Chapter 29
Anatomical Distribution of Nucleoside System in the Human Brain and Implications for Therapy

Zsolt Kovács and Arpád Dobolyi

Abstract Nucleosides have a wide range of physiological and pathophysiological roles in the human brain as modulators of a variety of neural functions. For example, adenosine, inosine, guanosine, and uridine participate in the mechanisms underlying memory, cognition, sleep, pain, depression, schizophrenia, epilepsy, Alzheimer's disease, Huntington's disease, and Parkinson's disease. Consequently, increasing attention is now being given to the specific role of nucleosides in physiological and pathological processes in the human brain. Different elements of nucleoside system, including nucleoside concentrations, metabolic enzyme activity, and expression of nucleoside transporters and receptors, may be changed under normal and pathological conditions. The alterations suggest that interlinked elements of the nucleoside system are functioning in a tightly concerted manner.

Nucleoside levels, activity of nucleoside metabolic enzymes, and expression of nucleoside transporters and receptors are unevenly distributed in the brain, suggesting that nucleosides have different roles in functionally distinct human brain areas. The aim of this chapter is to summarize our present knowledge of the anatomical distribution of nucleoside system in the human brain, placing emphasis on potential therapeutic pharmacological strategies.

Keywords Nucleosides • Anatomical distribution of nucleoside system • Human brain diseases and therapy

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Abbreviations

5′NT	5′-Nucleotidases
A_1 receptor/A_{2A} receptor/ A_{2B} receptor/A_3 receptor	$A_1R/A_{2A}R/A_{2B}R/A_3R$ subtype of adenosine receptors
AC	Adenylate cyclase
ADA	Adenosine deaminase
Ade	Adenine
ADK	Adenosine kinase
Ado	Adenosine
AMP	Adenosine monophosphate
CDP-choline	Cytidine diphosphocholine
cN	Cytoplasmic 5′-nucleotidases
CNS	Central nervous system
CNT transporters	Concentrative nucleoside transporters
CNT1/CNT2/CNT3 transporters	CNT1/CNT2/CNT3 subtype of concentrative nucleoside transporters
Cyd	Cytidine
EC	Extracellular
ENT transporters	Equilibrative nucleoside transporters
ENT1/ENT2/ENT3/ENT4 transporters	ENT1/ENT2/ENT3/ENT4 subtype of equilibrative nucleoside transporters
“es” nucleoside transporters	Equilibrative, NBTI sensitive type of ENT transporters
GABA	γ-Aminobutyric acid
GDA	Guanine deaminase
GMP	Guanosine monophosphate
Gn	Guanine
Guo	Guanosine
Hyp	Hypoxanthine
IMP	Inosine monophosphate
Ino	Inosine
NBTI	*S*-(4-nitrobenzyl)-6-thioinosine
PLC	Phospholipase C
PNP	Purine nucleoside phosphorylase
Urd	Uridine
Xn	Xanthine

29.1 Introduction

Nucleosides such as adenosine (Ado), guanosine (Guo), inosine (Ino), and uridine (Urd) have a role in the regulation of neuronal and glial functions in the brain (Burnstock et al. 2011; Dobolyi et al. 2011; Fields and Burnstock 2006; Haskó et al. 2004; Schmidt et al. 2007). In addition, nucleosides participate in physiological and pathophysiological processes in the brain, such as the regulation of sleep and memory, epilepsy, Parkinson's disease, and Alzheimer's disease (Dobolyi et al. 2011; Huang et al. 2011; Lopes et al. 2011; Sperlágh and Vizi 2011). Increasingly, nucleoside derivatives and uptake or metabolic inhibitors are being used in clinical or preclinical drug development for the treatment of different diseases, ranging from viral infections to neurodegenerative disorders (Boison 2011; Lopes et al. 2011; Parkinson et al. 2011).

Regional differences occur in the nucleoside system of the human central nervous system (CNS). Nucleoside levels, metabolic enzymes, transporters, and receptors are unevenly distributed in the human brain (Baldwin et al. 2005; Barnes et al. 2006; Dawson 1971; Fredholm et al. 2001; Jennings et al. 2001; Kovács et al. 1998, 2010a; Nagata et al. 1984; Norstrand et al. 1984; Norstrand and Glantz 1980; Pennycooke et al. 2001; Phillips and Newsholme 1979; Ritzel et al. 2001). In addition, nucleoside concentrations are dependent on age and gender (Kovács et al. 2010b). These results suggest region-, age-, and gender-dependent functions of nucleosides in the human brain. Correlations have been observed between the (1) *S*-(4-nitrobenzyl)-6-thioinosine (NBTI) binding site and the density of adenosine deaminase (ADA) immunoreactive neurons (Geiger and Nagy 1986), (2) regional differences in nucleoside levels and the nucleoside metabolic enzyme activities and distribution of adenosine receptors (Kovács et al. 2010a), (3) ENT1 subtype of equilibrative nucleoside transporters (ENT1) and A_1 adenosine receptor subtype (A_1R) density (Jennings et al. 2001), and (4) A_1R density and 5′-nucleotidase (5′NTs) levels (Fastbom et al. 1987). Interactions have also been observed between ADA and A_1Rs, resulting in the facilitation of agonist binding to A_1Rs and the enhancement of receptor functionality in the human caudate nucleus (Gracia et al. 2008). These results strengthen the hypothesis that the so-called "purinome" groups nucleoside and nucleotide receptors, transporters, metabolic enzymes and ligands together to organize purinergic signaling (Kovács and Dobolyi 2011; Volonté and D'Ambrosi 2009). Complex anatomical, biochemical, and pharmacological analyses of the purinome are necessary to understand the functions of nucleoside system and to develop novel and safe drugs to treat various CNS diseases.

The aim of this chapter is to summarize the anatomical distribution of the nucleoside system in the human brain and to examine their potential for the development of pharmacological therapies. We focus on four nucleosides, Ado, Ino, Guo, and Urd. The available knowledge regarding the physiological and/or pathophysiological role of other nucleosides in the human brain is too limited for comprehensive evaluation. We briefly summarize some relevant features of the brain nucleoside system. Then we describe the anatomical distribution of nucleoside levels, metabolic enzymes, transporters, and receptors. Finally, we discuss their potential as targets of pharmacological therapeutics.

29.2 Nucleosides in the Human Brain: Metabolism, Transporters, and Receptors

29.2.1 Metabolism

Ribonucleic acids (RNA) and deoxyribonucleic acids (DNA) are synthesized from nucleotides that are composed of nucleosides and phosphate moieties. Nucleosides contain purine or pyrimidine bases connected to a pentose moiety. The major purine ribonucleosides are Ado, Guo, Ino, while the major pyrimidine ribonucleosides are cytidine (Cyd), Urd, and thymidine (Thd) (Linden and Rosin 2006). Nucleosides are synthesized de novo in the liver and can be partly obtained from food. They are transported into the brain and metabolized to their corresponding nucleotides. De novo synthesis of nucleosides in the adult brain is limited. Therefore, a salvage mechanism in the brain preserves the purine and pyrimidine nucleosides and bases. The main precursors of nucleotides in the brain are Ado, adenine (Ade), hypoxanthine (Hyp), guanine (Gn), Urd, and Cyd. To maintain the synthesis of ribo- and deoxyribonucleotides, hypoxanthine phosphoribosyltransferase (HGPRT; hypoxanthine-guanine phosphoribosyltransferase) catalyzes the conversion of Hyp-inosine monophosphate (IMP) and Gn-guanosine monophosphate (GMP; Fig. 29.1). Adenosine kinase (ADK) converts Ado to adenosine monophosphate (AMP), but Ado can also be metabolized to IMP in salvage reactions. Ade is metabolized to AMP by the adenine phosphoribosyltransferase (APRT) salvage enzyme. Cytidine deaminase (CDA) and uridine-cytidine kinase (UCK) salvage Cyd and Urd (Ipata et al. 2011).

