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Potential therapeutic interest of adenosine A_{2A} receptors in psychiatric disorders

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Abstract

The interest on targeting adenosine A_{2A} receptors in the realm of psychiatric diseases first arose based on its tight physical and functional interaction with dopamine D_2 receptors. However, the role of central A_{2A} receptors is now viewed as much broader than just controlling D_2 receptor function. Thus, there is currently a major interest in the ability of A_{2A} receptors to control synaptic plasticity at glutamatergic synapses. This is due to a combined ability of A_{2A} receptors to facilitate the release of glutamate and the activation of NMDA. Therefore, A_{2A} receptors are now conceived as a normalizing device promoting adequate adaptive responses in neuronal circuits, a role similar to that fulfilled, in essence, by dopamine. This makes A_{2A} receptors a particularly attractive target to manage psychiatric disorders since adenosine may act as go-between glutamate and dopamine, two of the key players in mood processing. Furthermore, A_{2A} receptors also control glia function and brain metabolic adaptation, two other emerging mechanisms to understand abnormal processing of mood, and A_{2A} receptors are an important player in controlling the demise of neurodegeneration, considered an amplificatory loop in psychiatric disorders. Current data only provide an indirect confirmation of this putative role of A_{2A} receptors, based on the effects of caffeine (an antagonist of both A_1 and A_{2A} receptors) in psychiatric disorders. However, the introduction of A_{2A} receptors in clinics as anti-parkinsonian agents is hoped to bolster our knowledge on the role of A_{2A} receptors in mood disorders in the near future.

Keywords

adenosine; A_{2A} receptor; caffeine; mood disorders; psychiatric diseases; anxiety; depression; schizophrenia; attention deficit hyperactivity disorder; ADHD

INTRODUCTION

Psychiatric disorders are currently defined on the basis of behavioural modifications found in patients. Behavioural analysis essentially provides trends suggesting modified behavioural patterns in comparison with a standardised population, which in itself display intra- and inter-subject heterogeneity. There is currently no clear bio-marker to support the modified behavioural patterns. This might be one of the reasons justifying the difficulty in categorising psychiatric disorders, in spite of the tremendous effort in the refinement of neuropsychological tests.

This reality also makes it difficult to appreciate the relevance of novel molecular targets to develop drugs aimed at managing psychiatric conditions. In fact, the decision on pursuing a given molecular target to develop novel therapeutics is expected to be based on a strong scientific rational. This normally derives from the pathological changes that are characteristic of the disease conditions being targeted. In the case of brain disorders, one should ideally identify what brain areas are primarily affected and what are the main biochemical and/or neurochemical traits pathognomonic of the disease. For instance, it would be of great help deciding if the disease is mostly associated with neuronal or glial deficit. In case it would be mostly neuronal, one could seek for the brain circuits primarily affected, and the neurochemical systems suffering the most significant imbalance; if a glial deficit would be evident, then one could attempt defining if the disease results from a metabolic drift or if neuroinflammation deregulation plays a role. Finally, the issue of neurogenesis defaults as a possible cause of disease should also be considered. It is this general information that ultimately provides the scientific rationale to select any particular molecular target to develop novel therapeutic strategies.

In the case of psychiatric disorders, it is currently not possible to apply any solid anatomical or neurochemical rationale to sustain pursuing any particular molecular target for the development of novel drug-based therapeutic strategy. In fact, none of the questions listed above have received a clear answer in the case of the most common psychiatric disorders. Taking as examples the case of depressive disorders (the plural reflecting the idea that they are multiple defined clinical entities), the brain areas affected are rather broad and too many biochemical and/or neurochemical (or morphological) traits have been reported to allow any of them to be considered pathognomonic of these ‘diseases’ [1–5]. Different groups place different emphasis on whether ‘depression’ is primarily due to neuronal or glial modifications [6,7]. Accordingly, there is no clear definition of particular brain circuits affected in these conditions, nor there is any agreement on whether these conditions are due to metabolic [8–10] or neuroinflammatory deregulations [11,12]. Finally the currently holly grail of therapeutics (neurogenesis) actually seems to be a part in all physiological and pathological processes in the brain [13,14], making it difficult to anticipate how this can be manipulated as a therapeutic strategy.

Without a clear rationale to discuss the validity of considering any particular molecular target as a promising candidate to develop novel drugs to manage psychiatric conditions, one is left with the evaluation of the efficacy of novel drugs in alleviating the behavioural symptoms that are characteristic of these diseases. The development of drugs is normally carried out in a safer and faster manner using animal models of disease. And this constitutes the second major hurl to test the interest of potentially novel drugs to manage psychiatric disorders. In fact, there is currently no single animal model that satisfactory mimics the most common behavioural changes found in psychiatric disorders [15–17]. There are obviously animal models that replicate particular behavioural changes (but only a limited set) and some animal behavioural tests providing a reasonable predictability of the efficiency of some (but not all) of the drugs currently used to alleviate the symptoms of psychiatric disorders [18,19].

The recognition of our current limitations in exploring novel targets to develop new drug-based therapeutic strategies to manage psychiatric disorders should be kept in mind when evaluating the subsequently presented evidence suggesting the possible interest of adenosine A_{2A} receptors.

