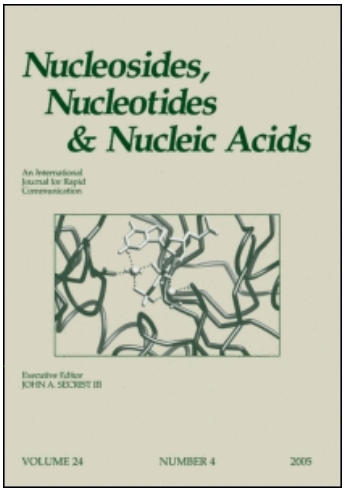

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ADENOSINE AND NEUROPSYCHIATRIC DISEASE

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Abstract: The nucleoside adenosine may act as an endogenous anticonvulsant, neuroprotective and "psychoprotective"agent. Possible clinical indications of adenosinergic drugs thus include epilepsy, ischemia, neurodegenerative diseases and sleep and anxiety as well as psychotic disorders.

The nucleoside adenosine is ubiquitous throughout all organs as a metabolite of energy metabolism. Its physiological role has been described by Newby as that of a retaliatory metabolite [1]. As such it is proposed to protect cells, organs and organisms from self-destructive overactivity by preventing exhaustion of their energy pools. In situations of increased activity of a certain cell or organ and consequent increased adenosine triphosphate use adenosine, the metabolite of adenosine triphosphate breakdown accumulates. High concentrations of adenosine slow down further adenosine triphosphate metabolism. Adenosine then is recycled to adenosine triphosphate. The consequent decrease of adenosine concentrations permits consumption of the newly synthesized adenosine triphosphate, the cycle may start again.

In the central nervous system adenosine is released as a consequence of neuronal activity, e.g. in form of adenosine triphosphate corelease with neurotransmitters [2]. Up to tenfold higher than normal adenosine concentrations have thus been measured after seizure activity [3]. High adenosine concentrations may be due not only to increased adenosine triphosphate consumption as in seizures, but also due to insufficient adenosine triphosphate synthesis as e.g. in ischemia [4].

Adenosine has therefore been proposed as an endogenous anticonvulsant and neuroprotective agent [5,6].

Not only are extracellular adenosine concentrations increased after seizures [3], but also adenosine A1 receptors and transport sites [7]. Methylxanthines, the classical adenosine receptor antagonists induce seizures although probably not exclusively via adenosine receptors [8]. Adenosine receptor agonists and transport inhibitors thus have been proven to be potent anticonvulsants in vitro and - when applied parenterally - in vivo in animal experiments [9-11], probably via inhibiting glutamate release as well as a direct postsynaptic effect. Their anticonvulsant effect in vivo, however can be abolished by preventing the concomitant decrease in body temperature [12] and paradoxically seizures induced by a xanthine derivative are actually enhanced by adenosine receptor agonists [8]. Given the low blood-brain barrier permeability of the investigated adenosine receptor agonists it is in fact questionable how much of the anticonvulsant effect seen in vivo is due to a central mechanism of action [13]. Clinical studies employing the xanthine oxidase inhibitor allopurinol as an anticonvulsant come to contradictory conclusions [14, 15]. With regard to clinical application of

the presently available adenosinergic drugs investigations are necessary that demonstrate an anticonvulsant effect during long-term oral medication at doses which do not cause marked sedation. The latter side effect is usually not well tolerated by patients suffering from epilepsy. In acute emergency situations which warrant parenteral application the presently available adenosine receptor agonists may well be effective, but may have a side - effect profile less favourable than that of exclusively centrally acting benzodiazepines, e.g. clonazepam.

As with convulsions, adenosine concentrations increase after ischemia [4]. Adenosine receptor antagonists have been demonstrated to increase neuronal cell death due to ischemia in an animal model of ischemia [16]. Adenosine A1 receptor agonists and adenosine deaminase inhibitors on the other hand considerably decrease ischemic damage in several animal models of ischemia when applied parenterally after the event [17,18], probably at least partly by inhibiting the release of excitatory amino acids. The adenosine transport inhibitor dipyridamole [19] in fact is given in combination with acetylsalicylic acid to prevent major stroke in patients experiencing transient ischemic attacks from emboli formed at heart valves although the long-term efficacy in preventing e.g. myocardial infarction is controversial [20]. Given the damage occuring to the blood brain barrier in situations of brain ischemia, the limited blood-brain barrier permeability of presently avialable adenosinergic drugs may not limit their efficay. Possible sedative side effects may actually be beneficial because quite often agitation is complicating the care for stroke patients. The potential for a major therapeutic breakthrough in the treatment of ischemic brain da-