The degradation pathway of adenine nucleotides in the brain can convert AMP to IMP-Ino-Hyp or Ado-Ino-Hyp (Fig. 29.1). These metabolic steps are catalyzed by cytoplasmic 5′-nucleotidases (cN, 5′NT), AMP deaminase (AMPDA), ADA, and purine nucleoside phosphorylase (PNP). *S*-adenosylhomocysteine (SAH) can be converted to Ado by adenosylhomocysteinase (SAHH, *S*-adenosylhomocysteine hydrolase). The main route of guanine-ribonucleotide catabolism is the GMP-Guo-Gn-xanthine (Xn) pathway catalyzed by cN, PNP, and guanine deaminase

Fig. 29.1 (continued) deaminase; I: Nucleoside transporters; II: ATP channels and transporters; III: K^+ channels; IV: Ca^{2+}-channels; A_1, A_{2A}, A_{2B} and A_3, A_4 Adenosine receptors types; *AC* Adenylate cyclase; *ADAi* Adenosine deaminase inhibitors; *Ade* Adenine; *AdeR* Adenine receptor; *ADKi* Adenosine kinase inhibitors; *Ado* Adenosine; *ADP* Adenosine diphosphate; *AMP* Adenosine monophosphate; *ATi* Adenosine transporter inhibitors; *ATP* Adenosine triphosphate; *cAMP* Cyclic adenosine monophosphate; *DAG* Diacylglycerol; G_i, G_0, G_s, G_q, G_{olf}: G-proteins (f.e. G_i: Inhibitory, G_s: Stimulatory); *GMP* Guanosine monophosphate; *Gn* Guanine; *GTP* Guanosine triphosphate; *Guo* Guanosine; *GuoR* Guo receptor; *Hyp* Hypoxanthine; *IMP* Inosine monophosphate; *Ino* Inosine; IP_3 Inositol 1,4,5-triphosphate; *MAPK* Mitogen-activated protein kinase; *MTA* 5′-deoxy-5′-methylthioadenosine; *PIP2* Phosphatidylinositol bisphosphate; *PKA* Protein kinase A; *PKC* Protein kinase C; *PLC* Phospholipase C; *SAH S*-adenosylhomocysteine; *sNUC* Synthetic nucleosides/nucleoside analogues; *UA* Uric acid; *UMP* Uridine monophosphate; *Ura* Uracil; *Urd* Uridine; *UrdR* Urd receptor; *UTP* Uridine triphosphate; *Xn* Xanthine; *XOi* Xanthine oxidase inhibitors

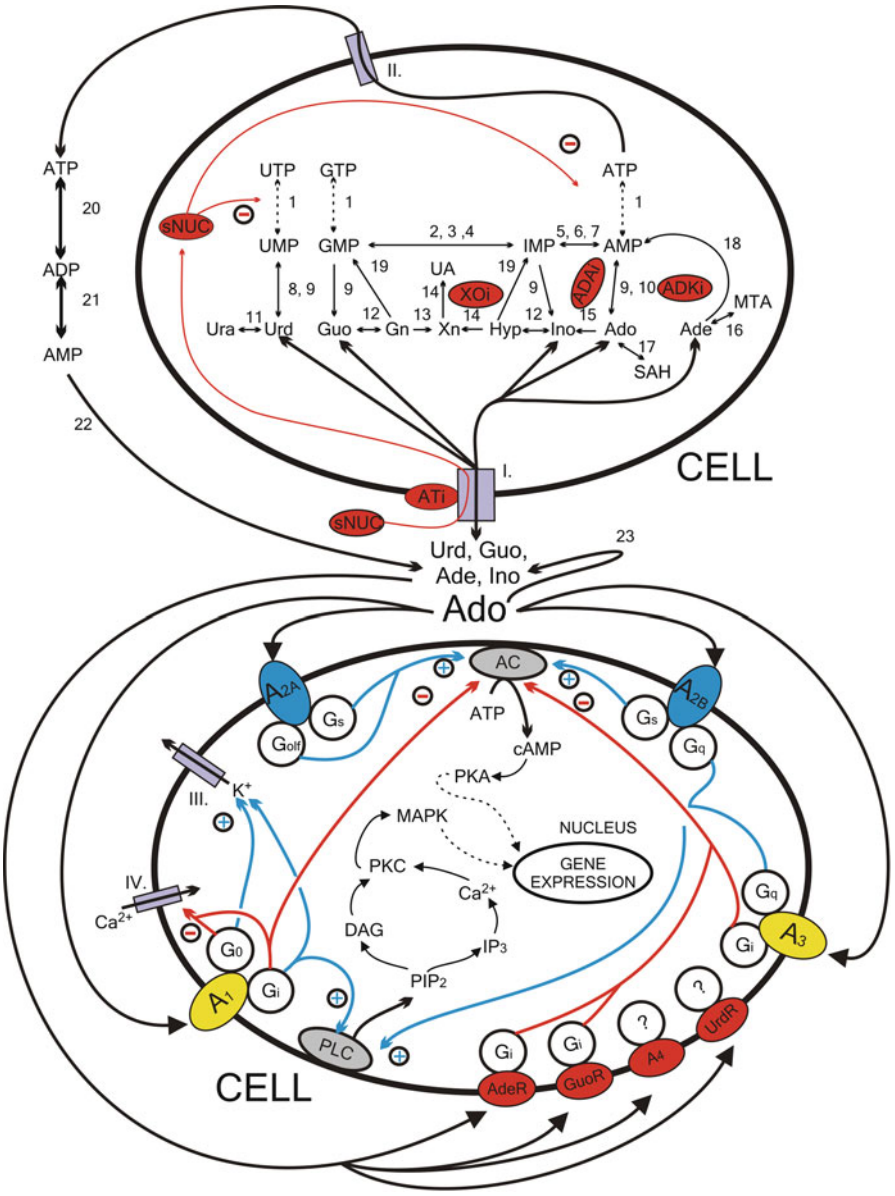

Fig. 29.1 Nucleoside production, transport and receptor signaling. *Abbreviations*: 1: Nucleoside mono- and diphosphate kinases and nucleoside di- and triphosphate phosphatases; 2: *GMPR* GMP reductase; 3: *GMPS* GMP synthetase; 4: *IMPDH* IMP dehydrogenase; 5: *AMPDA* AMP deaminase; 6: *ASL* Adenylosuccinate lyase; 7: *ASS* Adenylosuccinate synthetase; 8: *UCK* Uridine-cytidine kinase; 9: *5′NT* 5′-Nucleotidase; 10: *ADK* Adenosine kinase; 11: *UP* Uridine phosphorylase; 12: *PNP* Purine nucleoside phosphorylase; 13: *GDA* Guanine deaminase; 14: *XO* Xanthine oxidase; 15: *ADA* Adenosine deaminase; 16: *MTAP* 5′-deoxy-5′-methylthioadenosine phosphorylase; 17: *SAHH* S-adenosylhomocysteine hydrolase; 18: *APRT* Adenine phosphoribosyltransferase; 19: *HGPRT* Hypoxanthine phosphoribosyltransferase (hypoxanthine-guanine phosphoribosyltransferase); 20: ecto-ATPase; 21: ecto-ADPase; 22: *ecto-5′NT* ecto-5′-nucleotidase (eN); 23: *ecto-ADA* ecto-adenosine

(GDA; Fig. 29.1). In the final step of purine catabolism in the human brain, Xn is converted to uric acid (UA) by xanthine oxidase (XO). The following enzymes regulate the extracellular (EC) Ado concentration: ecto-5′-nucleotidase (eN), ecto-adenosine kinase (ecto-ADK), and ecto-adenosine deaminase (ecto-ADA) (Fernández et al. 2010; Firestein et al. 1999; Ipata et al. 2011; Yegutkin 2008; Zimmermann 1996) (Fig. 29.1).

29.2.2 Transporters

Nucleosides are transported into and released from brain cells via nucleoside transporters (Fig. 29.1). Two types of nucleoside transporters are expressed in the human brain. The equilibrative nucleoside transporter family (ENT transporters; bidirectional facilitated diffusion) contains four ENT transporter types: ENT1–ENT4. NBTI partially inhibits ENTs at the nM concentration range ("es": equilibrative, NBTI sensitive type of ENTs, e.g., ENT1), whereas NBTI insensitive transporters are inhibited by NBTI only at the μM concentration range ("ei": equilibrative, NBTI insensitive type of ENTs, e.g., ENT2). The concentrative nucleoside transporter family (CNT transporters; unidirectional, sodium-dependent) includes six CNT transporter types (N1–N6) that are classified based on the types of nucleosides transported and sodium transport coupling (Baldwin et al. 2005; Barnes et al. 2006; Jennings et al. 2001; Parkinson et al. 2011; Pennycooke et al. 2001; Ritzel et al. 2001).

29.2.3 Receptors

All four known adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3: also known as P1 receptors) have been identified in the human brain (Fredholm et al. 2001; Jennings et al. 2001). Adenosine receptors are G-protein-coupled receptors (GPCR; Fig. 29.1). A_1Rs couple to "inhibitory" G-proteins (G_i and G_0) and inhibit adenylate cyclase (AC). A_{2A}Rs and A_{2B}Rs, however, stimulate AC using "stimulatory" G-proteins (G_S). A_{2A}Rs may also activate AC via G_{olf}-proteins. Similar to A_1Rs, A_3Rs inhibit AC by coupling with G_i-proteins. G_q proteins can couple to A_{2B} and A_3Rs and stimulate phospholipase C (PLC) activity. A_1Rs can also stimulate PLC and modulate the activity of K^+ and Ca^{2+} channels. In addition, the existence of yet unidentified nucleoside receptors cannot be excluded. For example, a novel subtype of adenosine receptors (A_4) has been proposed based on electrophysiological and pharmacological criteria in the brain (Cornfield et al. 1992; Luthin and Linden 1995; Tucker and Linden 1993). It is also conceivable that Urd, Guo, and Ade have their own receptors (UrdR, GuoR, AdeR, respectively; Fig. 29.1) that are used to execute certain functions in the nervous system (Bender et al. 2002; Borrmann et al. 2009; Kimura et al. 2001; Schulte and Fredholm 2003; Traversa et al. 2002).

