[Frontiers in Bioscience 13, 2614-2632, January 1, 2008]

Adenosine receptor antagonists for cognitive dysfunction: a review of animal studies

Reinaldo Naoto Takahashi, Fabricio Alano Pamplona, Rui Daniel Schroder Prediger

Departamento de Farmacologia, Centro de Ciencias Biologicas, Universidade Federal de Santa Catarina, Campus Trindade, Florianopolis-SC 88049-900, Brazil

TABLE OF CONTENTS

1. ABSTRACT

Over the last decade, adenosine receptors in the central nervous system have been implicated in the modulation of cognitive functions. Despite the general view that endogenous adenosine modulates cognition through the activation of adenosine A_1 receptors, evidence is now emerging on a possible role of A_{2A} receptors in learning and memory. The present review attempts to examine results reported in different studies using diverse animal models, to provide a comprehensive picture of the recent evidence of a relationship between adenosinergic function and memory deficits. The present data suggest that caffeine (a nonselective adenosine receptor antagonist) and selective adenosine A_{2A} receptor antagonists can improve memory performance in rodents evaluated through different tasks. They might also afford protection against memory dysfunction elicited in experimental models of aging, Alzheimer's disease, Parkinson's disease and, in spontaneously hypertensive rats (SHR), a putative genetic model of attention deficit hyperactivity disorder (ADHD).

2. INTRODUCTION

Adenosine, an established neuromodulator, plays an important role in the regulation of synaptic transmission and neuronal excitability in the central nervous system (CNS) (1). The relevance of adenosine receptors was initially recognized on the basis of the ability of caffeine, the most widely consumed psychoactive substance, to act as a dual antagonist at A_1 and A_2 receptors (2). Four adenosine receptor subtypes (A_1, A_{2A}, A_{2B} and A_3) have been cloned and characterized from several mammalian species. They are all metabotropic G protein-coupled receptors (3) and were divided into two broad groups: A_1 and A_3 receptors usually couple to “inhibitory” G-proteins (Gi and Go); and A_{2A} and A_{2B} receptors couple to “stimulatory” G-proteins (Gs) (4). However, all adenosine receptors are fundamentally pleiotropic receptors, as they can potentially couple to different G proteins and to different transducing systems, according to their degree of activation and their particular cellular and subcellular localization (5).

The main effects of adenosine are mediated by the activation of high affinity receptors (A_1 and A_{2A}), which are probably of physiological importance. The adenosine A_1 receptor is the most abundant adenosine receptor, and is highly expressed in the neocortex, cerebellum, hippocampus, and dorsal horn of the spinal cord. The adenosine A_{2A} receptor is highly expressed in the striato-pallidal neurons and olfactory bulb, and lower levels also occur in other brain regions such as the hippocampus (3, 6). Low levels of adenosine will act preferentially on adenosine A_1 receptors, whereas higher levels will act preferentially on adenosine A_{2A} receptors (7, 8). In some conditions (e.g. aging) the relative importance of the "inhibitory" adenosine A_1 receptor and the "excitatory" adenosine A_{2A} receptors is unbalanced, i.e. the ability of adenosine A_1 receptor agonists to inhibit neurotransmitter release and synaptic transmission is reduced, whereas that of adenosine A_{2A} receptor agonists to facilitate neurotransmission is increased (9-11). This apparent loss of an adenosinergic inhibitory tonus and the appearance of a stimulatory one in aged individuals may be important to the enhancement of synaptic efficacy and might be a consequence of the decreased number of functional synapses. At the same time, a physiological cost may be represented by an increased vulnerability of senescent neurons to excitatory amino acid toxicity, since adenosine lacks its A_1 receptor-mediated neuroprotective effects in the aged brain (12-14).

Different pharmacological tools, as well as knockout mice strains, are available for the investigation of the involvement of adenosine receptors in different cognitive functions. Selective adenosine A1 receptor agonists include *N6*-cyclopentyladenosine (CPA) and 2-chloro-*N6*-cyclopentyladenosine (CCPA), and selective antagonists include 8-cyclopenthyl-1,3-dipropylxanthine (DPCPX). Selective adenosine A2A receptor agonists include *N6*-[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl]adenosine (DPMA) and 2-[*p*-(2-carbonyl-ethyl)-phenylethylamino]-5-N-ethylcarboxamidoadenosine (CGS 21680) and antagonists include ([7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine (SCH 58261) and 4-(2-[7-amino-2-{2-furyl}{1,2,4}triazolo-{2,3-a}{1,3,5}triazin-5-yl-amino]ethyl)-phenol (ZM241385) (15). It is also important to note that adenosine A1 and A2A receptors can interact at a subcellular level, so that blockade of one receptor subtype can lead to a disinhibition of the other, and vice-versa (5). The practical consequence of this is that, in some situations, the blockade of adenosine A_1 receptors can enhance, via disinhibition, agonistic actions at adenosine A2A receptors. Adenosine A2B receptors are expressed at low levels in the brain (16) and might be relevant in pathological conditions. The A3 receptor, apparently, has intermediate levels of expression in the human cerebellum and hippocampus and low levels in the rest of the brain (3). Because of their low abundance in the brain, the role of adenosine A2B and A3 receptors has received considerably less attention. It is hoped that greater experimental efforts, as well as novel tools will lead to a new perspective on the possible relevance of these less abundant adenosine receptor subtypes.

Considerable evidence supports a modulatory role for adenosine in learning and memory, including basic cellular mechanisms involved in memory formation, such as the hippocampal long-term potentiation (LTP) (17) and long-term depression (LTD) (18). Although clinical studies on the effects of caffeine (a nonselective adenosine receptor antagonist) consumption on cognitive performance in non-demented humans have yielded inconsistent results (19-23), preclinical psychopharmacological studies have provided valuable insights into the involvement of adenosine receptors in learning and memory processes. Administration of adenosine (mainly A_1) receptor agonists disrupts learning and memory in rodents (24-27), while the nonselective adenosine receptor blockade by theophylline or caffeine, as well the selective blockade of adenosine A_1 and A_{2A} receptors, facilitates rodent learning and memory in diverse behavioral tasks (28-32). Of high interest, caffeine and selective adenosine (mainly A_{2A}) receptor antagonists have been suggested to afford protection against memory dysfunction elicited in experimental models of aging (33), Alzheimer's disease (AD) (34, 35) and Parkinson's disease (PD) (36, 37), as well as in a putative genetic model of attention deficit hyperactivity disorder (ADHD) in spontaneously hypertensive rats (SHR) (38, 39). The present review attempts to examine results reported in different studies using animal models of these conditions, to provide a comprehensive and updated picture of the relationships between adenosinergic function and cognitive deficits.

3. BASIC ASPECTS OF ADENOSINE AS A NEUROMODULATOR RELEVANT FOR COGNITIVE FUNCTIONS

The notion that adenosine can act as a neuromodulator to interfere with cognitive processes probably stemed from the general belief that caffeine, through nonselective blockade of adenosine receptors, enhances cognition in humans. Indeed cognitive benefits of caffeine have been reported (20-22, 40, 41), but longitudinal studies have indicated that the effects of habitual caffeine intake are limited (19, 23). The reason for this inconsistency in the literature can be largely attributed to methodological issues. For instance, there is considerable variability in doses of caffeine administered, with some using single acute doses equivalent to over five-fold the amount found in the average cup of coffee. In general, observations point to an inverted U-shaped dose-response curve for caffeine: lower doses have positive effects on performance, while doses above 500 mg either have no effect or actually decrease performance (42-44). Also the periods of caffeine abstention prior to testing vary widely from 1 h (45) to up to 3 weeks (46).

A recurrent theme in the literature concerns the issue if the behavioral and subjective effects of caffeine are truly beneficial, or merely represent an alleviation of caffeine withdrawal symptoms which include headache, drowsiness and lethargy, and decreased energy and concentration (47, 48). This withdrawal reversal hypothesis holds that regular caffeine consumers experience a perturbation of mood and behavior during acute withdrawal

that is reversed by caffeine consumption, and that caffeine then merely restores normal functioning (49, 50). Some studies have shown considerable support for the withdrawal reversal hypothesis (50-52). For example, Rogers and coworkers (52) have demonstrated that caffeine enhances mood and performance in regular caffeine users who abstain overnight, but not in caffeine non-consumers. However, other studies (20, 22) have indicated that caffeine improves cognitive performance and mood in both consumers and non-consumers.

After consuming caffeine, human subjects report that they feel energetic, alert, imaginative, efficient, self-confident, are more able to concentrate and motivated to work (53). Caffeine intake also improves vigilance and performance in mnemonic tasks, being easily manifested in prolonged sessions (54). These short examples illustrate how the term "cognition" may refer to different mental processes, including acquisition (perception) of information, processing, memory storage and recollection, and the planning and execution of actions. Revelle and coworkers (55) have shown a complex interaction between the effects of caffeine on performance and parameters such as personality and time of day. In this context, adenosine figures as a central mediator, affecting the sleep/wake cycle and attention (6). Adenosine functions as a natural sleep-promoting agent, accumulating during periods of sustained wakefulness and decreasing during sleep (56, 57). Although caffeine might exert similar basic effects on different brain structures, the functional consequences of these effects may be quite different in distinct task paradigms and under different arousal states. This constitutes a major problem in determining the effects of caffeine on human information processing. For example, an increase in arousal improves the performance of tasks where relatively few sources of information have to be monitored, particularly under conditions when the need for selective attention is stressed by time pressure. On the other hand, when multiple sources of information or working memory have to be used, an increase in arousal and attentional selectivity has no apparent beneficial effect on performance, which may consequently even decrease (58). Although there is no clear agreement on the specific effects of caffeine on human cognitive functions, there is a strong indication that caffeine affects attentional processes (59).

Before reviewing the animal studies implicating adenosine and its receptors in learning and memory processes, is important to emphasize that there are distinct types and phases of memory. According to their duration memories can be classified as working memory (immediate memory lasting seconds or a few minutes), short-term memory (which develops in a few seconds or minutes and lasts for several hours) and long-term memory (which consolidates slowly and is relatively permanent), where short- and long-term memory are identified as separate entities (60, 61). These distinct types of memory can be evaluated in animal studies through the use of different behavioral tasks. With regard to the phases of memory, a first characteristic of memory is the temporal aspect of its formation. Acquisition of information, which is very labile at first, is consolidated over time (62). Acknowledging this coordinated process of memory formation, it is useful to define the effects of drugs on the distinct phases of memory. Given before training, drugs can act on the acquisition/early consolidation of memories, given shortly after training they can interfere in early/late consolidation, and given before testing, they can interfere in retrieval.

Endogenous adenosine modulates long-term synaptic plasticity phenomena, such as LTP (17), LTD and long-term depotentiation (18, 63). In accordance with the notion that synaptic plasticity is the basis for learning and memory in different brain areas, adenosine correspondingly modulates rodent performance in various learning and memory paradigms (64). The acquisition of inhibitory avoidance (25, 27, 65) and contextual conditioned fear (24) is impaired by systemic administration of adenosine A_1 receptor agonists prior to training, while the acquisition of tone fear conditioning is not (24). Moreover, the retrieval of conditioned fear is impaired following administration of adenosine A_1 receptor agonists prior to testing (24). On the other hand, whereas systemic administration of adenosine A_1 receptor antagonists does not affect the consolidation of inhibitory avoidance, it is improved by injection of adenosine A_{2A} receptor antagonists (29, 66). Conversely adenosine A_1 receptor antagonists improve consolidation of inhibitory avoidance when microinjected into the cingulate cortex, immediately after training (30). Also in the cingulate cortex, adenosine A_1 or A_{2A} receptor activation impairs the retrieval of inhibitory avoidance, while the antagonism of A_1 or A_{2A} receptors has no effect at all (67). These differences between the effects of systemically administered versus centrally microinjected adenosine receptor suggest that the functional role of the adenosinergic system in long-term memory consolidation depends on the integration between multiple memory systems rather, than being restricted to a single brain area. Certainly additional brain systems need to be studied to further clarify the roles of adenosine receptor-mediated mechanisms in long-term memory processes.

Studies on the involvement of adenosine receptors in working memory are somewhat inconsistent. In the social recognition task, which is a short-term working memory mainly generated from olfactory cues (68), the recognition ability of rats is disrupted by systemic administration of either adenosine or of selective adenosine A_1 and A_{2A} receptor agonists, and it is improved by injection of caffeine or selective adenosine A_1 and A_{2A} receptor antagonists (31). The selective activation of adenosine A_1 (but not A_{2A}) receptors in the hippocampus disrupts the performance of rats in a runway-based working memory test (26). A novel strain of transgenic rats [TGR(NSEhA2A)], that overexpresses adenosine A_{2A} receptors mainly in the cerebral cortex, hippocampal formation and cerebellum do not display alteration in motor performance, anxiety-like behaviors or in hippocampal-dependent learning of spatial memory (69). However, these animals clearly present working memory deficits in the 6-arm radial tunnel maze, object recognition and in the water maze (69). However, Hooper *et al.* (70) demonstrated that the activation of adenosine A_{2A} receptors does not affect spontaneous alternation in mice.

