentiation in rat hippocampal slices. *Neuroscience* **122**, 111–121 (2003).
- 41. Cunha, R. A., Johansson, B., Fredholm, B. B., Ribeiro, J. A. & Sebastiao, A. M. Adenosine A_{2A} receptors stimulate acetylcholine release from nerve terminals of the rat hippocampus. *Neurosci. Lett.* **196**, 41–44 (1995).
- 42. Cunha, R. A. & Ribeiro, J. A. Purinergic modulation of [³H]GABA release from rat hippocampal nerve terminals. *Neuropharmacology* **39**, 1156–1167 (2000).
- 43. Fredholm, B. B. Adenosine A_1 -receptor-mediated inhibition of evoked acetylcholine release in the rat hippocampus does not depend on protein kinase C. *Acta Physiol. Scand.* **140**, 245–255 (1990).
- 44. Masino, S. A. *et al.* Modulation of hippocampal glutamatergic transmission by ATP is dependent on adenosine A1 receptors. *J. Pharmacol. Exp. Ther.* **303**, 356–363 (2002).
- 45. Pascual, O. *et al.* Astrocytic purinergic signaling coordinates synaptic networks. *Science* **310**, 113–116 (2005).
- 46. Wieraszko, A. & Ehrlich, Y. H. On the role of extracellular ATP in the induction of longterm potentiation in the hippocampus. *J. Neurochem.* **63**, 1731–1738 (1994).
- 47. Diogenes, M. J., Fernandes, C. C., Sebastiao, A. M. & Ribeiro, J. A. Activation of adenosine A_{2A} receptor facilitates brain-derived neurotrophic factor modulation of synaptic transmission in hippocampal slices. *J. Neurosci.* **24**, 2905–2913 (2004).
- 48. Kukley, M., Schwan, M., Fredholm, B. B. & Dietrich, D. The role of extracellular adenosine in regulating mossy fiber synaptic plasticity. *J. Neurosci.* **25**, 2832–2837 (2005).
- 49. Zhang, J. M. *et al.* ATP released by astrocytes mediates glutamatergic activitydependent heterosynaptic suppression. *Neuron* **40**, 971–982 (2003).
- 50. Gordon, G. R. *et al.* Norepinephrine triggers release of glial ATP to increase postsynaptic efficacy. *Nature Neurosci.* **8**, 1078–1086 (2005).
- 51. Rochon, D., Rousse, I. & Robitaille, R. Synapse–glia interactions at the mammalian neuromuscular junction. *J. Neurosci.* **21**, 3819–3829 (2001).
- 52. Robitaille, R. Modulation of synaptic efficacy and synaptic depression by glial cells at the frog neuromuscular junction. *Neuron* **21**, 847–855 (1998).
- 53. Drury, A. N. & Szent-Györgyi, A. The physiological activity of adenine compounds with special reference to their action upon the mammalian heart. *J. Physiol. (Lond.)* **68**, 213–237 (1929).
- 54. Burnstock, G. Purinergic nerves. *Pharmacol. Rev.* **24**, 509–581 (1972).
- 55. Vizi, E. S., Sperlagh, B. & Baranyi, M. Evidence that ATP released from the postsynaptic site by noradrenaline is involved in mechanical response of guinea-pig vas deferens: cascade transmission. *Neuroscience* **50**, 455–465 (1992).
- 56. Grafstein, B., Liu, S., Cotrina, M. L., Goldman, S. A. & Nedergaard, M. Meningeal cells can communicate with astrocytes by calcium signaling. *Ann. Neurol.* **47**, 18–25 (2000).
- 57. Chizh, B. A. & Illes, P. P2X receptors and nociception. *Pharmacol. Rev.* **53**, 553–568 (2001).
- 58. Zonta, M. *et al.* Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nature Neurosci.* **6**, 43–50 (2003).
- 59. Araque, A., Sanzgiri R. P., Parpura, V. & Haydon, P. G. Calcium elevation in astrocytes causes an NMDA receptor-dependent increase in the frequency of miniature synaptic currents in cultured hippocampal neurons. *J. Neurosci.* **18**, 6822–6829 (1998).
- 60. Wang, C. M., Chang, Y. Y., Kuo, J. S. & Sun, S. H. Activation of P_2X_7 receptors induced [3 H]GABA release from the RBA-2 type-2 astrocyte cell line through a Cl⁻/HCO₃⁻-dependent mechanism. *Glia* **37**, 8–18 (2002).
- 61. Hide, I. *et al.* Extracellular ATP triggers tumor necrosis factor-α release from rat microglia. *J. Neurochem.* **75**, 965–972 (2000).
- 62. Ishibashi, T. *et al.* Astrocytes promote myelination in response to electrical impulses. *Neuron* **49**, 823–832 (2006).