29.3 Anatomical Distribution of the Nucleoside System in the Human Brain

29.3.1 Distribution of Nucleoside Levels

The concentration of nucleotide triphosphates, such as adenosine triphosphate (ATP), guanosine triphosphate (GTP), uridine triphosphate (UTP), and cytidine triphosphate (CTP), are 2–3 orders of magnitude higher (0.2–5 mM) in the human brain than that of nucleosides are. Consequently, the degradation of nucleotide triphosphates (Fig. 29.1) may increase the levels of corresponding nucleosides over baseline concentrations. For example, a 5–60 min period of ischemia was found to cause rapid degradation of nucleotide triphosphates and increase the concentrations of nucleosides and their metabolites (Ado, Guo, Ino, Hyp, and Xn) by 2–150 times that of baseline (Berne et al. 1974; Bjerring et al. 2010; Eells and Spector 1983; Hagberg et al. 1987; Kovács et al. 2010a; Melani et al. 2003; Traut 1994).

Both animal and human experiments have determined that nucleoside concentrations are unevenly distributed in different brain areas (Kékesi et al. 2006; Kovács et al. 2010a, 2011). Kovács and colleagues (Kovács et al. 2005) developed an extrapolation method that allows realistic estimates of the in vivo nucleoside levels from postmortem frozen and microwave-treated brain bank samples. Using this method, a nucleoside map of the human brain, consisting of 61 brain and 4 spinal cord areas, was constructed. High Ado (15.9–23.9 pmol/mg), Urd (44.1–66.2 pmol/mg), Ino (107.7–161.5 pmol/mg), and Guo (17.7–26.4 pmol/mg) concentrations were observed in several regions, including the cochlear nuclei, vestibular nuclei, cerebellar cortex, supraoptic nucleus, flocculonodular lobe, spinal trigeminal nucleus, temporal and occipital cortices, caudate nucleus, nucleus basalis, medial geniculate body, amygdala, spinal central gray, and ventral horn of the spinal cord (Table 29.1). The lowest concentrations of Ado (1.4–7.9 pmol/mg), Urd (15.7–22.0 pmol/mg), Ino (29.8–53.8 pmol/mg), and Guo (4.1–8.8 pmol/mg) were measured in the entorhinal cortex, septum, habenula, zona incerta, substantia nigra, locus coeruleus, preoptic area, pulvinar, and inferior colliculus (Table 29.1). Nucleoside metabolites such as Hyp, Xn, and uracil/Ura, (Fig. 29.1) were also unevenly distributed in the human brain (Kovács et al. 2010a).

Age and gender may modulate nucleoside expression. For example, the levels of Ino and Ado in the frontal cortex increase with age. Urd, Ino, and Guo concentrations are higher in the frontal cortex and white matter of middle-aged women when compared to middle-aged men, whereas Ado levels are lower in the frontal cortex of both middle-aged and elderly women when compared to men (Kovács et al. 2010b). These results suggest that the nucleoside microenvironment in the human brain may be an important factor in the aging processes and nucleosides might play a part in the reduced vulnerability of female brains to excitotoxic insults (Kovács et al. 2010b).

Table 29.1 Levels of nucleosides, activity of some nucleoside metabolizing enzymes, and relative density of nucleoside transporters and adenosine receptors in the human CNS

Anatomical distribution of nucleoside system	
Nucleosides in the CNS	
Nucleosides	*Nucleoside levels (pmol/mg wet weight)*
Ado	High (15.9–23.9): cochlear nuclei, vestibular nuclei, cerebellar cortex, supraoptic nucleus, flocculonodular lobe
	Intermediate (8.0–15.8): spinal cord (ventral and dorsal horn)$^{+}$, amygdala^{+}, temporal^{+}, and prefrontal cortex^{+}, caudate nucleus^{+}, mediodorsal thalamic nucleus^{+}
	Low (1.4–7.9): frontal, somatosensory, cingulate, and entorhinal cortex; hippocampus, nuclei of diagonal band, septum, globus pallidus externa, ventral lateral nucleus, habenula, pulvinar, zona incerta, preoptic area, paraventricular nucleus, dorsomedial nucleus (hypothalamus), lateral hypothalamic area, substantia nigra, inferior colliculus, locus coeruleus, dorsal vagal nuclei, nucleus accumbens^{+}, spinal central gray[1]
Ino	High (107.7–161.5): cochlear nuclei, spinal trigeminal nucleus
	Intermediate (53.9–107.6): frontal, temporal, somatosensory^{+}, prefrontal^{+}, cingulate^{+}, and occipital cortex; caudate nucleus, substantia innominata, nucleus basalis, nucleus accumbens^{+}, reticular formation (medulla oblongata), amygdala^{+}, cerebellar nuclei, spinal cord (ventral and dorsal^{+} horn), mediodorsal thalamic nucleus^{+}, spinal cord (white matter)
	Low (29.8–53.8): entorhinal and parahippocampal cortex; hippocampus, nuclei of diagonal band, habenula, pulvinar, zona incerta, paraventricular nucleus, substantia nigra, inferior colliculus, locus coeruleus[1]
Guo	High (17.7–26.4): cochlear nuclei; temporal and occipital cortex; caudate nucleus, nucleus basalis, medial geniculate body, amygdala^{+}
	Intermediate (8.9–17.6): insular, prefrontal^{+}, entorhinal^{+}, cingulate^{+}, and somatosensory cortex^{+}; white matter (cerebral and cerebellar), nuclei of diagonal band, substantia innominata, lateral geniculate body, hippocampus^{+}, nucleus accumbens^{+}, cerebellar nuclei, mediodorsal thalamic nucleus^{+}, spinal cord (ventral and dorsal^{+} horn)
	Low (4.1–8.8): septum, habenula, pulvinar, zona incerta, paraventricular nucleus, lateral hypothalamic area, substantia nigra, superior colliculus, inferior colliculus, locus coeruleus, spinal cord (white matter)[1]
Urd	High (44.1–66.2): cochlear nuclei, temporal and occipital cortex, cerebellar cortex, amygdala^{+}, spinal central gray, spinal cord (ventral horn)
	Intermediate (22.1–44.0): cerebral and cerebellar white matter, somatosensory^{+}, prefrontal^{+}, cingulate^{+}, insular and entorhinal cortex; hippocampus^{+}, caudate nucleus, globus pallidus externa, anterior nuclei (thalamus), substantia nigra, inferior colliculus, nucleus accumbens^{+}, locus coeruleus, inferior olive, reticular formation (medulla oblongata), cerebellar nuclei, mediodorsal thalamic nucleus^{+}, spinal cord (white matter), spinal cord (dorsal horn)$^{+}$
	Low (15.7–22.0): ventral anterior nucleus, zona incerta, preoptic area, motor facial nucleus[1]

(continued)

Table 29.1 (continued)

Metabolic enzymes of nucleosides in the CNS	
Enzymes	*Activity level*
5′NT	nmol/h/mg protein: High (749–1,123): temporal cortex, thalamus (medial and lateral), colliculus superior Intermediate (375–748): parietal lobe, cingulate cortex, insula, caudate nucleus, putamen, pallidum (internal), claustrum, thalamus (anterior), subthalamic nucleus, nucleus ruber, substantia nigra, amygdala, hypothalamus, midbrain (paramedian) Low (210–374): cerebellar cortex, lateral geniculate body, pallidum (external), centrum semiovale, corpus callosum, mamillary body, internal capsule[2]
ADA	nmol of ammonia/min/g of wet weight: High (387–579): white matter of frontal, orbital and temporal lobe Intermediate (194–386): gray matter of frontal, occipital, orbital, parietal and temporal lobe; pons, putamen, hippocampus, caudate nucleus, globus pallidus, thalamus, midbrain, cerebellar white matter, white matter of parietal, cingulate, and occipital lobe; corpus callosum Low (16–193): gray matter of cingulate cortex and cerebellum; hypothalamus, medulla oblongata, spinal cord[3]
ADK	nmol/min/g wet weight: High (16.4–19.4): hypothalamus, pons, hind brain Intermediate (13.1–16.3): cerebellum, temporal cortex, corpus callosum, occipital cortex Low (9.8–13.0): parietal lobe, frontal cortex[4]
PNP	Substrate transformed (μmol)/min/g wet weight: High (223–261): pons, midbrain, thalamus, white and gray matter of occipital lobe, amygdala Intermediate (183–222): caudate nucleus, white matter of cerebellum, medulla oblongata, white matter of frontal lobe, gray matter of temporal, parietal, and frontal lobe; corpus callosum Low (143–182): gray matter of cerebellum, white matter of temporal and parietal lobe, putamen, spinal cord[5]
GDA	Substrate transformed (μmol)/min/mg protein High (12.9–19.2): thalamus, mamillary body Intermediate (6.5–12.8): parietal cortex, caudate nucleus, putamen, pons (basis), hippocampus, substantia nigra Low (0.005–6.4): cerebellum, olivary nucleus, corpus callosum, lateral geniculate body[6]