Considering this contribution of both adenosine receptor subtypes in cognitive processes, one can ponder about the mnemonic effects of widely used nonspecific antagonists, such as caffeine or theophylline. *Do they improve or disrupt learning and memory?* Available animal data shows that this depends on drug dosage and the memory phase evaluated. While relatively low doses (0.3-3 mg/kg) of caffeine improve consolidation in the reference version of the water maze (39, 71), active avoidance (72) and inhibitory avoidance (73, 74) tasks in rodents, high caffeine doses (30-100 mg/kg) disrupt acquisition in the inhibitory avoidance (27, 73), contextual fear (75), open field habituation (73) and water maze reference tasks (76). There is no consensus about the effects of caffeine in long-term memory retrieval, with some studies showing improvement (71, 73), while others have indicated either no effect at all (39, 77) or even impairment in retrieval (75). Interestingly, the disruption of either acquisition or retrieval induced by caffeine occurs only at high doses (at least 30 mg/kg), which might reflect sensorial distortion due to loss of specificity, rather than specific mnemonic effects of the drug (53).

The above mentioned evidence suggests that adenosine tonically inhibits memory formation through activation of the more prevalent adenosine A_1 receptors (6). We can thus hypothesize that the improvement in memory acquisition induced by acute caffeine is associated preferentially with the blockade of adenosine A_1 receptors. However, this picture can change following repeated administration of either caffeine or selective adenosine A_1 receptor antagonists. Daily injections of an adenosine A_1 receptor antagonist produced a slight deterioration in spatial learning and memory in mice. Conversely, long-term treatment with an adenosine A_1 receptor agonist actually improved performance dramatically (78). The long-term caffeine treatment induces adaptive changes in the adenosinergic system, which seem to be related more to plasticity in adenosine A_1 receptors rather than in A_{2A} receptors (79). Inhibition of LTP by the activation of adenosine A_1 receptors, or the enhancement of LTP by the activation of A_{2A} receptors, both depend critically on the amount of adenosine available. Thus, low levels of adenosine will act preferentially on adenosine A_1 receptors, whereas higher levels will activate preferentially on adenosine A_{2A} receptors (7, 8). Certainly, the role of the more recently described adenosine A_3 receptor in synaptic plasticity cannot be overlooked (80). The subsequent sections of the present review will address the changes observed in the adenosinergic systems of animals, modeling some cognitive dysfunctions such as aging, AD, PD and ADHD, to highlight the promising therapeutic effects of adenosine receptor antagonists as cognitive enhancers in such conditions.

4. EFFECTS OF ADENOSINE RECEPTOR ANTAGONISTS ON COGNITIVE DEFICITS IN AGED RODENTS AND MODELS OF ALZHEIMER'S DISEASE

As a result of the intense worldwide demographic changes, rising of life expectancy and the increase in aged populations, the importance of diseases affecting elderly people has become a major public health focus (81). The number of individuals suffering from these diseases is likely to grow, especially if no attention is given to the development of novel therapeutic approaches. For instance, in the year 2000 there were about 25 million elderly people suffering from dementia, and there are estimates that this number will raise to 63 million in 2030 and to 114 million in 2050. Almost half of dementia cases occur in less developed countries, which is in sharp contrast to how care resources are distributed worldwide and how the scientific databases and research on dementia are represented (82). Among the many forms that dementia may manifest, AD accounts for about 50-60% of the cases (81). The term "AD" was originally used to designate individuals with presenile onset of symptoms, whereas the expression "senile dementia" was used when onset of cognitive deficits occurred after 65 years of age. Based largely on the great similarities between cognitive deficits and physiological alterations observed in patients suffering from AD or senile dementia, these disorders have been considered to represent a single, homogeneous disease. However, in early-onset AD the symptoms, occurrence of physiopatological alterations and the decline in the cholinergic system underlying cognitive dysfunctions are more severe than in senile dementia (81, 83, 84). It is still uncertain, though, if they constitute separate diseases or form part of a continuum of an intensified aging process (85). The pathogenesis of AD includes characteristic microscopic lesions called "neuritic plaques" and "neurofibrillary tangles" in structures of the medial temporal lobe and brain cortex, together with a loss of neurons and synapses. Several pathogenic mechanisms underlying these changes have been postulated, but aggregation of β-amyloid (Aβ) peptides and their deposition in plaques are pivotal events (81). Initially, Aβ found in senile plaques was thought to be an abnormal protein. However, this is not true, since Aβ is produced constitutively during normal cell metabolism (86). Therefore, the role of Aβ aggregation in AD has been reviewed and nowadays the central hypothesis for the cause of AD is the "amyloid cascade hypothesis", which states that an imbalance between the production and clearance of Aβ in the brain gives rise to the neurodegenerative process (87).

Animal models of dementia (including AD) are thus based on the biological alterations observed in these human pathologies. While cognitive deficits associated with aging are obviously achieved by letting animals live until advanced age, developing animal models of AD is not so simple. Unlike nonhuman primates and a few other animals (88), aging rodents do not spontaneously develop the characteristic hallmarks of AD, i.e. the amyloid plaques and neurofibrillary tangles. However, their use in research is supported by the occurrence of senescence-related cognitive decline and behavioral alterations that correlate with AD-like neurochemical alterations, such as a marked age-associated hypofunctioning of the cholinergic system (89, 90). Based on the same principle that AD patients present a reduction in cholinergic functions, pharmacologically-induced animal models are available,

Table 1. Effects of adenosine receptor antagonists on the cognitive deficits in aged rodents

Animal model	Learning task	Drug treatment	Action	Result	Ref
22 month-old Wistar rats	Lashley III maze	Guarana extract, 0.3 – 3 mg/ml, v.o. ad libitum for 12 months	Guarana extract possesses nonselective A_1/A_{2A} antagonists, such as caffeine and theophylline	↔	102
22 month-old Wistar rats	Lashley III maze	Caffeine, 0.1 mg/ml, v.o. ad libitum for 12 months	Nonselective A_1/A_{2A} antagonist	↔	102
12 month-old Wistar rats	Social recognition	Caffeine, 10-30 mg/kg, i.p., 30 min before 1st trial	Nonselective A_1/A_{2A} antagonist	↑	33
12 month-old Wistar rats	Social recognition	ZM241385, 0.5-1 mg/kg, i.p. 30 min before 1st trial	Selective A_{2A} antagonist	↑	33
12 month-old Wistar rats	Social recognition	DPCPX, 1-3 mg/kg, i.p. 30 min before 1st trial	Selective A_1 antagonist	↔	33

Ref: reference, ↑: Increase ↔: no change

including scopolamine-induced amnesia and animals with lesions of the basal forebrain, in particular the nucleus basalis magnocellularis, where most of the somata of cholinergic neurons is found (91, 92). Although valuable for studying the cognitive deficits related to cholinergic hypofunction, their use is limited by the fact that they are not progressive, and cholinergic hypofunction itself is not directly related to the development of neurodegeneration in AD, but rather a consequence of it. Another approach to inducible models of AD comprises the central injection of Aβ peptides into healthy adult animals. A great advantage of this model is that AD can be mimicked in rodents by a single intracerebroventricular (i.c.v.) injection of Aβ peptides, inducing stable long-term deficits. Depending on where they are infused, Aβ can lead to AD-like behavioral alterations, such as decreased exploration (93), deficits in spatial and nonspatial learning and memory (93-96), disruption of cholinergic functions (93, 95) and loss of functional synapses (94, 97). These models based on intracerebral Aβ injection support the hypothesis that these peptides play a central role in AD pathogenesis and allow preclinical tests of drugs. More recently, transgenic mice that overexpress APP and present high levels of Aβ peptides that accumulate with aging have been developed (88). The first transgenic model developed was with PDAPP mice (98), but there are now several APP mutated transgenic mice available which constitute the most promising models in AD research (99).

Scientific support for the idea that adenosine receptor antagonists, such as caffeine, could be useful to prevent the cognitive deficits observed in dementia is provided by an epidemiological study showing an inverse correlation between coffee intake and the occurrence of AD later on in life (100). Caffeine improves the cognitive deficits caused by scopolamine administration in humans, thus strengthening the notion that antagonism of adenosine receptors reverses cholinergic hypofunction caused by muscarinic receptor blockade (101). Evidence from animal models is in line with these findings. Tables 1 and 2 summarize the available data concerning the effects of adenosine receptor antagonists in animal models of aging and AD-like cognitive deficits. As far as we know, the first attempt to prove that antagonism of adenosine receptors improves age-related cognitive deficits in animals came with a study comparing the beneficial effects of chronic treatment with either caffeine or an extract of a Brazilian plant named guarana, (*Paullinia cupana*) to ameliorate the deficits of 22 month-old rats in a complex Lashley III maze (102). The phytochemical analysis of guarana extracts reveals the presence of various methylxantine derivatives, including caffeine, theophylline and theobromine. Indeed, both caffeine- and guarana-treated aging rats showed a trend towards memory improvement in the Lashley maze, whereas guarana also improved memory deficits presented by scopolamine-treated rats and mice in the step-through inhibitory avoidance task (102). In line with these results, the performance of scopolamine-treated rats in the step-down inhibitory avoidance was improved after i.c.v. injection of theophylline, another nonselective adenosine receptor antagonist (103). Selective adenosine A_1 or A_3 receptor antagonists also improve scopolamine-induced deficits in rats tested in the step-through inhibitory avoidance task (66, 104, 105) and in the Y-maze spontaneous alternation task (66, 104, 105).

A functional link between a hypofunctioning cholinergic system and age-related cognitive deficits was reported in an elegant experiment showing that the medial prefrontal cortex of aged rats is less liable to release acetylcholine upon depolarization (106). There is an inverse relationship between the cholinergic and adenosinergic systems in aging. While acetylcholine content tends to be reduced in aged brains, adenosine content is increased (9, 11, 103). Since adenosine can reduce the release of several neurotransmitters, including acetylcholine (107, 108), it might be postulated that adenosine "accumulation" plays an important role in age-related cognitive deficits and hence may be considered an interesting target for pharmacological manipulation. Indeed, while evaluating olfactory working memory of aged rats we showed that caffeine administration improves the deficits in social recognition presented by 12 month-old rats (33). Similar results were obtained by selective blockade of adenosine A_{2A} (but not $A_{1)}$ receptors. Such results further highlight the importance of adenosine A_{2A} receptors in the accessory olfactory bulb of rodents (109), and suggest that adenosinergic neurotransmission changes, including imbalance in the expression of adenosine A_1 and A_{2A} receptors, may occur during aging and contribute to the cognitive deficits (1, 10, 110).

Aging in rats has been found to increase the number of adenosine A_{2A} receptors, as well as their coupling to G protein and their efficiency to increase cAMP in different brain areas (10, 110). Conversely, expression of adenosine A_1 receptors is reduced in the brain of aged rodents (110, 111). Such findings indicate that, with aging, there is a reduced ability of adenosine A_1 receptor agonists to inhibit neurotransmission, and an increased efficiency of adenosine A_{2A} receptor agonists to facilitate neurotransmitter release and synaptic transmission

Table 2. Effects of adenosine receptor antagonists on the cognitive deficits in animal models of Alzheimer's disease

Animal model	Learning task	Drug treatment	Action	Result	Ref
β-amyloid 25-35 peptide injected i.c.v. in Swiss albino mice	Y-maze spontaneous alternation task Step-down inhibitory avoidance	Caffeine, 80 mg/kg, i.p. 30 min before β-amyloid treatment Caffeine, 1 mg/ml, v.o. ad libitum + acute i.p. injection of 30 mg/kg 30 min before β-amyloid Caffeine, 30 mg/kg, i.p. for 4 days	Nonselective A_1/A_{2A} antagonist	↑	35
β-amyloid 25-35 peptide injected i.c.v. in Swiss albino mice	Y-maze spontaneous alternation task Step-down inhibitory avoidance	SCH58261, 0.5 mg/kg, i.p. for 4 days	Selective A_{2A} antagonist	↑	35
APPsw trangenic mice	Water maze reference task Water maze cued task Circular platform Radial arm water maze	Caffeine, 0.3 mg/ml, v.o. ad libitum for 4 months.	Nonselective A_1/A_{2A} antagonist	↑	34
Scopolamine-treated Sprague-Dawley rats	Step-down inhibitory avoidance	Theophylline	Nonselective A_1/A_{2A} antagonist	↑	103
Scopolamine-treated Sprague-Dawley rats	Step-through inhibitory avoidance	BIIP20, 1-3 mg/kg, v.o. 90 min pretraining	Selective A_1 antagonist	↑	66
Scopolamine-treated Wistar rats	Step-through inhibitory avoidance	FR194921, 0.3-1 mg/kg, i.p. immediately posttraining	Selective A_1 antagonist	↑	104
Scopolamine-treated Swiss albino mice	Y-maze spontaneous alternation task Step-through inhibitory avoidance	IB-MECA, 0.05-0.11 mg/kg, i.p. 20 min pretraining	Selective A_3 antagonist	↑	105

Ref: reference, ↑: Increase

(9-11). The aged brain lacks tonic basal adenosine A_1 receptor-mediated activity and displays changes in ATP/adenosine metabolism that favor neurotransmission involving adenosine A_{2A} receptors (9). Of note, the adenosine A_{2A} receptors in aged brains lack somehow the ability to inhibit the binding and function of adenosine A_1 receptors, which may be essential for A_{2A} receptor-mediated facilitation of synaptic transmission in young rats (10, 108). This suggests that the function of adenosine A_{2A} receptors shifts from being mainly a modulator of A_1 receptor-mediated responses in young rats to a direct facilitatory system, independent of A_1 receptors, in aged rats (10). This apparent loss of an adenosinergic inhibitory tonus and the appearance of a stimulatory one in aged individuals may be important to the enhancement of synaptic efficacy and might constitute a response to the decreased number of functional synapses. As mentioned in the Introduction, a physiological cost may be represented by an increased vulnerability of senescent neurons to excitatory amino acid toxicity, since in the aged brain adenosine lacks its A_1 receptor-mediated neuroprotective effects (12-14).