- 63. Neary, J. T., Kang, Y., Willoughby, K. A. & Ellis, E. F. Activation of extracellular signalregulated kinase by stretch-induced injury in astrocytes involves extracellular ATP and $P₂$ purinergic receptors. *J. Neurosci.* **23**, 2348–2356 (2003).
- 64. Kucher, B. M. & Neary, J. T. Bi-functional effects of $ATP/P₂$ receptor activation on tumor necrosis factor-α release in lipopolysaccharide-stimulated astrocytes. *J. Neurochem.* **92**, 525–535 (2005).
- 65. Sanz, J. M. & DiVirgilio, F. Kinetics and mechanism of ATP-dependent IL-1 β release from microglial cells. *J. Immunol.* **164**, 4893–4898 (2000).
- 66. Ciccarelli, R. *et al.* Activation of A1 adenosine or mGlur3 metabotropic glutamate receptors enhances the release of nerve growth factor and S-100 β protein from cultured astrocytes. *Glia* **27**, 275–281 (1999).
- 67. Lazarowski, E. R., Boucher, R. C. & Harden, T. K. Mechanisms of release of nucleotides and integration of their action as P_2X - and P_2Y -receptor activating molecules. *Mol. Pharmacol.* **64**, 785–795 (2003).
- 68. Maienschein, V., Marxen, M., Volknandt, W. & Zimmermann, H. A plethora of presynaptic proteins associated with ATP-storing organelles in cultured astrocytes. *Glia* **26**, 233–244 (1999).
- 69. Coco, S. *et al.* Storage and release of ATP from astrocytes in culture. *J. Biol. Chem.* **278**, 1354–1362 (2003).
- 70. Suadicani, S. O. Brosnan, C. F. & Scemes, E. P2X₇ receptor mediate ATP release and amplification of astrocytic intercellular calcium signaling. *J. Neurosci.* **26**, 1378–1385 (2003).
- 71. Arcuino, G. *et al.* Intercellular calcium signaling mediated by point-source burst release of ATP. *Proc. Natl Acad. Sci. U S A* **99**, 9840–9845 (2002).
- 72. Darby, M., Kuzmiski, J. B., Panenka, W., Feighan, D. & MacVicar, B. A. ATP release from astrocytes during swelling activates chloride channels. *J. Neurophysiol.* **89**, 1870–1877 (2003).
- 73. Cunha, R. A., Vizi, E. S., Ribeiro, J. A. & Sebastiao, A. M. Preferential release of ATP and its extracellular catabolism as a source of adenosine upon high- but not low-frequency stimulation of rat hippocampal slices. *J. Neurochem.* **67**, 2180–2187 (1996).
- 74. Stevens, B. *et al.* Adenosine: an activity-dependent axonal signal regulating MAP kinase and proliferation in developing Schwann cells. *Neuron Glia Biol.***1**, 23–34 (2004).
- Neary, J. T., Whittemore, S. R., Zhu, O. & Norenberg, M. D. Synergistic activation of DNA synthesis in astrocytes by fibroblast growth factors and extracellular ATP. *J. Neurochem*. **63**, 490–494 (1994).
- 76. Mishra, S. K. Extracellular nucleotide signaling in adult neural stem cells: synergism with growth factor-mediated cellular proliferation. *Development* **133**, 675–684 (2006).
- 77. Abbracchio, M. P. *et al.* Effects of ATP analogues and basic fibroblast growth factor on astroglial cell differentiation in primary cultures of rat striatum. *Int. J. Dev. Neurosci.* **13**, 685– 693 (1995).
- 78. Arthur, D. B., Akassoglou, K. & Insel, P. A. P_2Y_2 receptor activates nerve growth factor/TrkA signaling to enhance neuronal differentiation. *Proc. Natl Acad. Sci. USA* **102**, 19138–19143 (2005).
- 79. Ryten, M., Hoebertz, A. & Burnstock, G. Sequential expression of three receptor subtypes for extracellular ATP in developing rat skeletal muscle. *Dev. Dyn.* **221**, 331–341 (2001).
- 80. Ryten, M., Dunn, P. M., Neary, J. T. & Burnstock, G. ATP regulates the differentiation of mammalian skeletal muscle by activation of a P₂X₅ receptor on satellite cells. *J. Cell Biol.* **158**, 345–355 (2002).
- 81. Kuperman, A. S., Volpert, W. A. & Okamoto, M. Release of adenine nucleotide from nerve axons. *Nature* **204**, 1000–1001 (1964).
- 82. Neary, J. T. Trophic actions of extracellular ATP on astrocytes, synergistic interactions with fibroblast growth factors and underlying signal transduction mechanisms. *Ciba Found. Symp*. **198**, 130–139 (1996).