Nucleoside transporters in the CNS	
Transporter family (gene)	*Relative density (by comparison of different brain areas with each other)*
ENT1 (SLC29A1)	High: frontal and parietal cortex Intermediate: temporal and occipital cortex, thalamus, midbrain, caudate nucleus, putamen, globus pallidus Low: medulla oblongata, pons, cerebellum, hippocampus[7]
ENT2 (SLC29A2)	High: midbrain, pons, cerebellum Intermediate: medulla oblongata, thalamus Low: frontal, occipital, temporal, and parietal cortex; hippocampus, caudate nucleus, putamen, globus pallidus[7]

(continued)

Table 29.1 (continued)

Nucleoside transporters in the CNS	
ENT3 (SLC29A3)	High: occipital and temporal lobe, corpus callosum, medulla oblongata, putamen Intermediate: frontal lobe, paracentral gyrus, pons, hippocampus, nucleus accumbens, thalamus, spinal cord, cerebellum (right) Low: parietal lobe, cerebellum (left), amygdala, caudate nucleus, substantia nigra, pituitary gland[8]
ENT4 (SLC29A4)	High: temporal lobe, paracentral gyrus, amygdala, caudate nucleus, hippocampus, medulla oblongata, putamen Intermediate: parietal and occipital lobe, pons, cerebellum (right), corpus callosum, thalamus, pituitary gland, spinal cord, substantia nigra, nucleus accumbens Low: frontal lobe, cerebellum (left)[9]
CNT1 (N2/cit; SLC28A1)	Uniform distribution[10]
CNT2 (N1/cif; SLC28A2)	High: cerebellum, putamen, hippocampus, medulla oblongata Intermediate/low: amygdala, cerebral cortex, frontal, occipital, and temporal lobe; substantia nigra, thalamus, spinal cord[10]
CNT3 (N3/cib; SLC28A3)	High: hippocampus, medulla oblongata, pituitary gland Intermediate/low: frontal, parietal and occipital lobe; corpus callosum, cerebellum, amygdala, caudate nucleus, putamen, thalamus, temporal lobe, paracentral gyrus, pons, substantia nigra, nucleus accumbens, spinal cord[11]

Adenosine receptors in the CNS	
Receptor type	*Relative density (by comparison of different brain areas with each other)*
A_1	High: frontal, parietal and occipital cortex; caudate nucleus, putamen, globus pallidus Intermediate: temporal cortex, thalamus, hippocampus Low: medulla oblongata, midbrain, pons, cerebellum[7]
A_{2A}	High: caudate nucleus, putamen, globus pallidus, nucleus accumbens[7,12] Intermediate/low: frontal, temporal, parietal, and occipital cortex; thalamus, hippocampus, medulla oblongata, midbrain, pons, cerebellum[7]
A_{2B}	Uniform distribution[13]
A_3	High: cerebellum, hippocampus Intermediate/low: other brain areas[13]

The levels of nucleosides in brain and spinal cord areas were compared to the grand average concentration values of the total brain and spinal cord areas (Kovács et al. 2010a). We also listed some brain and spinal cord areas, which are implicated in particular CNS diseases, even though their nucleoside levels did not differ from average values (these brain areas are labeled by "+")

References: [1]Kovács et al. 2010a; [2]Nagata et al. 1984; [3]Norstrand et al. 1984; [4]Phillips and Newsholme 1979; [5]Norstrand and Glantz 1980; [6]Dawson 1971; [7]Jennings et al. 2001; [8]Baldwin et al. 2005; [9]Barnes et al. 2006; [10]Pennycooke et al. 2001; [11]Ritzel et al. 2001; [12]Svenningsson et al. 1997; [13]Fredholm et al. 2001; *Abbreviations*: Nucleosides—*Ado* Adenosine, *Guo* Guanosine, *Ino* Inosine, *Urd* Uridine; Nucleoside metabolizing enzymes—*5′NT* 5′-Nucleotidase, *ADA* Adenosine deaminase, *ADK* Adenosine kinase, *GDA* Guanine deaminase, *PNP* Purine nucleoside phosphorylase. For nucleoside transporter and nucleoside receptor abbreviations, see text

29.3.2 Distribution of Nucleoside Metabolic Enzymes

Nucleoside metabolic enzymes form a complex network, including several alternative metabolic pathways (Ipata et al. 2011; Kovács et al. 2011) (Fig. 29.1). The distribution and activity of nucleoside metabolic enzymes are uneven in the human brain, reflecting spatial differences in the nucleoside metabolic network. The distribution of 5′NTs, ADA, ADK, PNP, and GDA (Fig. 29.1) activities in the human brain have been previously described (Dawson 1971; Nagata et al. 1984; Norstrand et al. 1984; Norstrand and Glantz 1980) (Table 29.1).

The activities of 5′NT, PNP, and GDA are high in the thalamus (Table 29.1). High to intermediate activity of 5′NT was found in several brain regions, including the temporal cortex, colliculus superior, basal ganglia, nucleus ruber, substantia nigra, amygdala, and hypothalamus. In contrast, the cerebellar cortex, lateral geniculate body, pallidum, corpus callosum, and mamillary body showed low activity levels of this enzyme.

Interestingly, the white matter of frontal, orbital, and temporal lobes contain the highest ADA activity, while only intermediate activity has been observed in the gray matter of these brain areas (Table 29.1). An intermediate ADA activity was also found, e.g., in the basal ganglia, pons, hippocampus, and thalamus. On the contrary, low ADA activity was measured in the cerebellum, hypothalamus, medulla oblongata, and spinal cord. Others have observed the highest level of ADA activity in the hypothalamus (Phillips and Newsholme 1979).

High ADK activity has been found in the hypothalamus, pons, and hind brain. The temporal and occipital cortices and cerebellum show intermediate ADK activity, whereas the parietal lobe and frontal cortex contain low levels of this enzyme (Table 29.1). GDA activity is also high in the mamillary body. Intermediate GDA activity was measured in the parietal cortex, basal ganglia, substantia nigra, and hippocampus, with the lowest activity in the cerebellum. High PNP activity was also revealed in the pons, midbrain and amygdala whereas low enzyme activity was demonstrated, e.g., in the putamen and spinal cord.

Spatial differences in the distribution of nucleosides are correlated with nucleoside metabolic enzyme activities and the neuron–glia ratio in the human brain (Kovács et al. 2010a). Nucleoside metabolism is different in neuronal and glial cells (Ceballos et al. 1994; Zoref-Shani et al. 1995). Consequently, alterations in the glia/neuron may cause regional differences in nucleoside levels. However, the correlation between the neuron–glia ratio and nucleoside levels in the human brain is weak (Kovács et al. 2010a). Importantly, the neuron–glia ratio is changed in some brain areas implicated in the development of major depressive and bipolar disorders, schizophrenia, Huntington's and Alzheimer's disease, and frontotemporal dementia (Bowley et al. 2002; Brauch et al. 2006; Harper et al. 2008; Öngür et al. 1998; Roos et al. 1985).

Table 29.1 shows that altered nucleoside metabolic enzyme activity may result in an uneven distribution of nucleosides and their metabolites in the human brain (Kovács et al. 2010a). For example, high or intermediate 5′NT activity and low or intermediate ADA/ADK activity can generate elevated Ado, Ino, and Guo levels

(Fig. 29.1) in the temporal cortex and caudate nucleus (Table 29.1). High 5′NT, PNP and GDA activities may result in low Guo levels in thalamic areas, such as the habenula, pulvinar, and zona incerta (Table 29.1).

Altogether, these results suggest that the uneven distribution of nucleoside levels may be due to complex interactions between regionally different glia–neuron ratios and nucleoside metabolic enzyme activities.

29.3.3 Distribution of Nucleoside Transporters

The distribution of nucleoside transporters in the human brain is uneven, and the regionally different distribution of nucleoside transporters reflects the functional significance of nucleoside neuromodulation in different brain areas (Baldwin et al. 2005; Barnes et al. 2006; Jennings et al. 2001; Pennycooke et al. 2001; Ritzel et al. 2001).