Interestingly, in contrast with what occurs for adenosine A_1 receptors, the inactivation of adenosine A_{2A} receptors confers neuroprotection in diverse brain regions ranging from substantia nigra, striatum to hippocampus and cortex against injuries due to excitotoxicity, mitochondrial toxicity or brain ischemia (112-114). Thus adenosine A_{2A} receptor antagonists can provide such a broad spectrum of neuroprotection seems to be associated to the modulation of common cellular processes (such as glutamate release and neuroinflammation) to influence functional outcome during brain injury (115).

The same pattern of A_{2A} receptor-mediated excitotoxicity is observed in the Aβ animal model of AD. The massive neurotoxicity induced by incubation of cerebellar neurons with the $A\beta_{25-35}$ peptide is reduced in the presence of caffeine or selective adenosine A_{2A} receptor antagonist, but not in the presence an adenosine A_1 receptor antagonist (116). In the same way, acute treatment with a high dose of caffeine (80 mg/kg, i.p.), or chronic treatment with a intermediate one (30 mg/kg, i.p.), has been shown to prevent the memory deficits induced by i.c.v. administration of $A\beta_{25-35}$ in mice evaluated in the step-down inhibitory avoidance and the Y-maze spontaneous alternation tasks 7 days after peptide injection (79). The authors argue that the chronic treatment with caffeine takes advantage of the fact that adenosine A_1 receptor-mediated responses are desensitized (i.e. by tolerance) due to caffeine administration, whereas adenosine A_{2A} receptor-mediated responses are not (79). Interestingly, these effects can be mimicked by intraperitoneal (i.p.) treatment with caffeine or a selective adenosine A_{2A} receptor antagonist from 2 days before, to 1 day after, $A\beta_{25-35}$ i.c.v. administration (35). This study emphasizes the importance of adenosine A_{2A} receptors in the cognitive deficits induced by Aβ peptides and suggests that parallel to what occurs in aged rats, an imbalance in the adenosine-mediated neurotransmission may occur in this model.

Caffeine's also display neuroprotective effects against Aβ peptides in transgenic APPsw mice (34). Such lines of transgenic animals which overexpress APP have the advantage that they accumulate Aβ peptides in the brain over time, with consequent progressive cognitive deficits, better reflecting the human condition (117, 118). Daily oral treatment with caffeine (0.3 mg/ml) over 6 months improved the cognitive deficits presented by 10 month-old APPsw mice in spatial reference, working memory and strategy-shift tasks of the water maze, and reduced soluble and insoluble $A\beta_{1-40}$ peptide levels in the hippocampus. Caffeine also reduced the production of $A\beta_{1-40}$ and $A\beta_{1-42}$ peptides in APPsw cultured neurons (34). Finally, this elegant study investigated the expression of brain adenosine receptors in APPsw transgenic mice.

Surprisingly, unlike the shift in adenosine A_{2A}/A_1 receptor subtype expression observed with aging of non-trangenic animals, the brains of APPsw mice displayed an increase in the expression of adenosine A_1 receptors in the frontal cortex and of A_{2A} receptors in the hippocampus, and a reduction in the total brain adenosine content. Notably, oral chronic treatment of APPsw mice with caffeine (1.5 mg/mouse) increased brain adenosine levels, but did not alter the patterns of adenosine receptors expression, locomotion, anxiety-like behavior or body weight (34), suggesting that caffeine intake at this dosage range is harmless to such animals.

Taken together, evidence from animal models indicates that our comprehension of the role of the adenosinergic system in dementia is still far from complete. While there is a clearer picture in studies focusing on age-related cognitive deficits, there is no direct link with those focusing on Aβ peptides in animal models of AD. Possibly, studies combining data from both types of approaches will enable a more desired view.

5. EFFECTS OF ADENOSINE RECEPTOR ANTAGONISTS ON LEARNING AND MEMORY IMPAIRMENTS IN RODENT MODELS OF PARKINSON'S DISEASE

PD is the second most common neurodegenerative disorder, following AD, affecting approximately 1% of the population older than 50 years (119). Current estimates from the American Parkinson's Disease Foundation mention 1.5 million American citizens suffering from this disease. Since the incidence of the disease increases with age (the most important risk factor), it is likely that the number of people suffering from PD will rise as improved health care lengthens the average life span. Classically, PD is considered to be a motor system disease and its diagnosis is based on the presence of a set of cardinal motor signs (e.g. rigidity, bradykinesia, rest tremor and postural reflex disturbance). These symptoms of PD result mainly from the progressive degeneration of dopamine neurons of the substantia nigra pars compacta (SNc) that project predominantly to the striatum (120), a fact that contributes to the prevailing view that the basal ganglia are mainly concerned with motor control functions (121). Unfortunately, the patients only fulfill these clinical criteria when 60-70% of the neurons of the SNc are degenerated and the striatal dopamine content is reduced by 80% (122-125).

In addition to motor control, the basal ganglia system is also implicated in learning and memory processes (126). Subtle cognitive impairments consisting mainly of executive dysfunction with secondary visuospatial and mnemonic disturbances can be observed in the early stages of PD (127, 128). In about 20-40% of patients, these problems may eventually proceed to dementia, which constitutes an important risk factor for caregiver distress, decreased quality of life, and nursing home placement (129). Even non-demented PD patients have been reported to present visuospatial working memory deficits (128, 130-132) and habit learning deficits (133, 134). Although there are reports of declarative (or episodic) memory impairments in PD (135, 136), they are less severe in comparison to other neurodegenerative disorders such as AD (127, 135, 137).

Comprehension of the role of adenosine in the basal ganglia and its anatomical and functional relationship with the striatal dopamine D_1 and D_2 receptors has increased over the last years. Adenosine receptors are densely expressed in the striatum and exert a modulatory influence on dopamine neurotransmission (138, 139). There is considerable evidence for an antagonistic interaction between A_{2A} and D_2 and also A_1 and D_1 receptors in the striatum (140, 141), and both caffeine and adenosine A_{2A} receptor antagonists exert neuroprotective actions on dopamine neurons in the SNc (112). Caffeine also directly increases dopamine release from striatal nerve terminals (142), an effect which is also mimicked by the selective adenosine A_{2A} receptor antagonist ZM241385 in striatal synaptosomes (143). These putative anti-Parkinson effects may explain the finding that the risk of PD is significantly reduced among coffee drinkers and that caffeine is the constituent responsible (144-147). Based on these promising effects, adenosine receptor antagonists are being pursued as putative drugs to treat PD (148, 149).

PD is one of many human diseases which do not appear to have arisen spontaneously in animals. However, the characteristic features of the disease can be mimicked in animals more or less faithfully through the administration of various neurotoxic agents that disturb dopaminergic neurotransmission (150-152). Currently, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) represents the most important and frequently used neurotoxin applied in animal models of PD. Bilateral infusion of MPTP directly into the rat SNc causes a partial loss of dopaminergic neurons and depletion of striatal dopamine, resulting in sensorial and memory deficits with no major motor impairments, thus modeling the early phase of PD (153-156).

The fact that most of the drugs currently available for the PD treatment (such as levodopa) are more efficient in alleviating motor, rather than cognitive, impairments has led many researchers to postulate non-dopaminergic mechanisms for the cognitive symptoms of this disease (157-160). In accordance with this idea, the administration of benserazide/levodopa to MPTP-lesioned rats, at a dose that restores the striatal dopamine levels, fails to reverse MPTP-induced learning and memory impairment (161). The failure of levodopa to improve the memory deficits in both clinical studies and in bilaterally MPTP-lesioned rats reinforces the adequacy of this animal model to explore the potential of alternative drug therapies for the treatment of PD-related cognitive impairments.

As mentioned in section 3, the results obtained in different laboratories suggest that caffeine as well as selective adenosine A_1 and A_{2A} receptor antagonists can improve rodent learning and memory in diverse behavioral tasks (28-32). However, very few studies have specifically assessed the effects of caffeine or selective adenosine

Table 3. Effects of adenosine receptor antagonists on the cognitive deficits in animal models of Parkinson's disease

Animal model	Learning task	Drug treatment	Action	Result	Ref
MPTP bilaterally injected in the SNc of Wistar rats	Two-way active avoidance	Caffeine, 0.1-0.3 mg/kg, i.p., 45 min pretraining	Nonselective A_1/A_{2A} antagonist	↑	36
Reserpine-treated Wistar rats	Social recognition	Caffeine, 10-30 mg/kg, i.p., 30 min before 1st trial	Nonselective A_1/A_{2A} antagonist	↑	37
Reserpine-treated Wistar rats	Social recognition	ZM241385, 0.5-1 mg/kg, i.p. 30 min before 1st trial	Selective A_{2A} antagonist	↑	37
Reserpine-treated Wistar rats	Social recognition	DPCPX, 1-3 mg/kg, i.p. 30 min before 1st trial	Selective A_1 antagonist	↔	37

Ref: reference, ↑: Increase ↔: no change

receptor antagonists on the cognitive impairment observed in animal models of PD. As indicated in Table 3, Gevaerd *et al.* (36) were the first to report that acute administration of caffeine (0.1-0.3 mg/kg, i.p.) reverses the impairing effect of MPTP-induced SNc lesion on the avoidance scores in the training and test sessions of a two-way active avoidance task in rats.

Another animal model widely used for investigating symptomatic anti-Parkinsonian treatments is the systemic administration of reserpine, a drug that inhibits monoamine storage in intracellular granules, and hence causes their depletion in nerve terminals and induces transient hypolocomotion and muscular rigidity (162-164). More recently, the use of low doses of reserpine (0.5 – 1.0 mg/kg) in rodents has been proposed as a behavioral approach to study the cognitive deficits (165) and depressive symptoms (166) associated with PD. Prediger *et al.* (167) demonstrated that acute reserpine treatment (1.0 mg/kg, i.p.), 24 h before the experiments, induced pronounced deficits in social recognition memory in rats. Interestingly, the reserpine-induced deficits in social recognition memor are reversed by acute administration (30 min prior to testing) of caffeine (10 or 30 mg/kg, i.p.) or the selective adenosine A_{2A} receptor antagonist ZM241385 (0.5 or 1.0 mg/kg, i.p.), but not by the adenosine A_1 receptor antagonist DPCPX (0.5 or 3.0 mg/kg, i.p.) (37). However, these same authors already had shown that these doses of DPCPX prolong social recognition memory of non-reserpinized adult rats (31). These results suggest an increased contribution of adenosine A_{2A} receptors (in detriment of A_1 receptors) in the cognitive deficits induced by reserpine administration in rats, reinforcing previous results obtained in different animal models of PD. In addition, caffeine and selective adenosine A_{2A} receptor antagonists promote contralateral rotation behavior in rats with unilateral lesions of the SNc induced by 6-hydroxydopamine (6-OHDA) (139) and reduced catalepsy induced by dopamine D_2 receptor antagonists in rats (168). Moreover, the blockade of adenosine A_{2A} receptors enhances the locomotor deficits seen in dopamine-deficient (169) and dopamine D_2 receptor-deficient mice (112, 170), as well as attenuates MPTP-induced loss of striatal dopamine and of dopamine transporter binding sites (112).

Overall, from these limited results in this field it appear that caffeine and selective adenosine A_{2A} receptor antagonists might be particularly useful to restore impaired learning and memory processes in MPTP and reserpine-treated rats.

6. COGNITIVE EFFECTS OF ADENOSINE RECEPTOR ANTAGONISTS ON THE SPONTANEOUSLY HYPERTENSIVE RAT (SHR) STRAIN, A RODENT MODEL OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

ADHD is a complex psychiatric disorder that usually manifests itself during childhood and it is characterized by three main symptoms: hyperactivity, inattention and impulsivity (171, 172, 173). The occurrence of ADHD in children is typically associated with poor academic performance, probably reflecting learning disabilities and/or attentional problems (174, 175). While hyperactive/impulsive symptoms tend to decrease with age, the inattention does not (176). ADHD patients present a disturbance in the central dopaminergic system, but other neurochemical pathways may also be implicated in their behavioral abnormalities (172, 177-179). Pharmacotherapy using psychostimulant medications such as methylphenidate or antidepressants is rigorously the only form of treatment available for ADHD. However, a great number of patients are considered non-responders due to insufficient symptom reduction or inability to tolerate these medications (180, 181). About 30 years ago, a series of clinical studies showed the beneficial effects of caffeine to ameliorate ADHD symptoms in children (182-184). These studies were largely neglected, probably due to the large availability of psychostimulant medicines manufactured by pharmaceutical companies in the 70's (185). More recently, there has been a new wave of scientific interest in the potential of caffeine for ADHD treatment, with special regard to the improvement of the cognitive deficits associated with this disease (186). Some clinicians consider caffeine consumption by the ADHD patients as a form of self-treatment, although no empirical studies have been carried out to adequately test this hypothesis (186). Epidemiological data have indicated a lower prevalence rate of ADHD in countries where the population ingests large daily amounts of caffeine (184, 187). This section will focus on recent reports of the effects of caffeine and selective adenosine A_1 and A_{2A} receptor antagonists in the cognitive performance of SHR, a validated animal model of ADHD. Although the SHR are considered to be the most promising and suitable model of ADHD, reflecting many behavioral and neurochemical aspects of the disease, there are other interesting animal models of ADHD (178).