mage due to adenosinergic drugs therefore exists. The investigated animal models in fact are very similar to clinical situations as cardiac arrest, perinatal hypoxia and transient ischemia, there are, however differences to the typical clinical situation of major stroke. In the animal models a temporary ischemia is induced by vessel occlusion in otherwise healthy animals which then is completely reversed before the therapeutic intervention shortly after (minutes). In the clinical situation of major stroke typically a primarily irreversible blood clot is formed in older patients with cardiovascular problems, particularly of the heart. This blood clot and thus ischemia are still present when the therapeutic intervention is possible (usually hours later). Future studies with appropriate animal models and clinical studies will have to evaluate the effectiveness of adenosinergic drugs under such circumstances. The problem of cardiovascular side effects in elderly patients may be minimized by employing reversible transport or metabolism inhibitors instead of receptor agonists. They act by enhancing the effect of endogenous adenosine released due to ischemia and therefore possess a marked site of event - specific action profile. At present, adenosinergic drugs therefore hold most promise in situations with spontaneous reperfusion as in cardiac arrest, perinatal hypoxia and transient ischemia.

The physiological role of adenosine in brain can be understood not only as that of a retaliatory metabolite. It acts as a inhibitory neuromodulator, partly by inhibiting the release of excitatory neurotransmitters [21]. Among these excitatory neurotransmitters whose release is inhibited by adenosine is the excitatory amino acid glutamate. Adenosine A1 receptors are localized presynaptically on glutamatergic

neurons throughout the brain, e.g. in hippocampus [22]. Pathological situations in the brain as epilepsy and ischemia can thus be characaterized as situations of disturbed glutamate-adenosine balance with relative glutamatergic hyperfunction and relative adenosinergic hypofunction.

Relative excess of glutamate (or other excitatory amino acids) either due to genetic factors or environmental factors, e.g. nutrition has been proposed as the primary metabolic defect in several neurodegenerative diseases as different as Alzheimer`s disease, Chorea Huntington, Parkinson`s disease and Amytrophic lateral sclerosis [23,24]. A potential neuroprotective role could therefore be envisioned for adenosinergic drugs in these diseases, but only few studies are available at present. Some symptoms were ameliorated by an adenosine A1 agonist in an animal model of Parkinson`s disease [25]. The L-type calcium channel antagonist and potent adenosine transport inhibitor nimodipine [26] is currently under investigation as a nootropic in dementia of Alzheimer type [27]. *Future studies will have to assess the long-term* efficacy of orally applied adenosinergic drugs in these disorders.

Other diseases of the brain characterized by incoherent overactivity and loss of protection from outside stimuli are so-called psychiatric diseases of the brain. They include sleep disorders, anxiety disorders and psychotic disorders. Adenosine A1 receptors are upregulated after sleep deprivation and in animal models of anxiety [28, 29]. Adenosine receptor antagonists increase locomotor activity and wakefulness and antagonize the effects of neuroleptics [30,31]. Adenosine receptor A1 and A2 agonists, transport and deaminase inhibitors on the other hand reduce locomotor activity,

induce sleep and mimic the behavioral profile of neuroleptics when applied parenterally [32-34,36] and orally [35]. At least some of these effects are mediated by a central site of action [37]. The clinical effects of the adenosine receptor antagonists caffeine and theophylline in humans are well characterized. They induce sleep disturbances, anxiety, panic attacks, a clinical syndrome called caffeinism, which is characterized by symptoms of anxiety disorders and depression, and exacerbation of schizophrenic syndromes [38-41]. A possible general "psychoprotective" role may therefore be postulated for adenosine [42]. Accordingly, adenosine transport inhibitors are currently under investigation as hypnotics (mioflazine and derivatives) [43] and as a treatment of panic disorder (dipyridamole). S-adenosylmethionine, a precursor of S-adenosylhomocysteine which is an additional possible source of brain adenosine besides adenosine triphosphate has been investigated as an antidepressant [44]. Future studies will primarily have to assess long-term efficacy of orally applied adenosinergic drugs with better blood-brain barrier permeability. Given the long-term administration necessary in these diseases possible immunosuppressive effects and even a small potential of abuse may become relevant and will have to be looked for in future studies [45,46]. Compared to presently available drugs, e.g. benzodiazepines adenosinergic drugs may have advantages (low potential for abuse ?) and disadvantages (risk of immunosuppression ?).

The standard drug for adenosinergic drugs for many of the above mentioned indications, e.g. epilepsy, sleep and anxiety disorders thus are the benzodiazepines. Adenosinergic drugs will have to prove their superiority to benzo-

diazepines or drugs like carbamazepine, imipramine and haloperidol. In diseases where at present no therapeutic drug is available, e.g. ischemia and neurodegenerative diseases adenosinergic drugs may be more readily employed than in diseases where already useful, if not optimal drugs are available.

In summary, possible clinical indications of adenosinergic drugs include neurological diseases of the brain like epilepsy, ischemia and neurodegenerative diseases, but also psychiatric diseases of the brain as sleep, anxiety and psychotic disorders. Future animal and clinical studies will have to evaluate their effectiveness and safety as well as their superiority to presently available drugs. Reversible inhibitors of adenosine transport or metabolism may prove to be preferable to receptor agonists in some circumstances.

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