- 83. Pinto-Duarte, A., Coelho, J. E., Cunha, R. A., Ribeiro, J. A. & Sebastiao, A. M. Adenosine A_{2A} receptors control the extracellular levels of adenosine through modulation of nucleoside transporters activity in the rat hippocampus. *J. Neurochem.* **93**, 595–604 (2005).
- 84. Lee, F. S. & Chao, M. V. Activation of Trk neurotrophin receptors in the absence of neurotrophins. *Proc. Natl Acad. Sci. USA* **98**, 3555–3560 (2001).
- 85. Abbracchio, M. P. *et al. Trophic roles of P2-purinoceptors in central nervous system astroglial cells* (eds Chadwick, D. J. and Goode, J.) Ciba Foundation Symposium No. 198, 142–148 (John Wiley and Sons, Chichester, 1996).
- 86. Stevens, B. *Cross-talk between growth factor and purinergic signaling regulates Schwann cell proliferation* (eds Chadwick, D. J. and Goode, J.) Novartis Symposium Foundation No. 276, 162–180 (2006).
- 87. Hindley, S., Herman, M. A. & Rathbone, M. P. Stimulation of reactive astrogliosis *in vivo* by extracellular adenosine diphosphate or an adenosine A2 receptor agonist. *J. Neurosci. Res.* **38**, 399–406 (1994).
- 88. Brambilla, R., Cottini, L., Fumagalli, M., Ceruti, S. & Abbracchio, M. P. Blockade of A_{2A} adenosine receptors prevents basic fibroblast growth factor-induced reactive astrogliosis in rat striatal primary astrocytes. *Glia* **43**, 190–194 (2003).
- 89. Brambilla, R. *et al.* Identification of a novel P₂ receptor associated with cyclooxygenase-2 induction and reactive astrogliosis. *Drug Dev. Res.* **53**, 148–157 (2001).
- 90. Burnstock, G.in: *Current Topics in Membranes* Vol. 54 (ed. Schwiebert, E. M.) 307–368 (Academic, San Diego, 2003).
- 91. Fields, R. D. *Purinergic Signaling in Neuron–Glia Interactions* (eds Chadwick, D. J. and Goode, J.) Novartis Foundation Symposium No. 276 (John Wiley & Sons, New York, 2006).
- 92. Zimmermann, H. Signalling via ATP in the nervous system. *Trends Neurosci.* **17**, 420– 426 (1994).
- 93. Fowler, J. C., Gervitz, L. M., Hamilton, M. E. & Walker, J. A. Systemic hypoxia and the depression of synaptic transmission in rat hippocampus after carotid artery occlusion. *J. Physiol. (Lond.)* **550**, 961–972 (2003).
- 94. Tsuda, M. *et al.* P₂X₄ receptors induced in spinal microglia gate tactile allodynia after nerve injury. *Nature* **424**, 778–783 (2003).
- 95. Kaya, N., Tanaka, S. & Koike, T. ATP selectively suppresses the synthesis of the inflammatory protein microglial response factor (MRF)-1 through Ca²⁺ influx via P_2X_7 receptors in cultured microglia. *Brain Res.* **952**, 86–97 (2002).
- 96. Jacobson, K. A. & Gao, Z. G. Adenosine receptors as therapeutic targets. *Nature Rev. Drug Discov.* **5**, 247–264 (2006).
- 97. Hauser, R. A. & Schwarzschild, M. A. Adenosine A_{2A} receptor antagonists for Parkinson's disease: rationale, therapeutic potential and clinical experience. *Drugs Aging* **22**, 471–482 (2005).
- 98. Parvathenani, L. K. *et al. P₂X₇* mediates superoxide production in primary microglia and is up-regulated in a transgenic mouse model of Alzheimer's disease. *J. Biol. Chem.* **278**, 13309–13317 (2003).
- 99. Malva, J. O., Silva, A. P. & Cunha, R. A. Presynaptic modulation controlling neuronal excitability and epileptogenesis: role of kainate, adenosine and neuropeptide Y receptors. *Neurochem. Res.* **28**, 1501–1515 (2003).
- 100. Tian, G. F. *et al.* An astrocytic basis of epilepsy. *Nature Med.* **11**, 973–981 (2005).
- 101. Burnstock, G. *Purinergic Signalling An Overview* (eds Chadwick, D. J. and Goode, J.) Novartis Foundation Symposium No. 276, 26–53 (John Wiley & Sons, New York, 2006).
- 102. Burnstock, G. & Knight, G. E. Cellular distribution and functions of P_2 receptor subtypes in different systems. *Int. Rev. Cytol.* **240**, 31–304 (2004).