Behavioral studies have shown a reduced performance of SHR in cognitive tests as compared to other commonly used rat strains. For instance, SHR present learning deficits in the conditional avoidance task (188), the two-way shuttle box avoidance task (189), the radial-

Table 4. Effects of adenosine receptor antagonists on the cognitive deficits in spontaneously hypertensive rats SHR, an animal model of attention deficit hyperactivity disorder ADHD

Animal model	Learning task	Drug treatment	Action	Result	Ref
SHR	Social recognition	Caffeine, 3-10 mg/kg, i.p., 30 min before 1st trial	Nonselective A_1/A_{2A} antagonist	↑	38
SHR	Water maze reference task	Caffeine, 1-10 mg/kg, i.p., 30 min before training	Nonselective A_1/A_{2A} antagonist	↑	39
SHR	Water maze reference task	Caffeine, 3 mg/kg, i.p., posttraining or 30 min pretest	Nonselective A_1/A_{2A} antagonist	↔	39
SHR	Object recognition	Caffeine, 3-10 mg/kg, i.p., 30 min before presentation or discrimination phases	Nonselective A_1/A_{2A} antagonist	↑	Data not published
SHR	Social recognition	ZM241385, 0.5-1 mg/kg, i.p. 30 min before 1st trial	Selective A_{2A} antagonist	↑	38
SHR	Social recognition	DPCPX, 1-3 mg/kg, i.p. 30 min before 1st trial	Selective A_1 antagonist	↔	38

Ref: reference, ↑: Increase ↔: no change

arm maze task (190-192), the social recognition task (38), and the spatial version of the water maze task (39, 193-195). Some studies have also focused on the contribution of the poor attentional performance of SHR rats to their learning dysfunctions (193, 196). The usefulness of the SHR strain for the study of cognitive dysfunctions presented by ADHD is further validated pharmacologically by its sensitivity to alleviation by methylphenidate, the first-choice drug for ADHD treatment (197). The aim of this section is to review the effects of adenosine receptor antagonists in the SHR strain, in order to explore the potentiality of the adenosinergic system as a possible therapeutic target for cognitive improvement in ADHD. Table 4 summarizes the experimental data available on this issue. The first reports of the caffeine effects in the cognitive performance of SHR came two years ago (38, 39). In the social recognition model of olfactory working memory, SHR spent more time investigating the juvenile rat in the first 3-min exposure in comparison to Wistar rats, and they showed a clear impairment in the social recognition ability when the same juvenile rat was re-exposed 30 min later (38). A minute-by-minute analysis of the same data revealed that SHR rats do not habituate well to the presence of the juvenile rat. This is interpreted as impairment in short-term working memory and was confirmed by the use of the habituation-dishabituation paradigm (38). Administration of caffeine (3-10 mg/kg, i.p.) prior to the first juvenile exposure improved the ability of SHR to habituate to the juvenile rat and reduced the investigation time during the re-exposure of the familiar juvenile (30 min later). The effects of adenosine receptors in the olfactory working memory of SHR were further explored using the selective adenosine A_1 and A_{2A} receptor antagonists DPCPX (1-3 mg/kg, i.p.) and ZM241385 (0.5-1 mg/kg, i.p.), respectively. In contrast to what was found in "normal" rats (see section 3), the ADHD-like behavior of SHR was improved only by the selective blockade of adenosine A_{2A} receptor, but not by the blockade of the A_1 subtype. This indicates that some behavioral imbalance in the adenosinergic tonus must contribute to the working memory deficits presented by SHR (38).

Besides the deficits in olfactory working memory, evidence shows long-term memory dysfunction in SHR (see above). However, it is not entirely clear whether SHR present learning disabilities or impairment in some of the specific phases of memory processes (i.e., consolidation and/or evocation). A recent report using the water maze reference task tried to provide some clues on this issue (39). The authors used an "extended" water maze protocol to test the following hypothesis: "*If the SHR had more opportunity to learn, would they still present memory deficits?*" It was observed that using a training protocol of 10 trials in a single day, rather than the more common training protocol with 4-6 trials over 4 days, the SHR will no longer present memory retention deficits in a probe test done 48 h later. This data suggests that SHR do not have deficits in memory consolidation and/or evocation, but in fact they have learning disabilities that may be surpassed using a more intensive training schedule (39). Interestingly, the pretraining administration of caffeine (1-10 mg/kg, i.p.) also successfully improved SHR's performance. However, neither post-training nor pretest administration of caffeine (3 mg/kg, i.p.) were effective to improve the spatial learning deficits of SHR in the water maze task (39). Regarding the ability of selective adenosine receptor antagonists to improve SHR's spatial learning/memory, at least to our knowledge, there are no data available. As can be seen in Figure 1B,C, the higher doses of both DPCPX (3 mg/kg, i.p.) and ZM241385 (1 mg/kg, i.p.) improved the learning abilities of SHR, indicating the participation of both adenosine A_1 and A_{2A} receptors in the spatial learning deficits verified in SHR. These treatments did not alter the swim speed during the first water maze trial (Figure 1D). As expected, the learning improvement induced by the pharmacological blockade of adenosine A_1 or A_{2A} receptors led to a consequent improvement in memory retention (Figure 2). Both antagonists (DPCPX and ZM241385) reduced the latencies of SHR to enter the platform zone for the first time during the probe trial (Figure 2A). However, only DPCPX-treated rats exhibited an increased number of entries and increased distance traveled in the quadrant where the platform was located during training trials (i.e. the SE quadrant) (Figure 2B,C). The percentage of time spent swimming in this quadrant was not altered due to drug treatment (Figure 2D). The plots of the swim pathways illustrated in Figure 2E reinforce the striking improvement in the SHR's performance due to administration of selective adenosine receptor antagonists.

It seems to occur a distinct contribution of the adenosine A_1 and A_{2A} receptors to the performance of SHR in the social recognition and water maze reference tasks. This probably reflects distinct requirements of neural substrates underlying the execution of these behavioral paradigms. The adenosine A_{2A} receptor seems to be a more relevant pharmacological target for improvement of SHR's performance in the social recognition, while the blockade of the adenosine A_1 receptor subtype exerted a major impact on the performance of the same rat strain in the spatial version of the water maze task. Since in these

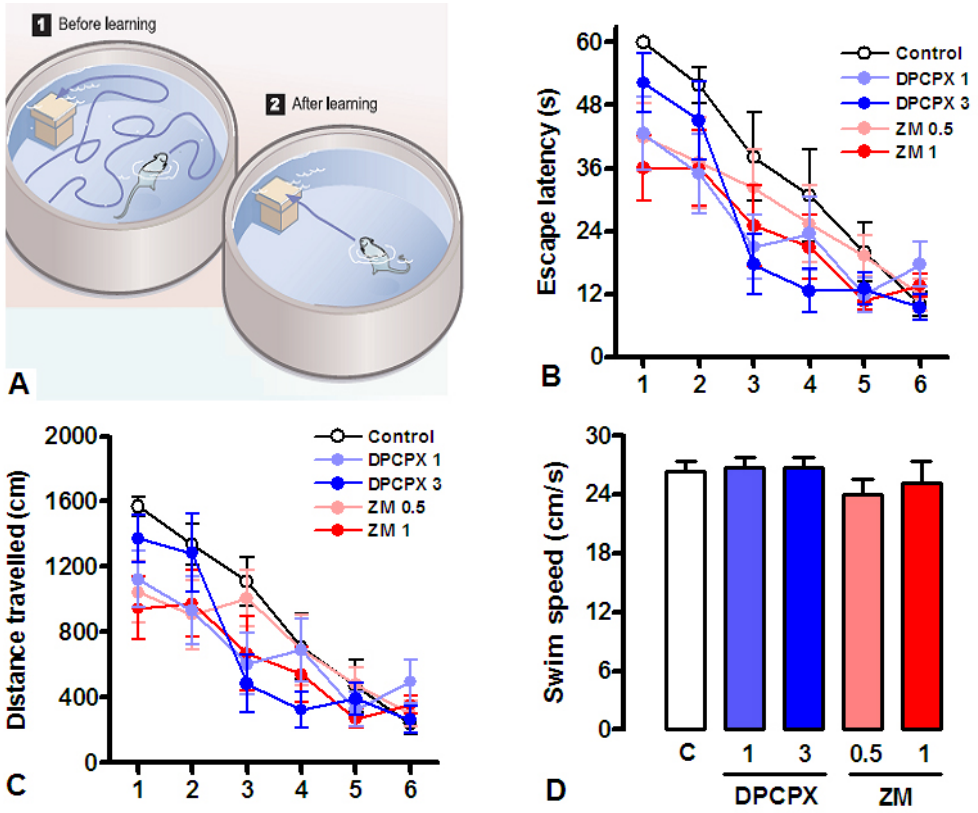

Figure 1. Schematic drawing of the procedure used for training the spontaneously hypertensive rats (SHR) in the water maze reference task. The platform was maintained in a fixed position in the center of the SE quadrant throughout the 6 trials of the training session (A). Effects of DPCPX (1, 3 mg/kg, i.p.) and ZM241385 (0.5, 1 mg/kg, i.p.), selective antagonists of A1 and A2a adenosine receptors, respectively, on the performance of SHR rats in the training session of the water maze spatial reference task. Data are presented as mean ± S.E.M. of the escape latencies (B), distance traveled (C) during the 6 trials and speed (D) during the 1st trial. Analysis of variance (ANOVA) revealed that both DPCPX (3 mg/kg) and ZM241385 (1 mg/kg) improved the performance of SHR rats in the training session. There were no alterations in the swim speed parameter.

previous studies the adenosinergic drugs were administered systemically, it is not possible to determine their exact site of action. Of note, the olfactory bulb and the hippocampus, which are highly implicated in the social recognition memory and spatial learning, present high expression of adenosine A_{2A} (109) and A_1 receptors (198), respectively. In addition, adenosine A_{2A} receptors modulate the release of different neurotransmitters in the olfactory bulb of rodents, including norepinephrine and dopamine that are involved in social memory (167, 199). On the other hand, evidence suggests that adenosine A_1 receptors, modulates neurotransmitter release (1) and neuronal excitability (198) in the rat hippocampus.

At this point, one important question might be raised: "*Why does caffeine (and selective adenosine receptor antagonists) improve learning of SHR but not of normal rats?*" This question is quite far from being answered, particularly regarding ADHD-like learning dysfunctions, due to the lack of sufficient experimental data. We presume that the answer may rely on alterations in the adenosinergic system of SHR. For instance, SHR present reduced activity of adenosine deaminase, the enzyme that catabolizes adenosine to inosine, which results in an increased amount of adenosine available for neuromodulation in the brain of SHR (200). As previously mentioned in the section 3, a greater availability of adenosine in the synaptic cleft increases the contribution of A_{2A} receptors to the final cellular response. Also, there is evidence of a reduced affinity of A_1 receptors in SHR's brain (201), which is an additional indication of the importance of the adenosine A_{2A} receptors in the cognitive functions (or dysfunctions) presented by this strain. Studies in human subjects also point to distinct effects of caffeine in ADHD patients and healthy subjects, somehow yielding greater cognitive improvements in the former (186). We believe that the behavioral data presented here, as well as the suggestion of a shift in the importance of adenosine receptor subtype observed in SHR neurotransmission, may contribute to future promising studies in this field.

Finally, results from previous clinical studies on the efficacy of caffeine have been inconsistent, with some authors demonstrating an improvement of general condition in ADHD (183, 187, 202), while others have not found convincing positive caffeine effects at all (203-205). These studies, performed with a small number of subjects, have

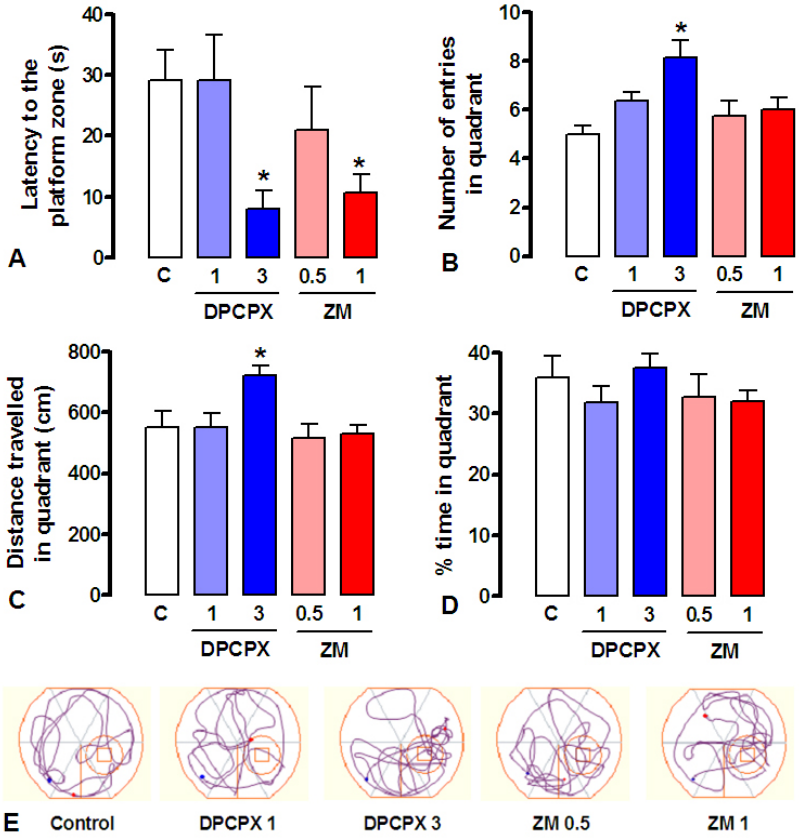

Figure 2. Performance of spontaneously hypertensive rats (SHR) in the probe test of the water maze reference task. Forty-eight hours after the training session, the animals were placed in the water maze for 60 s in the absence of the platform. The rats were treated with DPCPX (1, 3 mg/kg, i.p.) or ZM241385 (0.5, 1 mg/kg, i.p.) before the training session. Data are represented as mean ± S.E.M. of the latency to reach the platform zone (A), number of entries in the SE quadrant (B), distance traveled in the SE quadrant (C) and percentage of time in the SE quadrant (D). Track plots showing the swim pathways of one representative animal of each experimental group in the probe test (E). * $p<0.05$ compared to the control group (Newman-Keuls post hoc test).

no substantial impact on the alteration of clinical treatment strategies, despite the fact that they have not been systematically refuted. For this reason, the consensus in the field is that adjunctive caffeine is not contra-indicated for the treatment of ADHD, but it is also not a viable replacement for the currently used drugs (206). Although research is at a very early stage, the findings reviewed above further highlight the cognitive-enhancing properties of caffeine in the social recognition and water maze tasks evaluated in the SHR animal model of ADHD.