ENT1 expression is high in the frontal and the parietal cortices, whereas the occipital and temporal lobe shows the highest ENT3 activity and high or intermediate ENT4 activity (Table 29.1). Intermediate or low ENT3 and ENT4 density occurs in the frontal and parietal lobes. Low levels of ENT1 expression are found in the medulla oblongata and the pons, whereas these brain areas show high to intermediate ENT2 expression. ENT2 expression is low in cortical areas and the basal ganglia. All ENT transporters are expressed at intermediate levels in the thalamus. The hippocampus shows low or intermediate ENT levels with the exception of ENT4, which is expressed at high levels in this brain area.

CNT transporters are also widely distributed in the human brain. Relatively high expression of CNT subtypes (CNT1, CNT2, and CNT3) occurs in the cerebellum, putamen, hippocampus, and medulla oblongata (Table 29.1).

29.3.4 Distribution of Nucleoside Receptors

The distribution of adenosine receptors in the brain reflects the physiological activity and effects of Ado in brain structures, whereas changes in the density of adenosine receptors may indicate functional and pathological changes (Boison 2005; Fastbom et al. 1986, 1987; Jenner et al. 2009).

Adenosine receptors are unevenly distributed in the human brain (Fredholm et al. 2001; Jennings et al. 2001) (Table 29.1). High expression of A_1Rs has been measured in several cerebral cortical areas and the basal ganglia. The temporal cortex, thalamus, and hippocampus contain intermediate levels of A_1Rs, whereas the cerebellum, midbrain, pons, and medulla oblongata show low density of this adenosine receptor type. A_{2A}Rs are expressed at high levels in the basal ganglia and high A_3R density occurs in the cerebellum and hippocampus. In other brain areas, A_{2A} and A_3Rs are expressed at lower levels. Uniform distribution of A_{2B}Rs, however, has been shown to occur.

29.4 Implications for Therapy

Drugs acting on the nucleoside system are widely used for therapeutic purposes (Table 29.2, Fig. 29.1). Nucleoside metabolic enzyme inhibitors are used in anticancer therapies and the treatment of gout. In addition, several different nucleoside transport inhibitors are used as coronary vasodilators. Drugs acting on adenosine receptors are also used as vasodilators and to treat cardiac arrhythmias, carcinomas, rheumatoid arthritis, acute renal failure, and asthma. In addition, some synthetic nucleosides (nucleoside drugs) are used in antiviral and anticancer therapies.

Some drugs acting on the adenosine system have already been tested for the potential to treat brain disorders (Table 29.2). Based on its distribution and physiological roles in the CNS, the adenosine system has much wider potential for the treatment of pain, movement and mood disorders, schizophrenia, epilepsy, drug addiction, insomnia, multiple sclerosis, dementias, and stroke. Guanosine and Ino may also be neuroactive purines with therapeutic potential (Deutsch et al. 2005; Schmidt et al. 2007). The recent discovery of pyrimidine nucleotide receptors and the emerging neural functions of Urd imply that this pyrimidine nucleoside could also have therapeutic applications in the future (Cansev 2006; Connolly and Duley 1999; Dobolyi et al. 2011).

In the following sections, we discuss several neurological disorders where drugs acting on the nucleoside system may have therapeutic potential (Table 29.2).

29.4.1 Movement Disorders

The initiation of movement is governed by the interaction of the motor cortex, the thalamus, and a circuit consisting of several members of the basal ganglia, including the striatum, globus pallidus, and substantia nigra. The underlying pathologies for Parkinson's and Huntington's diseases are loss of nigrostriatal dopaminergic cells and degeneration of GABA/enkephalin neurons projecting from the striatum to the external globus pallidus, respectively (Harris et al. 2009).

Nucleosides and nucleoside metabolic enzymes are found in brain areas involved in movement disorders (Dawson 1971; Kovács et al. 2010a; Nagata et al. 1984; Norstrand et al. 1984; Norstrand and Glantz 1980) (Table 29.1). Nucleoside transporters are present in the caudate nucleus, putamen, globus pallidus, and substantia nigra (Barnes et al. 2006; Jennings et al. 2001; Ritzel et al. 2001). Caudate nucleus, putamen, and globus pallidus contain high levels of A_1 and A_{2A}Rs (Jennings et al. 2001). In particular, striatopallidal GABAergic enkephalin-containing neurons in the basal ganglia show the highest expression of A_{2A}Rs (Durieux et al. 2011; Popoli et al. 2007). These A_{2A}Rs tightly interact structurally and functionally with the dopamine D2 receptor and have been suggested to drive striatopallidal output balance (Xu et al. 2005).

Table 29.2 Some of the drugs (licensed or in preclinical/clinical stages of development) that modulate the nucleoside system and their potential therapeutic applications in the brain

Nucleoside system and therapy			
Based on inhibition of nucleoside metabolic emzymes			
Enzyme inhibitor name: (pre)clinical or licensed	*Inhibited enzyme*	*Applications and ongoing clinical trials*	*Potential therapeutic applications of enzyme inhibitors in the brain*
Pentostatin (2′-deoxycoformycin; Nipent®)	ADA: adenosine deaminase	Anticancer therapy (e.g., hairy cell myelogenous leukemia; cutaneous T-cell lymphomas; psoriasis; cancer of colon and rectum)	Neuroprotective, antiepileptic, antinociceptive and antiinflammatic effects (ADK or XO inhibition)
Peldesine	PNP: purine nucleoside phosphorylase		
Raltitrexed (Tomudex®)	TS: thymidylate synthase		Antipsychotic effects (schizophrenia, mania; ADK, ADA, or XO inhibition)
Tiazofurin (Tiazole™)	IMPDH: IMP dehydrogenase		
Allopurinol (Aloprim®)	XO: xanthine oxidase	Gout	
GP-3269	ADK: adenosine kinase	Pain, epilepsy	

Based on nucleoside transporters		
Nucleoside transport inhibition		
Transporter inhibitor name: (pre)clinical or licensed	*Applications and ongoing clinical trials*	*Potential therapeutic applications of transport inhibitors in the brain*
Dipyridamole (Persantine®)	Coronary vasodilator; platalet aggregation inhibitor	Ischemic cerebral injury; psychosis; seizures; pain; insomnia; inflammatory diseases; potentiation of cytotoxic effects (in chemotherapy); drug addiction and alcoholism
Dilazep (Cormelian®)		
Cilostazol (Pletal®)		
Lidoflazine (Clinium®)		
Nimodipine (Nimotop®)	Prevention of vasospasm and ischemic damage	
Propentofylline	Alzheimer disease; vascular dementia	

Nucleoside drugs (synthetic nucleosides)

Nucleoside drug name:	*Nucleoside transporter (involved in uptake of drug)*	*Applications and ongoing clinical trials*	*Potential therapeutic applications of nucleoside drugs in the brain*
Didanosine (ddI; Videx®)	ENT1, ENT2, ENT3, CNT2, CNT3	Antiviral therapy (e.g., HIV, types 1 and 2; hepatitis B and C; influenza A and B; paramyxoviruses)	Multiple sclerosis (Cladribine)
Zidovudine (AZT; Retrovir®)	ENT2, ENT3, CNT1, CNT3		
Zalcitabine (ddC; Hivid®)	ENT1, ENT2, ENT3, CNT1, CNT3		
Stavudine (d4T; Zerit®)	CNT1		
Ribavirine (Virazole®)	ENT1, CNT2, CNT3		
Lamivudine (3TC; Epivir®)	ENT1, CNT1		
Cladribine (2-CdA; Leustatin®)	ENT1, ENT3, CNT2, CNT3	Anticancer therapy (e.g., hairy cell, acute and chronic lymphocytic leukemia; pancreatic, lung, bladder, and breast cancer)	
Cytarabine (Ara-C; Cytosar®)	ENT1, CNT1		
Fludarabine (F-AraA; Fludara®)	ENT1, CNT3		
Gemcitabine (dFdC; Gemzar®)	ENT1, ENT2, CNT1, CNT3		

Based on adenosine receptors

Agonists

Ado receptor type	*Receptor agonist name: (pre) clinical or licensed*	*Applications and ongoing clinical trials*	*Potential therapeutic applications of agonists in the brain*
A_1	Adenosine (Adenocard®)	Arrhythmia	Neuroprotection, ischemia; sleep disorders; multiple sclerosis; Huntington's disease; antiepileptic and antinociceptive effects
	Selodenoson		
	Tecadenoson		
	GW-493838	Pain and migraine	
A_{2A}	Regadenoson	Coronary vasodilator	Multiple sclerosis; infectious meningitis; sleep disorders; psychosis; cognitive disorders
	Binodenoson		
A_{2B}	LUF5835	–	Sepsis
A_3	IB-MECA	Colon carcinoma; rheumatoid arthritis	Neuroprotection, ischemia

(continued)

Table 29.2 (continued)