7. SUMMARY AND PERSPECTIVE

The findings presented in this review suggest that the role of the adenosinergic system in learning and memory processes is more complex than first believed, and that it must involve integration between the different types of memory and specific phases of memory, as well as the existence of different subtypes of adenosine receptors which are differentially expressed in specific brain areas. Nonetheless, recent studies have emphasized the promising therapeutic effects of adenosine receptor antagonists as cognitive enhancers. Acute doses of a nonselective adenosine receptor antagonist such as caffeine can improve rodent learning and memory in certain tasks. The occurrence of interactions and/or plasticity between adenosine A_1 and A_{2A} receptors in different brain areas associated with learning and memory processes, makes it difficult to attribute behavioral effects explicitly to a single subtype of adenosine receptors. It is conceivable that adenosine A_{2A} receptors have low expression in a healthy brain, suggesting that A_1 receptor-mediated neurotransmission would be much more relevant for mnemonic functions in "physiological" conditions. However, this pattern of expression and the functional importance of each adenosine receptor subtype can change in certain non-homeostatic (i.e., "pathological") conditions. In particular, caffeine and selective adenosine A_{2A} receptor antagonists might afford protection against memory dysfunction elicited in experimental models of aging, AD, PD and, in the SHR strain, a putative genetic model of ADHD. In addition, the results indicating the potential of selective adenosine A_3 receptor antagonists to improve cognitive deficits in scopolamine-treated animals points to a possible relevance of this less abundant adenosine receptor in cognitive functions. Therefore, it is hoped that greater experimental efforts, as well as novel tools, will help clarify more precisely the contribution of each

adenosine receptor subtype in cognitive disorders. This approach may also provide new clues as to the neurochemical basis of memory. Finally, the development of more efficacious compounds targeting adenosine A_{2A} and perhaps A_3 receptors will greatly aid research in this area.

8. ACKNOWLEDGEMENTS

The authors gratefully acknowledge Prof. Giles A. Rae for editorial assistance. Some of the research reviewed in this article was supported by the Brazilian agencies Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenacão de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Apoio à Pesquisa Científica e Tecnológica do Estado de Santa Catarina (FAPESC).

9. REFERENCES

1. Cunha, R. A.: Adenosine as a neuromodulator and as a homeostatic regulator in the nervous system: different roles, different sources and different receptors. *Neurochem Int* 38, 107-125 (2001)
2. Snyder, S. H., J. J. Katims, Z. Annau, R. F. Bruns & J. W. Daly: Adenosine receptors and behavioral actions of methylxanthines. *Proc Natl Acad Sci U S A* 78, 3260-3264 (1981)
3. Fredholm, B. B., I. J. AP, K. A. Jacobson, K. N. Klotz & J. Linden: International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. *Pharmacol Rev* 53, 527-552 (2001)
4. Linden, J.: Molecular approach to adenosine receptors: receptor-mediated mechanisms of tissue protection. *Annu Rev Pharmacol Toxicol* 41, 775-787 (2001)
5. Cunha, R. A.: Neuroprotection by adenosine in the brain: From A_1 receptor activation to A_{2A} receptor blockade. *Purinergic Signal* 1, 111-134 (2005)
6. Ribeiro, J. A., A. M. Sebastiao & A. de Mendonca: Adenosine receptors in the nervous system: pathophysiological implications. *Prog Neurobiol* 68, 377-392 (2003)
7. Almeida, T., R. J. Rodrigues, A. de Mendonca, J. A. Ribeiro & R. A. Cunha: Purinergic P2 receptors trigger adenosine release leading to adenosine A2A receptor activation and facilitation of long-term potentiation in rat hippocampal slices. *Neuroscience* 122, 111-121 (2003)
8. Cunha, R. A., P. Correia-de-Sa, A. M. Sebastiao & J. A. Ribeiro: Preferential activation of excitatory adenosine receptors at rat hippocampal and neuromuscular synapses by adenosine formed from released adenine nucleotides. *Br J Pharmacol* 119, 253-260 (1996)
9. Cunha, R. A., T. Almeida & J. A. Ribeiro: Parallel modification of adenosine extracellular metabolism and modulatory action in the hippocampus of aged rats. *J Neurochem* 76, 372-382 (2001)
10. Lopes, L. V., R. A. Cunha & J. A. Ribeiro: Increase in the number, G protein coupling, and efficiency of facilitatory adenosine A2A receptors in the limbic cortex, but not striatum, of aged rats. *J Neurochem* 73, 1733-1738 (1999)
11. Sperlagh, B., G. Zsilla, M. Baranyi, A. Kekes-Szabo & E. S. Vizi: Age-dependent changes of presynaptic neuromodulation via A1-adenosine receptors in rat hippocampal slices. *Int J Dev Neurosci* 15, 739-747 (1997)
12. Halle, J. N., C. E. Kasper, J. M. Gidday & B. J. Koos: Enhancing adenosine A1 receptor binding reduces hypoxic-ischemic brain injury in newborn rats. *Brain Res* 759, 309-312 (1997)
13. Johansson, B., L. Halldner, T. V. Dunwiddie, S. A. Masino, W. Poelchen, L. Gimenez-Llort, R. M. Escorihuela, A. Fernandez-Teruel, Z. Wiesenfeld-Hallin, X. J. Xu, A. Hardemark, C. Betsholtz, E. Herlenius & B. B. Fredholm: Hyperalgesia, anxiety, and decreased hypoxic neuroprotection in mice lacking the adenosine A1 receptor. *Proc Natl Acad Sci U S A* 98, 9407-9412 (2001)
14. Meldrum, B. & J. Garthwaite: Excitatory amino acid neurotoxicity and neurodegenerative disease. *Trends Pharmacol Sci* 11, 379-387 (1990)
15. Jacobson, K. A. & Z. G. Gao: Adenosine receptors as therapeutic targets. *Nat Rev Drug Discov* 5, 247-264 (2006)
16. Dixon, A. K., A. K. Gubitz, D. J. Sirinathsinghji, P. J. Richardson & T. C. Freeman: Tissue distribution of adenosine receptor mRNAs in the rat. *Br J Pharmacol* 118, 1461-1468 (1996)
17. de Mendonca, A. & J. A. Ribeiro: Endogenous adenosine modulates long-term potentiation in the hippocampus. *Neuroscience* 62, 385-390 (1994)
18. de Mendonca, A., T. Almeida, Z. I. Bashir & J. A. Ribeiro: Endogenous adenosine attenuates long-term depression and depotentiation in the CA1 region of the rat hippocampus. *Neuropharmacology* 36, 161-167 (1997)
19. Hameleers, P. A., M. P. Van Boxtel, E. Hogervorst, W. J. Riedel, P. J. Houx, F. Buntinx & J. Jolles: Habitual caffeine consumption and its relation to memory, attention, planning capacity and psychomotor performance across multiple age groups. *Hum Psychopharmacol* 15, 573-581 (2000)
20. Haskell, C. F., D. O. Kennedy, K. A. Wesnes & A. B. Scholey: Cognitive and mood improvements of caffeine in habitual consumers and habitual non-consumers of caffeine. *Psychopharmacology (Berl)* 179, 813-825 (2005)
21. Johnson-Kozlow, M., D. Kritz-Silverstein, E. Barrett-Connor & D. Morton: Coffee consumption and cognitive function among older adults. *Am J Epidemiol* 156, 842-850 (2002)
22. Smit, H. J. & P. J. Rogers: Effects of low doses of caffeine on cognitive performance, mood and thirst in low and higher caffeine consumers. *Psychopharmacology (Berl)* 152, 167-173 (2000)
23. van Boxtel, M. P., J. A. Schmitt, H. Bosma & J. Jolles: The effects of habitual caffeine use on cognitive change: a longitudinal perspective. *Pharmacol Biochem Behav* 75, 921-927 (2003)
24. Corodimas, K. P. & H. Tomita: Adenosine A1 receptor activation selectively impairs the acquisition of contextual fear conditioning in rats. *Behav Neurosci* 115, 1283-1290 (2001)
25. Normile, H. J. & R. A. Barraco: N6-cyclopentyladenosine impairs passive avoidance retention by selective action at A1 receptors. *Brain Res Bull* 27, 101-104 (1991)

26. Ohno, M. & S. Watanabe: Working memory failure by stimulation of hippocampal adenosine A1 receptors in rats. *Neuroreport* 7, 3013-3016 (1996)
27. Zarrindast, M. R. & B. Shafaghi: Effects of adenosine receptor agonists and antagonists on acquisition of passive avoidance learning. *Eur J Pharmacol* 256, 233-239 (1994)
28. Hauber, W. & A. Bareiss: Facilitative effects of an adenosine A1/A2 receptor blockade on spatial memory performance of rats: selective enhancement of reference memory retention during the light period. *Behav Brain Res* 118, 43-52 (2001)
29. Kopf, S. R., A. Melani, F. Pedata & G. Pepeu: Adenosine and memory storage: effect of A(1) and A(2) receptor antagonists. *Psychopharmacology (Berl)* 146, 214-219 (1999)
30. Pereira, G. S., T. Mello e Souza, E. R. Vinade, H. Choi, C. Rodrigues, A. M. Battastini, I. Izquierdo, J. J. Sarkis & C. D. Bonan: Blockade of adenosine A1 receptors in the posterior cingulate cortex facilitates memory in rats. *Eur J Pharmacol* 437, 151-154 (2002)
31. Prediger, R. D. & R. N. Takahashi: Modulation of short-term social memory in rats by adenosine A1 and A(2A) receptors. *Neurosci Lett* 376, 160-165 (2005)
32. Suzuki, F., J. Shimada, S. Shiozaki, S. Ichikawa, A. Ishii, J. Nakamura, H. Nonaka, H. Kobayashi & E. Fuse: Adenosine A1 antagonists. 3. Structure-activity relationships on amelioration against scopolamine- or N6-((R)-phenylisopropyl)adenosine-induced cognitive disturbance. *J Med Chem* 36, 2508-2518 (1993)
33. Prediger, R. D., L. C. Batista & R. N. Takahashi: Caffeine reverses age-related deficits in olfactory discrimination and social recognition memory in rats. Involvement of adenosine A1 and A2A receptors. *Neurobiol Aging* 26, 957-964 (2005)
34. Arendash, G. W., W. Schleif, K. Rezai-Zadeh, E. K. Jackson, L. C. Zacharia, J. R. Cracchiolo, D. Shippy & J. Tan: Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain beta-amyloid production. *Neuroscience* 142, 941-952 (2006)
35. Dall'Igna, O. P., P. Fett, M. W. Gomes, D. O. Souza, R. A. Cunha & D. R. Lara: Caffeine and adenosine A(2a) receptor antagonists prevent beta-amyloid (25-35)-induced cognitive deficits in mice. *Exp Neurol* 203, 241-245 (2007)
36. Gevaerd, M. S., R. N. Takahashi, R. Silveira & C. Da Cunha: Caffeine reverses the memory disruption induced by intra-nigral MPTP-injection in rats. *Brain Res Bull* 55, 101-106 (2001)
37. Prediger, R. D., C. Da Cunha & R. N. Takahashi: Antagonistic interaction between adenosine A2A and dopamine D2 receptors modulates the social recognition memory in reserpine-treated rats. *Behav Pharmacol* 16, 209-218 (2005)
38. Prediger, R. D., D. Fernandes & R. N. Takahashi: Blockade of adenosine A2A receptors reverses short-term social memory impairments in spontaneously hypertensive rats. *Behav Brain Res* 159, 197-205 (2005)
39. Prediger, R. D., F. A. Pamplona, D. Fernandes & R. N. Takahashi: Caffeine improves spatial learning deficits in an animal model of attention deficit hyperactivity disorder (ADHD) -- the spontaneously hypertensive rat (SHR). *Int J Neuropsychopharmacol* 8, 583-594 (2005)
40. Jarvis, M. J.: Does caffeine intake enhance absolute levels of cognitive performance? *Psychopharmacology (Berl)* 110, 45-52 (1993)
41. Rees, K., D. Allen & M. Lader: The influences of age and caffeine on psychomotor and cognitive function. *Psychopharmacology (Berl)* 145, 181-188 (1999)
42. Anderson, K. J. & W. Revelle: Impulsivity, caffeine, and proofreading: a test of the Easterbrook hypothesis. *J Exp Psychol Hum Percept Perform* 8, 614-624 (1982)
43. Kaplan, G. B., D. J. Greenblatt, B. L. Ehrenberg, J. E. Goddard, M. M. Cotreau, J. S. Harmatz & R. I. Shader: Dose-dependent pharmacokinetics and psychomotor effects of caffeine in humans. *J Clin Pharmacol* 37, 693-703 (1997)
44. Patat, A., P. Rosenzweig, M. Enslen, S. Trocherie, N. Miget, M. C. Bozon, H. Allain & J. M. Gandon: Effects of a new slow release formulation of caffeine on EEG, psychomotor and cognitive functions in sleep-deprived subjects. *Hum Psychopharmacol* 15, 153-170 (2000)
45. Warburton, D. M., E. Bersellini & E. Sweeney: An evaluation of a caffeinated taurine drink on mood, memory and information processing in healthy volunteers without caffeine abstinence. *Psychopharmacology (Berl)* 158, 322-328 (2001)
46. Heatherley, S. W., H. E. Sears, R. C. Hayward, M. Kane & P. J. Rogers: Time-course of mood and performance effects of long-term caffeine withdrawal. *Appetite* 43, 114 (2004)
47. Lane, J. D. & B. G. Phillips-Bute: Caffeine deprivation affects vigilance performance and mood. *Physiol Behav* 65, 171-175 (1998)
48. Phillips-Bute, B. G. & J. D. Lane: Caffeine withdrawal symptoms following brief caffeine deprivation. *Physiol Behav* 63, 35-39 (1997)
49. James, J. E.: Does caffeine enhance or merely restore degraded psychomotor performance? *Neuropsychobiology* 30, 124-125 (1994)
50. Rogers, P. J. & C. Dernoncourt: Regular caffeine consumption: a balance of adverse and beneficial effects for mood and psychomotor performance. *Pharmacol Biochem Behav* 59, 1039-1045 (1998)
51. Richardson, N. J., P. J. Rogers, N. A. Elliman & R. J. O'Dell: Mood and performance effects of caffeine in relation to acute and chronic caffeine deprivation. *Pharmacol Biochem Behav* 52, 313-320 (1995)
52. Rogers, P. J., J. Martin, C. Smith, S. V. Heatherley & H. J. Smit: Absence of reinforcing, mood and psychomotor performance effects of caffeine in habitual non-consumers of caffeine. *Psychopharmacology (Berl)* 167, 54-62 (2003)
53. Fredholm, B. B., K. Battig, J. Holmen, A. Nehlig & E. E. Zvartau: Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev* 51, 83-133 (1999)
54. Koelega, H. S.: Stimulant drugs and vigilance performance: a review. *Psychopharmacology (Berl)* 111, 1-16 (1993)
55. Revelle, W., M. S. Humphreys, L. Simon & K. Gilliland: The interactive effect of personality, time of day, and caffeine: a test of the arousal model. *J Exp Psychol Gen* 109, 1-31 (1980)
56. Benington, J. H., S. K. Kodali & H. C. Heller: Stimulation of A1 adenosine receptors mimics the

electroencephalographic effects of sleep deprivation. *Brain Res* 692, 79-85 (1995)
57. Porkka-Heiskanen, T., R. E. Strecker, M. Thakkar, A. A. Bjorkum, R. W. Greene & R. W. McCarley: Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. *Science* 276, 1265-1268 (1997)
58. Kenemans, J. L. & M. M. Lorist: Caffeine and selective visual processing. *Pharmacol Biochem Behav* 52, 461-471 (1995)
59. Lorist, M. M. & M. Tops: Caffeine, fatigue, and cognition. *Brain Cogn* 53, 82-94 (2003)
60. Izquierdo, I., J. H. Medina, M. R. Vianna, L. A. Izquierdo & D. M. Barros: Separate mechanisms for short- and long-term memory. *Behav Brain Res* 103, 1-11 (1999)
61. Izquierdo, L. A., D. M. Barros, M. R. Vianna, A. Coitinho, T. deDavid e Silva, H. Choi, B. Moletta, J. H. Medina & I. Izquierdo: Molecular pharmacological dissection of short- and long-term memory. *Cell Mol Neurobiol* 22, 269-287 (2002)
62. McGaugh, J. L.: Memory--a century of consolidation. *Science* 287, 248-251 (2000)
63. de Mendonca, A., A. R. Costenla & J. A. Ribeiro: Persistence of the neuromodulatory effects of adenosine on synaptic transmission after long-term potentiation and long-term depression. *Brain Res* 932, 56-60 (2002)
64. de Mendonca, A. & J. A. Ribeiro: Adenosine and synaptic plasticity. *Drug Development Research* 52, 283-290 (2001)
65. Tabata, K., K. Matsumoto, Y. Murakami & H. Watanabe: Ameliorative effects of paeoniflorin, a major constituent of peony root, on adenosine A1 receptor-mediated impairment of passive avoidance performance and long-term potentiation in the hippocampus. *Biol Pharm Bull* 24, 496-500 (2001)
66. Pitsikas, N. & F. Borsini: The adenosine A1 receptor antagonist BIIP 20 counteracts scopolamine-induced behavioral deficits in the passive avoidance task in the rat. *Eur J Pharmacol* 328, 19-22 (1997)
67. Pereira, G. S., J. I. Rossato, J. J. Sarkis, M. Cammarota, C. D. Bonan & I. Izquierdo: Activation of adenosine receptors in the posterior cingulate cortex impairs memory retrieval in the rat. *Neurobiol Learn Mem* 83, 217-223 (2005)
68. Dantzer, R., R. M. Bluthe, G. F. Koob & M. Le Moal: Modulation of social memory in male rats by neurohypophyseal peptides. *Psychopharmacology (Berl)* 91, 363-368 (1987)
69. Gimenez-Llort, L., S. N. Schiffmann, T. Shmidt, L. Canela, L. Camon, M. Wassholm, M. Canals, A. Terasmaa, A. Fernandez-Teruel, A. Tobena, E. Popova, S. Ferre, L. Agnati, F. Ciruela, E. Martinez, J. Scheel-Kruger, C. Lluis, R. Franco, K. Fuxe & M. Bader: Working memory deficits in transgenic rats overexpressing human adenosine A2A receptors in the brain. *Neurobiol Learn Mem* 87, 42-56 (2007)
70. Hooper, N., C. Fraser & T. W. Stone: Effects of purine analogues on spontaneous alternation in mice. *Psychopharmacology (Berl)* 123, 250-257 (1996)
71. Angelucci, M. E., C. Cesario, R. H. Hiroi, P. L. Rosalen & C. Da Cunha: Effects of caffeine on learning and memory in rats tested in the Morris water maze. *Braz J Med Biol Res* 35, 1201-1208 (2002)
72. Yonkov, D. I.: Possible role of brain dopaminergic systems in the memory effects of central stimulants. *Methods Find Exp Clin Pharmacol* 6, 235-239 (1984)
73. Angelucci, M. E., M. A. Vital, C. Cesario, C. R. Zadusky, P. L. Rosalen & C. Da Cunha: The effect of caffeine in animal models of learning and memory. *Eur J Pharmacol* 373, 135-140 (1999)
74. Cestari, V. & C. Castellano: Caffeine and cocaine interaction on memory consolidation in mice. *Arch Int Pharmacodyn Ther* 331, 94-104 (1996)
75. Corodimas, K. P., J. C. Pruitt & J. M. Stieg: Acute exposure to caffeine selectively disrupts context conditioning in rats. *Psychopharmacology (Berl)* 152, 376-382 (2000)
76. Kant, G. J.: Effects of psychoactive drugs or stress on learning, memory, and performance as assessed using a novel water maze task. *Pharmacol Biochem Behav* 44, 287-295 (1993)
77. Furusawa, K.: Drug effects on cognitive function in mice determined by the non-matching to sample task using a 4-arm maze. *Jpn J Pharmacol* 56, 483-493 (1991)
78. Von Lubitz, D. K., I. A. Paul, R. T. Bartus & K. A. Jacobson: Effects of chronic administration of adenosine A1 receptor agonist and antagonist on spatial learning and memory. *Eur J Pharmacol* 249, 271-280 (1993)
79. Quarta, D., S. Ferre, M. Solinas, Z. B. You, J. Hockemeyer, P. Popoli & S. R. Goldberg: Opposite modulatory roles for adenosine A1 and A2A receptors on glutamate and dopamine release in the shell of the nucleus accumbens. Effects of chronic caffeine exposure. *J Neurochem* 88, 1151-1158 (2004)
80. Costenla, A. R., L. V. Lopes, A. de Mendonca & J. A. Ribeiro: A functional role for adenosine A3 receptors: modulation of synaptic plasticity in the rat hippocampus. *Neurosci Lett* 302, 53-57 (2001)
81. Blennow, K., M. J. de Leon & H. Zetterberg: Alzheimer's disease. *Lancet* 368, 387-403 (2006)
82. Wimo, A., B. Winblad, H. Aguero-Torres & E. von Strauss: The magnitude of dementia occurrence in the world. *Alzheimer Dis Assoc Disord* 17, 63-67 (2003)
83. Blennow, K., A. Wallin & C. G. Gottfries: Presence of parietal lobe symptomatology distinguishes early and late ons*et al*zheimer's disease. *Int J Geriatr Psychiat* 6, 147-154 (1991)
84. Roth, M.: The association of clinical and neurological findings and its bearing on the classification and aetiology of Alzheimer's disease. *Br Med Bull* 42, 42-50 (1986)
85. Brayne, C. & P. Calloway: Normal ageing, impaired cognitive function, and senile dementia of the Alzheimer's type: a continuum? *Lancet* 1, 1265-1267 (1988)
86. Haass, C., M. G. Schlossmacher, A. Y. Hung, C. Vigo-Pelfrey, A. Mellon, B. L. Ostaszewski, I. Lieberburg, E. H. Koo, D. Schenk, D. B. Teplow & *et al.*: Amyloid beta-peptide is produced by cultured cells during normal metabolism. *Nature* 359, 322-325 (1992)
87. Hardy, J. & D. J. Selkoe: The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 297, 353-356 (2002)
88. Van Dam, D. & P. P. De Deyn: Drug discovery in dementia: the role of rodent models. *Nat Rev Drug Discov* 5, 956-970 (2006)