Based on adenosine receptors

Antagonists

Ado receptor type	*Receptor antagonist name: (pre) clinical or licensed*	*Applications and ongoing clinical trials*	*Potential therapeutic applications of antagonists in the brain*
A_1	Adentri®	Acute renal failure	Dementia; cognitive and anxiety disorders; antimetastatic therapy
	FR194921	Dementia and anxiety disorders	
A_{2A}	Istradefylline (KW6002)	Parkinson's disease	Antidepressant effect; neuroprotection, ischemia; epilepsy; cocaine abuse; pain; migraine; Alzheimer's and Huntington's disease; sleep disorders
	Preladenant		
	BIIB014		
	ST-1535		
A_{2B}	Enprofylline	Asthma	Alzheimer's disease
A_3	MRE 3008F20	–	Neuroprotection, stroke

References—Based on inhibition of nucleoside metabolic emzymes: Akhondzadeh et al. 2006; Boison et al. 2012; Bzowska et al. 2000; De Clercq 2004; De Mattia and Toffoli 2009; Erion et al. 1997; Jacobson and Gao 2006; Kaiser and Quinn 1999; Kowaluk and Jarvis 2000; Lara et al. 2006; Lehman 2002; Marro et al. 2006; McGaraughty et al. 2005; Nabhan et al. 2004; Robak et al. 2009; Togha et al. 2007; Weber et al. 1990; Weber and Prajda 1994; Wiesner et al. 1999; Willis et al. 1978. *Nucleoside transport inhibition*: Baldwin et al. 1999; Ciccarelli et al. 2001; Griffith and Jarvis 1996; Hanley and Hampton 1983; King et al. 2006; Kittner et al. 1997; Lara et al. 2006; Li et al. 2007; Mangravite et al. 2003; Noji et al. 2004; Pearce et al. 2008; Podgorska et al. 2005; Tomassoni et al. 2008; Weyrich et al. 2009. *Nucleoside drugs (synthetic nucleosides)*: Arias-Menendez 2002; Baldwin et al. 1999; Benesch and Urban 2008; Breckenridge 2005; De Clercq 2004, 2009, 2011; Franklin and Blanden 2007; Galmarini et al. 2002; King et al. 2006; Linker et al. 2008; Mangravite et al. 2003; Nabhan et al. 2004; Pastor-Anglada et al. 2005; Podgorska et al. 2005; Rando and Nguyen-Ba 2000; Robak et al. 2009; Van Rompay et al. 2003; Warnke et al. 2010; Zapor et al. 2004. *Adenosine receptor agonists*: Barrett et al. 2005; Beukers et al. 2004; Blum et al. 2003; Cunha 2005; Elzein and Zablocki 2008; Fredholm et al. 2001; Haskó et al. 2005; Headrick et al. 2011; Hendel et al. 2005; Jacobson and Gao 2006; Kaiser and Quinn 1999; Moreau and Huber 1999; Müller 2003; Paul and Pfammatter 1997; Peterman and Sanoski 2005; Popoli et al. 2007; Ribeiro et al. 2003; Zaza 2002. *Adenosine receptor antagonists*: Blum et al. 2003; Cunha 2005; Dall'Igna et al. 2003; Ferré et al. 2007; Fredholm et al. 2001; Gottlieb et al. 2002; Hauser et al. 2003, 2011; Headrick et al. 2011; Jacobson 1998; Jacobson and Gao 2006; Kaiser and Quinn 1999; Lopes et al. 2011; Merighi et al. 2003; Moreau and Huber 1999; Müller 2003; Pinna 2009; Popoli et al. 2007; Ribeiro et al. 2003; Schwarzschild et al. 2006; Varani et al. 2000; Volpini et al. 2003; Wardas 2002; Xu et al. 2005

In cases of dopaminergic hypofunction, $A_{2A}R$ activation contributes to the overdrive of the indirect pathway (Schiffmann et al. 2007). $A_{2A}R$ antagonists (Table 29.2), therefore, have the potential to restore this inhibitor imbalance. Consequently, these drugs have therapeutic potential in diseases of dopaminergic hypofunction such as Parkinson's disease. Indeed, $A_{2A}R$ antagonists have been effective in a variety of animal models of Parkinson's disease (Bastia et al. 2005; Chen et al. 2001; Hodgson et al. 2010; Kanda et al. 1998, 2000). Furthermore, caffeine ameliorates the freezing of gait that occurs in Parkinson's disease patients (Kitagawa et al. 2007). A number of clinical trials are under way to evaluate the potential of $A_{2A}R$ antagonists in the treatment of Parkinson's disease (Table 29.2), and the modulation of A_1 and $A_{2A}Rs$ may be effective in the treatment of Huntington's disease as well (Blum et al. 2003; Chou et al. 2005; Popoli et al. 2007).

Uridine might also be potentially effective in the treatment for Parkinson's disease. Coadministration of uridine monophosphate (UMP) and docosahexaenoic acid known to increase Urd levels and synapse formation in the brain increased striatal dopamine levels and alleviated the behavioral effects of 6-hydroxydopamine injections in a rat model of Parkinson's disease (Cansev et al. 2008).

29.4.2 Addiction

Although the different classes of drugs of abuse influence numerous neurotransmitter systems within the brain, all either directly or indirectly enhance the activity of the mesolimbic dopaminergic system. Within this system, ascending dopaminergic fibers project from the ventral tegmental area to the prefrontal cortex and nucleus accumbens, areas that are involved in the rewarding effects of drugs of abuse (Lajtha and Sershen 2010; Willuhn et al. 2010).

Similar to the striatum, the level of $A_{2A}Rs$ is also particularly high in the nucleus accumbens (Ferré et al. 2007; Svenningsson et al. 1997), an area that contains low to intermediate levels of nucleosides (Kovács et al. 2010a) and ENT3, ENT4, and CNT3 transporters (Baldwin et al. 2005; Barnes et al. 2006; Ritzel et al. 2001) (Table 29.1). Based on the presence of nucleoside transporters in the nucleus accumbens, transport inhibitors might have therapeutic potential in the treatment of drug addiction and alcoholism (Table 29.2). Indeed, adenosine transport in the nucleus accumbens decreases following chronic administration of morphine to rats (Brundege and Williams 2002). Adenosine may inhibit the reward process via $A_{2A}Rs$ (Baldo et al. 1999). In animal models, $A_{2A}R$ agonists inhibit cocaine self-administration, while antagonists reinstate this behavior (Knapp et al. 2001; Weerts and Griffiths 2003). Furthermore, mice lacking the $A_{2A}R$ exhibit attenuated reward processes (Castane et al. 2006). Some novel human data also supports the involvement of the adenosine system in addiction. An elevated $A_{2A}R$ binding affinity was found in platelets of patients suffering from pathological gambling (Martini et al. 2011). Clinical trials based on these data are expected in the near future (Lopes et al. 2011).

29.4.3 Pain Management

Nociceptive impulses first reach the posterior horn of the spinal cord. From here, information is transmitted to several brain regions involved in nociception. The reticular formation regulates arousal reactions and autonomic reflexes to pain, and thalamic nuclei relay and differentiate the nociceptive stimuli. Specific nuclei of the hypothalamus mediate autonomic and neuroendocrine responses. The limbic system mediates the emotional and motivation-related aspects of nociception, while the somatosensory cortex is mainly responsible for pain differentiation and localization (Apkarian et al. 2005). Additional pathways descending from a handful of brain regions, including the periaqueductal gray, rostroventromedial medulla, lateral reticular nucleus, and some brainstem monoamine cell groups, modulate nociception (Heinricher et al. 2009).

Nucleosides and their metabolic enzymes and transporters have been observed in different regions of large anatomical structures such as the spinal cord, medulla oblongata, midbrain, thalamus, hypothalamus, and diencephalon (Table 29.1). However, there is little data on the presence of nucleoside system in the specific areas of nociceptive circuitry in the brain, and further studies are needed. Nevertheless, a significant expression of A_1Rs has been described in primary sensory neurons associated with nociceptive pathways (Lima et al. 2010).

There is a great body of evidence indicating that the activation of A_1Rs produces antinociception (Curros-Criado and Herrero 2005). Mice lacking the A_1R exhibit hyperalgesia (Johansson et al. 2001). Consequently, drugs that target the nucleoside system have potential for the treatment of pain. GP-3269, an adenosine kinase inhibitor (Fig. 29.1), and GW-493838, an A_1R agonist, may be useful in the treatment of pain and migraines (Elzein and Zablocki 2008; Erion et al. 1997; Kowaluk and Jarvis 2000; McGaraughty et al. 2005; Wiesner et al. 1999) (Table 29.2). Guanosine was also found to have an antinociceptive effect in mice (Schmidt et al. 2009), suggesting that it may also be a potential target for the treatment of pain.

29.4.4 Mood Disorders

Anxiety, panic disorder, mania, and different forms of depression do not involve major neuronal degeneration in any brain regions. Nevertheless, animal studies and various imaging techniques have identified a number of limbic brain regions that play a role in the etiology of mood disorders. These regions include the prefrontal and cingulate cortices, septohippocampal circuits, amygdala, hypothalamus, and central gray matter of the midbrain (Garakani et al. 2006; Kalia 2005). Neurons in the locus coeruleus and raphe nuclei are thought to modulate these systems, explaining the effects of noradrenergic and serotonergic drugs on mood disorders (Fava 2003).

Only some of these structures have been studied for the presence of the elements of the nucleoside system (Table 29.1). The amygdala is particularly rich in nucleosides (Kovács et al. 2010a). Intermediate or high activities of 5´NT and PNP occur in the

amygdala and the frontal and cingulate cortices (Nagata et al. 1984; Norstrand and Glantz 1980). Intermediate/low CNT2 and CNT3 levels are also observed in the amygdala and frontal cortex (Ritzel et al. 2001). ENT4 is abundant only in the amygdala, while ENT1 is believed to be the major equilibrative nucleoside transporter subtype in the frontal cortex (Barnes et al. 2006; Jennings et al. 2001). A high level of A_1Rs is found in the frontal cortex. Similar to the stratium (Schiffmann et al. 2007), the cortex also contains adenosine receptors both pre- and postsynaptically (Kirmse et al. 2008). Some other important brain regions, including the periaqueductal gray and monoamine systems, however, have not been systematically investigated for the presence of nucleoside metabolic enzymes and transporters. Nevertheless, the nucleoside system is expected to be a target for new drugs to treat mood disorders (Boison et al. 2012). Caffeine, a competitive antagonist of the A_1 and A_{2A}Rs (Fredholm et al. 1999), promotes anxious behavior both in animal models and humans (Klein et al. 1991), and A_{2A}R polymorphisms are associated with increased incidence of panic disorder and depression (Hamilton et al. 2004; Lam et al. 2005; Tsai et al. 2006). In addition, mice lacking A_1 or A_{2A}Rs demonstrate anxiogenic-like behaviors (Gimenez-Llort et al. 2002; Johansson et al. 2001; Ledent et al. 1997). Indeed, the application of an A_1R antagonist might be an effective treatment strategy for patients with anxiety disorders (Table 29.2). Allopurinol has been found to elicit therapeutic effects in the treatment of mania (Akhondzadeh et al. 2006) (Table 29.2, Fig. 29.1). Chronically administrated Guo produced anxiolytic effects in mice (Vinadé et al. 2003), suggesting a potential role of this purine nucleoside in the management of anxiety.

29.4.5 Schizophrenia

Pharmacological studies indicate the involvement of dopaminergic and glutamatergic neurons in the etiology of schizophrenia. A leading current hypothesis is that schizophrenia arises due to abnormalities in the dopamine–glutamate system of the corticostriatal pallidothalamic circuit, including the prefrontal cortex, nucleus accumbens, ventral tegmental area, mediodorsal thalamic nucleus, and ventral pallidum. Some drugs inducing drug dependence, probably by increasing the level of dopamine in the nucleus accumbens, also cause hallucinations suggesting that surplus dopamine may be a common ethiological factor. In addition to abnormalities in the corticostriatal system, alterations in the ventral limbic circuits of the dopamine–glutamate system, including the hippocampus, enthorinal cortex, and basolateral amygdala, may also be involved (Ross et al. 2006).

There is an intermediate to high level of nucleosides in most of the brain regions implicated in schizophrenia (Kovács et al. 2010a) (Table 29.1), and the evidence suggests that schizophrenia is associated with a hypofunctioning adenosine system (Lara et al. 2006). Adenosine levels can be increased by inhibiting adenosine transporters or xanthine oxidase with dypiridamole or allopurinol, respectively (Fig. 29.1). Both of these treatments had beneficial antipsychotic effects in clinical

trials when administered in combination with haloperidol (Akhondzadeh et al. 2000, 2005) (Table 29.2). Furthermore, psychotic symptoms in schizophrenic patients are worsened by caffeine (Lucas et al. 1990). An interaction between adenosine and the dopamine system (Ferré et al. 1997) or the glutamate system (De Mendonca et al. 1995; Gerevich et al. 2002) could be driving these effects. Indeed, $A_{2A}R$ agonists and antagonists may have therapeutic potential for different types of psychosis (Table 29.2).

In animal models, some of the effects of haloperidol were augmented by coadministration with Urd (Agnati et al. 1989; Myers et al. 1994). Chronic Urd administration was also found to increase stereotypy scores and catalepsy induced by an acute haloperidol injection (Agnati et al. 1989). Furthermore, chronic Urd treatment reduced expression of dopamine receptors and enhanced their turnover rate in the striatum (Farabegoli et al. 1988). These data suggest that Urd coadministration might enhance the antipsychotic actions of traditional neuroleptics.

Moreover, the neuroprotective and neurotrophic effects of Guo may also be advantageous for the treatment of schizophrenia; Guo was found to attenuate hyperlocomotion induced by dizocilpine, a pharmacological model of schizophrenia, in mice (Tort et al. 2004).

29.4.6 Epilepsy

Epilepsy is characterized by a variety of recurrent symptoms resulting from the synchronous or sustained discharge of a group of neurons. The pathophysiology of epilepsy is poorly understood, and so far, there is no clear association between the abnormal function of a specific group of neurons and the genesis of seizures. There is some evidence, however, that the impairment of inhibitory signals, often occurring in the neocortex and hippocampus, may be primarily involved (Bertram 2009).

In the human hippocampus, ADA and GDA have intermediate activity (Dawson 1971; Norstrand et al. 1984) (Table 29.1). Adenosine and Ino levels are low, but intermediate concentrations of Guo and Urd are present (Kovács et al. 2010a). Based on their abundance, ENT4, CNT2, and CNT3 are believed to be the major nucleoside transporters in the hippocampus (Barnes et al. 2006; Ritzel et al. 2001). Furthermore, an intermediate level of A_1 and intermediate/low level of $A_{2A}R$ is present (Jennings et al. 2001). Indeed, the interaction of Ado with the inhibitory A_1R has been shown to have anticonvulsant effects in animal models (Barraco et al. 1984; Fedele et al. 2006). As A_1R agonists have peripheral cardiac and central sedative side-effects, adenosine kinase inhibitors (Fig. 29.1) have been used to indirectly increase Ado levels (Boison 2008). These drugs were shown to have anticonvulsant properties (McGaraughty et al. 2005). In particular, GP-3269, an adenosine kinase inhibitor, was found to be useful for the treatment of epilepsy (Erion et al. 1997; Kowaluk and Jarvis 2000; McGaraughty et al. 2005; Wiesner et al. 1999) (Table 29.2).

Recently, the distribution of A_{2A}Rs in the brain has been found to be altered in an animal model of human absence epilepsy (Wistar Albino Glaxo/Rijswijk rat: WAG/Rij), both before and after appearance of absence seizures (D'Alimonte et al. 2009). A low density of A_1Rs was also found in the thalamic reticular nucleus in another animal model of human absence epilepsy (Genetic Absence Epilepsy Rat from Strasbourg: GAERS) when compared with control animals (Ekonomou et al. 1998). These results suggest that adenosine receptors might represent a novel target for the treatment of absence epilepsy.

The anticonvulsant effects of Urd have also been hypothesized; Urd was found to reduce penicillin- (Roberts 1973; Roberts et al. 1974), pentylenetetrazole- (Dwivedi and Harbison 1975), and electroconvulsion-induced (Piccoli et al. 1971) seizures in experimental rodent models of epilepsy. Indeed, Urd is released following depolarization and inhibits unit activity (Dobolyi et al. 1999, 2000). Recently, Urd has been found to act as an antiepileptogen in hippocampal kindling models (Zhao et al. 2006, 2008). In addition, Guo prevented seizures induced by quinolinic acid and other glutamatergic agents (De Oliveira et al. 2004; Schmidt et al. 2000). These data suggest that Urd and Guo also have antiepileptic potential.

29.4.7 Insomnia

EEG recordings and other evidence indicate that sleep affects most cortical areas. Sleep waves are generated by an interaction between cortical and thalamic circuits, including thalamic reticular and relay nuclei. Sleep states are regulated by specific brain centers, and dysfunction of these regions leads to insomnia. Serotonergic and noradrenergic projections ascending from the brainstem and histaminergic cells in the tuberomamillary nucleus promote consciousness, while the preoptic area of the hypothalamus and cholinergic neurons in the basal forebrain and tegmental nuclei of the pons promote sleep. Orexinergic cells in the lateral hypothalamus may also have important on/off functions regarding sleep states (Datta and Maclean 2007; Saper 2006). The involvement of Ado in regulating sleep has long been suspected due to the hypnotic effects of adenosine analogues (Radulovacki 1985). The distribution of Ado and its inhibitory A_1R and increases of Ado levels in metabolically challenged cells are relatively ubiquitous. Furthermore, caffeine and theophylline are widely used as stimulants of the CNS. Therefore, the hypothesis emerged that, during daytime activity, ATP is degraded to adenosine, which could induce sleep. Indeed, prolonged wakefulness is known to increase Ado levels in the basal forebrain that, in turn, may decrease the activity of cholinergic cells to promote sleep (Porkka-Heiskanen and Kalinchuk 2011). A selective decrease in CNT2 mRNA levels was demonstrated in the cerebral cortex of sleep-deprived rats (Guillén-Gómez et al. 2004). These data suggest that adenosine receptor agonists and nucleoside transport inhibitors might be effective in the treatment of sleep disorders (Table 29.2).