89. Erickson, C. A. & C. A. Barnes: The neurobiology of memory changes in normal aging. *Exp Gerontol* 38, 61-69 (2003)
90. Sherman, K. A. & E. Friedman: Pre- and post-synaptic cholinergic dysfunction in aged rodent brain regions: new findings and an interpretative review. *Int J Dev Neurosci* 8, 689-708 (1990)
91. Ebert, U. & W. Kirch: Scopolamine model of dementia: electroencephalogram findings and cognitive performance. *Eur J Clin Invest* 28, 944-949 (1998)
92. Toledano, A. & M. I. Alvarez: Lesions and dysfunctions of the nucleus basalis as Alzheimer's disease models: general and critical overview and analysis of the long-term changes in several excitotoxic models. *Curr Alzheimer Res* 1, 189-214 (2004)
93. Harkany, T., I. Abraham, W. Timmerman, G. Laskay, B. Toth, M. Sasvari, C. Konya, J. B. Sebens, J. Korf, C. Nyakas, M. Zarandi, K. Soos, B. Penke & P. G. Luiten: Beta-amyloid neurotoxicity is mediated by a glutamate-triggered excitotoxic cascade in rat nucleus basalis. *Eur J Neurosci* 12, 2735-2745 (2000)
94. Medeiros, R., R. D. Prediger, G. F. Passos, P. Pandolfo, F. S. Duarte, J. L. Franco, A. L. Dafre, G. Di Giunta, C. P. Figueiredo, R. N. Takahashi, M. M. Campos & J. B. Calixto: Connecting TNF-alpha signaling pathways to iNOS expression in a mouse model of Alzheimer's disease: relevance for the behavioral and synaptic deficits induced by amyloid beta protein. *J Neurosci* 27, 5394-5404 (2007)
95. Nag, S., B. K. Yee & F. Tang: Reduction in somatostatin and substance P levels and choline acetyltransferase activity in the cortex and hippocampus of the rat after chronic intracerebroventricular infusion of beta-amyloid (1-40). *Brain Res Bull* 50, 251-262 (1999)
96. Nakamura, S., N. Murayama, T. Noshita, H. Annoura & T. Ohno: Progressive brain dysfunction following intracerebroventricular infusion of beta(1-42)-amyloid peptide. *Brain Res* 912, 128-136 (2001)
97. Prediger, R. D., J. L. Franco, P. Pandolfo, R. Medeiros, F. S. Duarte, G. Di Giunta, C. P. Figueiredo, M. Farina, J. B. Calixto, R. N. Takahashi & A. L. Dafre: Differential susceptibility following beta-amyloid peptide-(1-40) administration in C57BL/6 and Swiss albino mice: Evidence for a dissociation between cognitive deficits and the glutathione system response. *Behav Brain Res* 177, 205-213 (2007)
98. Games, D., D. Adams, R. Alessandrini, R. Barbour, P. Berthelette, C. Blackwell, T. Carr, J. Clemens, T. Donaldson, F. Gillespie & *et al.*: Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. *Nature* 373, 523-527 (1995)
99. Newman, M., F. I. Musgrave & M. Lardelli: Alzheimer disease: Amyloidogenesis, the presenilins and animal models. *Biochim Biophys Acta* 1772, 285-297 (2007)
100. Maia, L. & A. de Mendonca: Does caffeine intake protect from Alzheimer's disease? *Eur J Neurol* 9, 377-382 (2002)
101. Riedel, W., E. Hogervorst, R. Leboux, F. Verhey, H. van Praag & J. Jolles: Caffeine attenuates scopolamine-induced memory impairment in humans. *Psychopharmacology (Berl)* 122, 158-168 (1995)
102. Espinola, E. B., R. F. Dias, R. Mattei & E. A. Carlini: Pharmacological activity of Guarana (Paullinia cupana Mart.) in laboratory animals. *J Ethnopharmacol* 55, 223-229 (1997)
103. Jin, Z. L., J. Wen, W. P. Wang & W. T. He: The role of theophylline in the improvement of scop-induced learning and memory impairment. *Sheng Li Xue Bao* 52, 390-394 (2000)
104. Maemoto, T., M. Tada, T. Mihara, N. Ueyama, H. Matsuoka, K. Harada, T. Yamaji, K. Shirakawa, S. Kuroda, A. Akahane, A. Iwashita, N. Matsuoka & S. Mutoh: Pharmacological characterization of FR194921, a new potent, selective, and orally active antagonist for central adenosine A1 receptors. *J Pharmacol Sci* 96, 42-52 (2004)
105. Rubaj, A., W. Zgodzinski & M. Sieklucka-Dziuba: The influence of adenosine A3 receptor agonist: IB-MECA, on scopolamine- and MK-801-induced memory impairment. *Behav Brain Res* 141, 11-17 (2003)
106. Herzog, C. D., K. A. Nowak, M. Sarter & J. P. Bruno: Microdialysis without acetylcholinesterase inhibition reveals an age-related attenuation in stimulated cortical acetylcholine release. *Neurobiol Aging* 24, 861-863 (2003)
107. Corsi, C., M. Pazzagli, L. Bianchi, L. Della Corte, G. Pepeu & F. Pedata: *In vivo* amino acid release from the striatum of aging rats: adenosine modulation. *Neurobiol Aging* 18, 243-250 (1997)
108. Cunha, R. A., E. Milusheva, E. S. Vizi, J. A. Ribeiro & A. M. Sebastiao: Excitatory and inhibitory effects of A1 and A2A adenosine receptor activation on the electrically evoked [3H]acetylcholine release from different areas of the rat hippocampus. *J Neurochem* 63, 207-214 (1994)
109. Kaelin-Lang, A., T. Lauterburg & J. M. Burgunder: Expression of adenosine A2a receptors gene in the olfactory bulb and spinal cord of rat and mouse. *Neurosci Lett* 261, 189-191 (1999)
110. Cunha, R. A., M. C. Constantino, A. M. Sebastiao & J. A. Ribeiro: Modification of A1 and A2a adenosine receptor binding in aged striatum, hippocampus and cortex of the rat. *Neuroreport* 6, 1583-1588 (1995)
111. Pagonopoulou, O. & F. Angelatou: Reduction of A1 adenosine receptors in cortex, hippocampus and cerebellum in ageing mouse brain. *Neuroreport* 3, 735-737 (1992)
112. Chen, J. F., K. Xu, J. P. Petzer, R. Staal, Y. H. Xu, M. Beilstein, P. K. Sonsalla, K. Castagnoli, N. Castagnoli, Jr. & M. A. Schwarzschild: Neuroprotection by caffeine and A(2A) adenosine receptor inactivation in a model of Parkinson's disease. *J Neurosci* 21, RC143 (2001)
113. Chen, Q., A. H. Andersen, Z. Zhang, A. Ovadia, W. A. Cass, D. M. Gash & M. J. Avison: Functional MRI of basal ganglia responsiveness to levodopa in parkinsonian rhesus monkeys. *Exp Neurol* 158, 63-75 (1999)
114. Popoli, P., A. Pintor, M. R. Domenici, C. Frank, M. T. Tebano, A. Pezzola, L. Scarchilli, D. Quarta, R. Reggio, F. Malchiodi-Albedi, M. Falchi & M. Massotti: Blockade of striatal adenosine A2A receptor reduces, through a presynaptic mechanism, quinolinic acid-induced excitotoxicity: possible relevance to neuroprotective interventions in neurodegenerative diseases of the striatum. *J Neurosci* 22, 1967-1975 (2002)
115. Kalda, A., L. Yu, E. Oztas & J. F. Chen: Novel neuroprotection by caffeine and adenosine A(2A) receptor

antagonists in animal models of Parkinson's disease. *J Neurol Sci* 248, 9-15 (2006)
116. Dall'Igna, O. P., L. O. Porciuncula, D. O. Souza, R. A. Cunha & D. R. Lara: Neuroprotection by caffeine and adenosine A2A receptor blockade of beta-amyloid neurotoxicity. *Br J Pharmacol* 138, 1207-1209 (2003)
117. Dewachter, I., J. van Dorpe, K. Spittaels, I. Tesseur, C. Van Den Haute, D. Moechars & F. Van Leuven: Modeling Alzheimer's disease in transgenic mice: effect of age and of presenilin1 on amyloid biochemistry and pathology in APP/London mice. *Exp Gerontol* 35, 831-841 (2000)
118. Zhang, L., Y. Xing, C. F. Ye, H. X. Ai, H. F. Wei & L. Li: Learning-memory deficit with aging in APP transgenic mice of Alzheimer's disease and intervention by using tetrahydroxystilbene glucoside. *Behav Brain Res* 173, 246-254 (2006)
119. Duvoisin, R. C.: Parkinson's Disease. Raven Press, New York (1991)
120. Hirsch, E., A. M. Graybiel & Y. A. Agid: Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. *Nature* 334, 345-348 (1988)
121. Heikkila, R. E., P. K. Sonsalla & R. C. Duvoisin: Biochemical models of Parkinson's disease. In: Neuromethods. Drugs as Tools in Neurotransmitter Research. Eds: A. A. Boulton, G. B. Baker&A. V. Jurio. Humana Press, New York (1989)
122. Barrio, J. R., S. C. Huang & M. E. Phelps: Biological imaging and the molecular basis of dopaminergic diseases. *Biochem Pharmacol* 54, 341-348 (1997)
123. Jellinger, K. A.: Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. *Mol Chem Neuropathol* 14, 153-197 (1991)
124. Lindner, M. D., C. K. Cain, M. A. Plone, B. R. Frydel, T. J. Blaney, D. F. Emerich & M. R. Hoane: Incomplete nigrostriatal dopaminergic cell loss and partial reductions in striatal dopamine produce akinesia, rigidity, tremor and cognitive deficits in middle-aged rats. *Behav Brain Res* 102, 1-16 (1999)
125. Riederer, P. & S. Wuketich: Time course of nigrostriatal degeneration in Parkinson's disease. A detailed study of influential factors in human brain amine analysis. *J Neural Transm* 38, 277-301 (1976)
126. Brown, L. L., J. S. Schneider & T. I. Lidsky: Sensory and cognitive functions of the basal ganglia. *Curr Opin Neurobiol* 7, 157-163 (1997)
127. Bosboom, J. L., D. Stoffers & E. Wolters: Cognitive dysfunction and dementia in Parkinson's disease. *J Neural Transm* 111, 1303-1315 (2004)
128. Dubois, B. & B. Pillon: Cognitive deficits in Parkinson's disease. *J Neurol* 244, 2-8 (1997)
129. Aarsland, D., E. Tandberg, J. P. Larsen & J. L. Cummings: Frequency of dementia in Parkinson disease. *Arch Neurol* 53, 538-542 (1996)
130. Lewis, S. J., A. Dove, T. W. Robbins, R. A. Barker & A. M. Owen: Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *J Neurosci* 23, 6351-6356 (2003)
131. Owen, A. M., J. L. Iddon, J. R. Hodges, B. A. Summers & T. W. Robbins: Spatial and non-spatial working memory at different stages of Parkinson's disease. *Neuropsychologia* 35, 519-532 (1997)
132. Stebbins, G. T., J. D. Gabrieli, F. Masciari, L. Monti & C. G. Goetz: Delayed recognition memory in Parkinson's disease: a role for working memory? *Neuropsychologia* 37, 503-510 (1999)
133. Fama, R., E. V. Sullivan, P. K. Shear, M. Stein, J. A. Yesavage, J. R. Tinklenberg & A. Pfefferbaum: Extent, pattern, and correlates of remote memory impairment in Alzheimer's disease and Parkinson's disease. *Neuropsychology* 14, 265-276 (2000)
134. Knowlton, B. J., J. A. Mangels & L. R. Squire: A neostriatal habit learning system in humans. *Science* 273, 1399-1402 (1996)
135. Bondi, M. W. & A. W. Kaszniak: Implicit and explicit memory in Alzheimer's disease and Parkinson's disease. *J Clin Exp Neuropsychol* 13, 339-358 (1991)
136. Pillon, B., S. Ertle, B. Deweer, A. M. Bonnet, M. Vidailhet & B. Dubois: Memory for spatial location in 'de novo' parkinsonian patients. *Neuropsychologia* 35, 221-228 (1997)
137. Flowers, K. A., I. Pearce & J. M. Pearce: Recognition memory in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 47, 1174-1181 (1984)
138. Moreau, J. L. & G. Huber: Central adenosine A(2A) receptors: an overview. *Brain Res Brain Res Rev* 31, 65-82 (1999)
139. Svenningsson, P., C. Le Moine, G. Fisone & B. B. Fredholm: Distribution, biochemistry and function of striatal adenosine A2A receptors. *Prog Neurobiol* 59, 355-396 (1999)
140. Franco, R., S. Ferre, L. Agnati, M. Torvinen, S. Gines, J. Hillion, V. Casado, P. Lledo, M. Zoli, C. Lluis & K. Fuxe: Evidence for adenosine/dopamine receptor interactions: indications for heteromerization. *Neuropsychopharmacology* 23, S50-59 (2000)
141. Fuxe, K., S. Ferre, M. Zoli & L. F. Agnati: Integrated events in central dopamine transmission as analyzed at multiple levels. Evidence for intramembrane adenosine A2A/dopamine D2 and adenosine A1/dopamine D1 receptor interactions in the basal ganglia. *Brain Res Brain Res Rev* 26, 258-273 (1998)
142. Okada, M., K. Kiryu, Y. Kawata, K. Mizuno, K. Wada, H. Tasaki & S. Kaneko: Determination of the effects of caffeine and carbamazepine on striatal dopamine release by *in vivo* microdialysis. *Eur J Pharmacol* 321, 181-188 (1997)
143. Da Cunha, C., M. E. Angelucci, N. S. Canteras, S. Wonnacott & R. N. Takahashi: The lesion of the rat substantia nigra pars compacta dopaminergic neurons as a model for Parkinson's disease memory disabilities. *Cell Mol Neurobiol* 22, 227-237 (2002)
144. Fall, P. A., M. Fredrikson, O. Axelson & A. K. Granerus: Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. *Mov Disord* 14, 28-37 (1999)
145. Hellenbrand, W., A. Seidler, H. Boeing, B. P. Robra, P. Vieregge, P. Nischan, J. Joerg, W. H. Oertel, E. Schneider & G. Ulm: Diet and Parkinson's disease. I: A possible role for the past intake of specific foods and food groups. Results from a self-administered food-frequency

questionnaire in a case-control study. *Neurology* 47, 636-643 (1996)
146. Ross, G. W., R. D. Abbott, H. Petrovitch, L. R. White & C. M. Tanner: Relationship between caffeine intake and parkinson disease. *Jama* 284, 1378-1379 (2000)
147. Tan, E. K., C. Tan, S. M. Fook-Chong, S. Y. Lum, A. Chai, H. Chung, H. Shen, Y. Zhao, M. L. Teoh, Y. Yih, R. Pavanni, V. R. Chandran & M. C. Wong: Dose-dependent protective effect of coffee, tea, and smoking in Parkinson's disease: a study in ethnic Chinese. *J Neurol Sci* 216, 163-167 (2003)
148. Ferre, S., P. Popoli, L. Gimenez-Llort, R. Rimondini, C. E. Muller, I. Stromberg, S. O. Ogren & K. Fuxe: Adenosine/dopamine interaction: implications for the treatment of Parkinson's disease. *Parkinsonism Relat Disord* 7, 235-241 (2001)
149. Wardas, J., J. Konieczny & E. Lorenc-Koci: SCH 58261, an A(2A) adenosine receptor antagonist, counteracts parkinsonian-like muscle rigidity in rats. *Synapse* 41, 160-171 (2001)
150. Beal, M. F.: Experimental models of Parkinson's disease. *Nat Rev Neurosci* 2, 325-334 (2001)
151. Dauer, W. & S. Przedborski: Parkinson's disease: mechanisms and models. *Neuron* 39, 889-909 (2003)
152. Schober, A.: Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP. *Cell Tissue Res* 318, 215-224 (2004)
153. Da Cunha, C., M. S. Gevaerd, M. A. Vital, E. Miyoshi, R. Andreatini, R. Silveira, R. N. Takahashi & N. S. Canteras: Memory disruption in rats with nigral lesions induced by MPTP: a model for early Parkinson's disease amnesia. *Behav Brain Res* 124, 9-18 (2001)
154. Ferro, M. M., M. I. Bellissimo, J. A. Anselmo-Franci, M. E. Angellucci, N. S. Canteras & C. Da Cunha: Comparison of bilaterally 6-OHDA- and MPTP-lesioned rats as models of the early phase of Parkinson's disease: histological, neurochemical, motor and memory alterations. *J Neurosci Methods* 148, 78-87 (2005)
155. Harik, S. I., J. W. Schmidley, L. A. Iacofano, P. Blue, P. K. Arora & L. M. Sayre: On the mechanisms underlying 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
neurotoxicity: the effect of perinigral infusion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, its metabolite and their analogs in the rat. *J Pharmacol Exp Ther* 241, 669-676 (1987)
156. Miyoshi, E., S. Wietzikoski, M. Camplessei, R. Silveira, R. N. Takahashi & C. Da Cunha: Impaired learning in a spatial working memory version and in a cued version of the water maze in rats with MPTP-induced mesencephalic dopaminergic lesions. *Brain Res Bull* 58, 41-47 (2002)
157. Cools, R., R. A. Barker, B. J. Sahakian & T. W. Robbins: Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex* 11, 1136-1143 (2001)
158. Huber, S. J., H. G. Shulman, G. W. Paulson & E. C. Shuttleworth: Dose-dependent memory impairment in Parkinson's disease. *Neurology* 39, 438-440 (1989)
159. Poewe, W., W. Berger, T. Benke & L. Schelosky: High-speed memory scanning in Parkinson's disease: adverse effects of levodopa. *Ann Neurol* 29, 670-673 (1991)
160. Prasher, D. & L. Findley: Dopaminergic induced changes in cognitive and motor processing in Parkinson's disease: an electrophysiological investigation. *J Neurol Neurosurg Psychiatry* 54, 603-609 (1991)
161. Gevaerd, M. S., E. Miyoshi, R. Silveira, N. S. Canteras, R. N. Takahashi & C. Da Cunha: L-Dopa restores striatal dopamine level but fails to reverse MPTP-induced memory deficits in rats. *Int J Neuropsychopharmacol* 4, 361-370 (2001)
162. Carlsson, A.: Monoamine-depleting drugs. *Pharmacol Ther [B]* 1, 393-400 (1975)
163. Colpaert, F. C.: Pharmacological characteristics of tremor, rigidity and hypokinesia induced by reserpine in rat. *Neuropharmacology* 26, 1431-1440 (1987)
164. Gerlach, M. & P. Riederer: Animal models of Parkinson's disease: an empirical comparison with the phenomenology of the disease in man. *J Neural Transm* 103, 987-1041 (1996)
165. Alves, C. S., R. Andreatini, C. da Cunha, S. Tufik & M. A. Vital: Phosphatidylserine reverses reserpine-induced amnesia. *Eur J Pharmacol* 404, 161-167 (2000)
166. Skalisz, L. L., V. Beijamini, S. L. Joca, M. A. Vital, C. Da Cunha & R. Andreatini: Evaluation of the face validity of reserpine administration as an animal model of depression--Parkinson's disease association. *Prog Neuropsychopharmacol Biol Psychiatry* 26, 879-883 (2002)
167. Prediger, R. D., L. C. Batista, E. Miyoshi & R. N. Takahashi: Facilitation of short-term social memory by ethanol in rats is mediated by dopaminergic receptors. *Behav Brain Res* 153, 149-157 (2004)
168. Hauber, W., P. Neuscheler, J. Nagel & C. E. Muller: Catalepsy induced by a blockade of dopamine D1 or D2 receptors was reversed by a concomitant blockade of adenosine A(2A) receptors in the caudate-putamen of rats. *Eur J Neurosci* 14, 1287-1293 (2001)
169. Kim, D. S. & R. D. Palmiter: Adenosine receptor blockade reverses hypophagia and enhances locomotor activity of dopamine-deficient mice. *Proc Natl Acad Sci U S A* 100, 1346-1351 (2003)
170. Aoyama, S., H. Kase & E. Borrelli: Rescue of locomotor impairment in dopamine D2 receptor-deficient mice by an adenosine A2A receptor antagonist. *J Neurosci* 20, 5848-5852 (2000)
171. Swanson, J. M., J. A. Sergeant, E. Taylor, E. J. Sonuga-Barke, P. S. Jensen & D. P. Cantwell: Attention-deficit hyperactivity disorder and hyperkinetic disorder. *Lancet* 351, 429-433 (1998)
172. Taylor, E.: Clinical foundations of hyperactivity research. *Behav Brain Res* 94, 11-24 (1998)
173. Himelstein, J., J. H. Newcorn & J. M. Halperin: The neurobiology of attention-deficit hyperactivity disorder. *Front Biosci* 5, D461-478 (2000)
174. Davids, E., K. Zhang, F. I. Tarazi & R. J. Baldessarini: Animal models of attention-deficit hyperactivity disorder. *Brain Res Brain Res Rev* 42, 1-21 (2003)
175. Sagvolden, T. & J. A. Sergeant: Attention deficit/hyperactivity disorder--from brain dysfunctions to behaviour. *Behav Brain Res* 94, 1-10 (1998)

176. Mannuzza, S., R. G. Klein, A. Bessler, P. Malloy & M. LaPadula: Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. *Arch Gen Psychiatry* 50, 565-576 (1993)
177. Castellanos, F. X. & R. Tannock: Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat Rev Neurosci* 3, 617-628 (2002)
178. Sagvolden, T., E. B. Johansen, H. Aase & V. A. Russell: A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behav Brain Sci* 28, 397-419; discussion 419-368 (2005)
179. Swanson, J. M., P. Flodman, J. Kennedy, M. A. Spence, R. Moyzis, S. Schuck, M. Murias, J. Moriarity, C. Barr, M. Smith & M. Posner: Dopamine genes and ADHD. *Neurosci Biobehav Rev* 24, 21-25 (2000)
180. Wender, P. H.: Pharmacotherapy of attention-deficit/hyperactivity disorder in adults. *J Clin Psychiatry* 59 Suppl 7, 76-79 (1998)
181. Wilens, T. E., T. J. Spencer & J. Biederman: A review of the pharmacotherapy of adults with attention-deficit/hyperactivity disorder. *J Atten Disord* 5, 189-202 (2002)
182. Garfinkel, B. D., C. D. Webster & L. Sloman: Individual responses to methylphenidate and caffeine in children with minimal brain dysfunction. *Can Med Assoc J* 113, 729-732 (1975)
183. Garfinkel, B. D., C. D. Webster & L. Sloman: Responses to methylphenidate and varied doses of caffeine in children with attention deficit disorder. *Can J Psychiatry* 26, 395-401 (1981)
184. Schnackenberg, R. C.: Caffeine therapy for hyperkinetic children. *Curr Psychiatr Ther* 15, 39-44 (1975)
185. Sussman, S., M. A. Pentz, D. Spruijt-Metz & T. Miller: Misuse of "study drugs:" prevalence, consequences, and implications for policy. *Subst Abuse Treat Prev Policy* 1, 15 (2006)
186. Leon, M. R.: Effects of caffeine on cognitive, psychomotor, and affective performance of children with Attention-Deficit / Hyperactivity Disorder. *J Attent Dis* 4, 27-47 (2000)
187. Dalby, J. T.: Will population decreases in caffeine consumption unveil attention deficit disorders in adults? *Med Hypotheses* 18, 163-167 (1985)
188. Hecht, K., M. Poppei, T. Hecht, J. W. Postnow, V. Moritz & R. Baumann: Learning and memory processes during postnatal ontogenesis in rats with spontaneous hypertension. *Acta Biol Med Ger* 37, 1471-1478 (1978)
189. Sutterer, J. R., J. Perry & W. DeVito: Two-way shuttle box and lever-press avoidance in the spontaneously hypertensive and normotensive rat. *J Comp Physiol Psychol* 94, 155-163 (1980)
190. Mori, S., M. Kato & M. Fujishima: Impaired maze learning and cerebral glucose utilization in aged hypertensive rats. *Hypertension* 25, 545-553 (1995)
191. Nakamura-Palacios, E. M., C. K. Caldas, A. Fiorini, K. D. Chagas, K. N. Chagas & E. C. Vasquez: Deficits of spatial learning and working memory in spontaneously hypertensive rats. *Behav Brain Res* 74, 217-227 (1996)
192. Wyss, J. M., G. Fisk & T. van Groen: Impaired learning and memory in mature spontaneously hypertensive rats. *Brain Res* 592, 135-140 (1992)
193. De Bruin, N. M., A. J. Kiliaan, M. C. De Wilde & L. M. Broersen: Combined uridine and choline administration improves cognitive deficits in spontaneously hypertensive rats. *Neurobiol Learn Mem* 80, 63-79 (2003)
194. Gattu, M., J. R. Pauly, K. L. Boss, J. B. Summers & J. J. Buccafusco: Cognitive impairment in spontaneously hypertensive rats: role of central nicotinic receptors. I. *Brain Res* 771, 89-103 (1997)
195. Terry, A. V., Jr., C. M. Hernandez, J. J. Buccafusco & M. Gattu: Deficits in spatial learning and nicotinic-acetylcholine receptors in older, spontaneously hypertensive rats. *Neuroscience* 101, 357-368 (2000)
196. Jentsch, J. D.: Impaired visuospatial divided attention in the spontaneously hypertensive rat. *Behav Brain Res* 157, 323-330 (2005)
197. Fox, G. B., J. B. Pan, T. A. Esbenshade, Y. L. Bennani, L. A. Black, R. Faghih, A. A. Hancock & M. W. Decker: Effects of histamine H(3) receptor ligands GT-2331 and ciproxifan in a repeated acquisition avoidance response in the spontaneously hypertensive rat pup. *Behav Brain Res* 131, 151-161 (2002)
198. de Mendonca, A., A. M. Sebastiao & J. A. Ribeiro: Inhibition of NMDA receptor-mediated currents in isolated rat hippocampal neurones by adenosine A1 receptor activation. *Neuroreport* 6, 1097-1100 (1995)
199. Letty, S., R. Child, A. Dumuis, A. Pantaloni, J. Bockaert & G. Rondouin: 5-HT4 receptors improve social olfactory memory in the rat. *Neuropharmacology* 36, 681-687 (1997)
200. Davies, L. P., J. W. Hambley & G. A. R. Johnston: Reduced adenosine deaminase activity in the CNS of spontaneously hypertensive rats. *Neurochem Int* 10, 533-536 (1987)
201. Matias, A., F. J. Zimmer & R. Keil: Decreased affinity of central A1 adenosine receptors in spontaneously hypertensive rats. *Naunyn-Schmied Arch Pharmacol* 315, 59 (1992)
202. Reichard, C. C. & S. T. Elder: The effects of caffeine on reaction time in hyperkinetic and normal children. *Am J Psychiatry* 134, 144-148 (1977)
203. Arnold, L. E., J. Christopher, R. Huestis & D. J. Smeltzer: Methylphenidate vs dextroamphetamine vs caffeine in minimal brain dysfunction: controlled comparison by placebo washout design with Bayes' analysis. *Arch Gen Psychiatry* 35, 463-473 (1978)
204. Firestone, P., J. Davey, J. T. Goodman & S. Peters: The effects of caffeine and methylphenidate on hyperactive children. *J Am Acad Child Psychiatry* 17, 445-456 (1978)
205. Gross, M. D.: Caffeine in the treatment of children with minimal brain dysfunction or hyperkinetic syndrome. *Psychosomatics* 16, 26-27 (1975)
206. Castellanos, F. X. & J. L. Rapoport: Effects of caffeine on development and behavior in infancy and childhood: a review of the published literature. *Food Chem Toxicol* 40, 1235-1242 (2002)

Abbreviations: 6-OHDA: 6-hydroxydopamine, AD: Alzheimer's disease, ADHD: attention deficit hyperactivity disorder, APP: amyloid precursor protein, Aβ: β-amyloid

peptide, CCPA: 2-chloro-*N6*-cyclopentyladenosine, CGS 21680: 2-[*p*-(2-carbonyl-ethyl)-phenylethylamino]-5-*N*-ethylcarboxamidoadenosine, CNS: central nervous system, CPA: *N6*-cyclopentyladenosine, DPCPX: 8-cyclopenthyl-1,3-dipropylxanthine, DPMA: *N6*-[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl]adenosine, i.c.v.: intracerebroventricular, i.p.: intraperitoneal, LTD: long-term depression, LTP: long-term potentiation, MAO-B: monoamine oxidase B, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, PD: Parkinson's disease, SCH 58261: ([7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine, SHR: spontaneously hypertensive rats, SNc: substantia nigra pars compacta, ZM241385: 4-(2-[7-amino-2-{2-furyl}{1,2,4}triazolo-{2,3-a}{1,3,5}triazin-5-yl-amino]ethyl)-phenol

Key Words: Adenosine receptors, Adenosine antagonists, Cognitive dysfunction, Animal models, Aging, Alzheimer's disease, Parkinson's disease, Attention deficit hyperactivity disorder (ADHD), Spontaneously hypertensive rats (SHR).

Send correspondence to: Professor Reinaldo N. Takahashi, Departamento de Farmacologia, Centro de Ciencias Biologicas, Universidade Federal de Santa Catarina, Campus Trindade, Florianopolis-SC 88049-900, Brazil, Tel: 554837219764, Fax: 554833375479, E-mail: takahashi@farmaco.ufsc.br

http://www.bioscience.org/current/vol13.htm