Uridine was identified as an active component of a sleep-promoting substance purified from the brainstem of sleep-deprived rats (Borbely and Tobler 1989; Inoue 1986). Infusion of Urd increased slow wave and paradoxical sleep (Honda et al. 1984). Intraperitoneally injected Urd resulted in a dose-dependent appearance of slow-wave sleep when administered shortly before onset of the dark period (Honda et al. 1985). Based on these data, drugs elevating Urd levels in the brain should be tested for the treatment of insomnia in future studies.

29.4.8 Dementia

Alzheimer's disease is a progressive, degenerative disease of the brain that is the most common cause of dementia in the elderly. Typical pathological features of Alzheimer's disease are neuritic plaques and neurofibrillary tangles occurring primarily in the cholinergic basal forebrain and the hippocampus, frontal, parietal, and temporal lobes of the cerebral cortex (Peskind 1996).

The cerebral cortex and the basal forebrain contain all elements of the nucleoside system (Table 29.1). Neuroprotection achieved by manipulating the brain nucleoside system could be beneficial in the treatment of dementia. Animal models implicate the involvement of A_{2A}Rs in the development Alzheimer's disease. Caffeine and A_{2A}R antagonists prevent beta-amyloid (25–35)-induced cognitive deficits in mice (Dall'Igna et al. 2007). Additionally, caffeine elevates alertness and improves cognition in humans (Eskelinen et al. 2009; Ritchie et al. 2007). These effects might be due to altered acetylcholine release by A_{2A}Rs (Cunha et al. 1995; Jin and Fredholm 1997). In addition to receptor antagonists, propentofylline, an inhibitor of "es" nucleoside transporters, has established neuroprotective effects (Kittner et al. 1997), and its administration to patients with Alzheimer disease and vascular dementia resulted in functional improvements in clinical trials (Mielke et al. 1998).

Low to intermediate Ado levels but intermediate to high A_1R density has been observed in brain areas implicated in Alzheimer disease (Table 29.1), and loss of human hippocampal A_1Rs has been shown in dementia patients (Deckert et al. 1998). Therefore, A_1 receptor antagonists are potential targets for the treatment of dementia and cognitive disorders (Table 29.2). Administration of a nucleoside–nucleotide mixture reduced memory deterioration in elderly senescence-accelerated mice (Chen et al. 2000). In addition, age-dependent alterations in the adenosine system have been found (Kovács et al. 2010b; Meyer et al. 2007). These findings suggest that Ado might participate in the pathophysiology of learning and memory disorders, as well as the normal aging process.

In animal studies, Urd was found to improve certain types of memory function (Holguin et al. 2008; Teather and Wurtman 2003, 2005, 2006). Therefore, increased Urd formation may mediate the positive effects of cytidine diphosphocholine (CDP-choline) on verbal memory in aging humans (Spiers et al. 1996). Consequently, CDP-choline and other nutritional components that increase brain Urd levels (Wurtman et al. 2000) may be important, especially during the early phases of Alzheimer's disease (Van der Beek and Kamphuis 2008; Wurtman et al. 2009).

Recently, Guo has been found to protect against beta-amyloid-induced apoptosis (Pettifer et al. 2004). This effect appeared to be mediated by the antiapoptotic properties of Guo (Di Iorio et al. 2004). Guanosine was also found to modulate memory processes: its pretraining administration impaired retention of inhibitory avoidance responses in rats (Roesler et al. 2000). Furthermore, the amnesic effects associated with GMP pretreatment are also dependent on its conversion to Guo (Saute et al. 2006) (Fig. 29.1).

29.4.9 Stroke

In stroke, tissue damage is most often caused by ischemia resulting from an occluded blood vessel (Dietrich 1998). Neuroprotection by manipulation of brain nucleoside system may be beneficial in stroke victims. Adenosine and other nucleosides are elevated during ischemia (Rudolphi et al. 1992). While adenosine released from neurons or accumulated by the extracellular degradation of released ATP could reach a concentration efficient for the activation of adenosine receptors, a pathophysiological release from neurons as well as glial cells occurs during an ischemic event (Latini and Pedata 2001). Agonist stimulation of the A_1R may inhibit excessive neuronal firing and may enhance local cerebral blood flow (O'Regan 2005), reducing brain damage following experimentally induced ischemia in animals. Indeed, lacking the A_1 receptor exhibited decreased hypoxic neuroprotection in mice (Johansson et al. 2001). Thus, Ado may be involved in ischemic preconditioning, an endogenous neuroprotective mechanism (Liu et al. 2009). Consequently, drugs that act on adenosine receptors, adenosine metabolizing enzymes, and nucleoside transporters (Table 29.2, Fig. 29.1) and increase EC Ado levels could be targets for the development of clinical therapeutics suitable for treatment of ischemic brain disorders (Stone 2002; Von Lubitz 2001). Importantly, the effectiveness of all of these potential therapies may vary between patients due to differences in the spatial distribution of the nucleoside system (Table 29.1). Indeed, the nucleoside system may be modulated differently in men and women (Kovács et al. 2010b). Changes in nucleoside levels in female brain cortical samples may serve as a protective mechanism against excitotoxic insults, suggesting that several normal and pathological brain functions are based on gender-dependent nucleoside microenvironments in humans.

Other nucleosides might also have neuroprotective functions in response to ischemic injury, and increasing their expression might be beneficial both during and after an ischemic attack. In animal models, Guo had neuroprotective effects in both in vitro and in vivo stroke models (Chang et al. 2008). Inosine was also shown to reduce ischemic brain injury in rats (Shen et al. 2005). Inosine and Guo preserved the viability of cultured astrocytes, neurons (Jurkowitz et al. 1998; Litsky et al. 1999), and brain slices maintained under hypoxic or hypoglycemic conditions (Frizzo et al. 2002). The potential neuroprotective effects of Guo are also supported by the finding that neuronal and astrocytic cell cultures are able to release Guo and Ado under both basal and ischemic conditions (Ciccarelli et al. 2001).

29.4.10 Multiple Sclerosis

Multiple sclerosis is characterized by multiple symptoms of brain and spinal cord dysfunction that reflect degeneration of particular areas of the nervous system that are involved. The affected regions vary between patients and are not specific to the disease. The pathological hallmark is inflammatory demyelination and axonal lesions. Inflammation is primarily driven by autoreactive lymphocytes, which recruit immune cells, such as macrophages, causing tissue damage (Hauser and Oksenberg 2006).

A synthetic nucleoside, cladribine, was shown to be effective in the treatment of multiple sclerosis (Table 29.2). The biologic activity of cladribine is dependent on the preferential accumulation of cladribine phosphates in cells with a high intracellular ratio of deoxycytidine kinase to 5′NT. Cladribine-phosphates incorporate into DNA, interfering with DNA synthesis and repair and inhibiting enzymes involved in DNA metabolism, such as DNA polymerase and ribonucleotide reductase. This, in turn, leads to DNA strand breaks and, ultimately, cell death (Leist and Weissert 2011). Because activated macrophages, but not neuronal and glial cells, have a high deoxycytidine kinase to 5′NT ratio (Ceruti et al. 2000; Nagata et al. 1984), cladribine can selectively inhibit the damaging inflammatory process that occurs in multiple sclerosis.

Inosine may also have beneficial effects in the treatment of multiple sclerosis (Markowitz et al. 2009). These data suggest that regional differences in nucleoside system may influence the pathological processes of multiple sclerosis, but further studies are needed to confirm this hypothesis.

In conclusion, the current data suggest that nucleoside system offers promising drug targets for the treatment of a variety of brain disorders, including Alzheimer's, Huntington's and Parkinson's diseases, epilepsy, and schizophrenia. Unfortunately, although the nucleoside system has been implicated in the development and treatment of a number of brain disorders, a systematic investigation of the nucleoside system in most brain areas has not yet been performed. These data are needed to elucidate therapeutic strategies driven by the anatomical distribution of nucleoside system. In addition, attention must be given to the effects of gender and age in future studies. These data are eagerly awaited and will help form the foundation for studies of the physiological and pathophysiological functions of nucleosides and for the development of effective treatments for several CNS diseases.

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