PHYSIOLOGICAL ROLE(S) OF ADENOSINE A_{2A} RECEPTORS IN THE BRAIN

There are several reviews dealing with the localization and role of A_{2A} receptors in the brain [20–23]. This short overview is just supposed to recapitulate some features of central A_{2A}

receptors that might be relevant to the putative interest of this receptor in the realm of psychiatric disorders.

Until the beginning of this century, there was a general consensus that central A_{2A} receptors were confined to the basal ganglia, where they played a role in the control of signal processing in medium spiny neurons [24–27]. In fact, this particular pool of A_{2A} receptors is by far the most abundant in the mammalian brain, but this should not underscore the fact that A_{2A} receptors have a much broader distribution in different brain areas and in different cell types, albeit with a considerably lower density. These A_{2A} receptors in medium spiny neurons have been established to be determinant for the control of motor function, since their selective genetic elimination abrogates the ability of A_{2A} receptor to control motor function [28], probably the most evident behavioural effect caused by A_{2A} receptor ligands [23,29–31].

How these A_{2A} receptors located in medium spiny neurons act to control motor function is still an open issue (reviewed in [31]). There is a predominant trend arguing that the main action of these striatal A_{2A} receptors is the control of dopaminergic signalling, that plays a key role in striatal signal processing and thus in motor control [32]. In particular the pioneering work at the Karolinska Institute (reviewed in Ferré et al., present issue) clearly substantiated a tight interaction between A_{2A} and dopamine D_2 receptor signalling. However, it is also clear that A_{2A} receptors can control motor function in the absence of dopaminergic signalling [33,34]. This indicates that even striatal A_{2A} receptors work through dopamine-independent mechanisms to impact on brain function. In fact, A_{2A} receptors have been localized presynaptically in a majority of glutamatergic nerve terminals, where they form heteromers with A_1 receptors and where they play an important facilitatory role of cortico-striatal glutamatergic neurotransmission [35].

The concept of dopamine-independent effects of A_{2A} receptor function is particularly relevant in the case of extra-striatal A_{2A} receptors, where dopaminergic signalling is far less intense. The most compelling evidence come from the recent study using the brain-region specific A_{2A} receptor knockout models in which A_{2A} receptor was selectively deleted either in striatal neurons (striatum A_{2A} KO) or entire forebrain neurons (including striatum, cerebral cortex and hippocampus, forebrain A_{2A} KO) [36–38]. Using these novel knockout models, we recently showed that cocaine-induced psychomotor activity is enhanced in striatum A_{2A} KO mice, but attenuated in forebrain A_{2A} KO mice; urthermore, selective inactivation of A_{2A} receptor in extra-striatal cells by administering the A_{2A} receptor antagonist KW6002 to striatum A_{2A} KO mice attenuated cocaine effects, rather than enhanced cocaine effects by administering KW6002 into wild-type mice [39]. These results identify a critical role of A_{2A} receptors in extra-striatal neurons in providing a prominent excitatory effect on psychomotor activity [39]. Theprecise localization of these extra-striatal A_{2A} receptors involved in psychomotor is not clear yet, but several studies have found that these extra-striatal A_{2A} receptors are mostly synaptically-located in contrast to the most abundant striatal A_{2A} receptors [40]. In particular, extra-striatal A_{2A} receptors are located in glutamatergic synapses [41]. It is important to point out that those extra-striatal A_{2A} receptors also include the A_{2A} receptors localized in striatal glutamatergic terminals [35] (thus, the term extra-striatal can be a bit misleading). These A_{2A} receptors control both the release of glutamate [35,42,43] as well as NMDA receptors [44]. Interestingly, these receptors do not seem to be activated by ambient levels of adenosine [44–46]. Instead, they are selectively recruited upon high frequency trains of afferent stimulation that are normally used to trigger synaptic plasticity phenomena [44]. This is due to the fact that A_{2A} receptors seem to be selectively activated by a pool of adenosine formed upon the extracellular catabolism of ATP [44,47], which is mainly released upon higher frequencies of nerve stimulation [48]. This engagement of A_{2A} receptors selectively upon high frequency trains of stimulation designed to trigger plastic changes in excitatory synapses has lead to the proposal that the adenosine system would help defining salience of information in

excitatory circuits through a combined action of A_{2A} receptors, as an ancillary system of NMDA receptors, in synapses engaged in plastic changes, together with the action of inhibitory A_1 receptors (activated through astrocytic-mediated heterosynaptic depression) in non-stimulated synapses [21]. Hence A_{2A} receptors would play a selective role in controlling plastic changes in brain circuits, defining the threshold for induction of plastic changes in excitatory synapses.

Other possible physiological functions potentially controlled by A_{2A} receptors are also worth considering, although the weight of evidence in their support is currently weaker. One aspect that merits further investigation is the possible ability of A_{2A} receptors to control inhibitory transmission in brain circuits. Neurochemical findings showed that A_{2A} receptors controlled the evoked release of GABA from different preparations [49,50], but this has only received a direct electrophysiological support in the adult brain in the case of collateral projection between medium spiny neurons [51] and in their projection to the pallidus [52]. This topic is of particular relevance given the importance of long-distance interneurons and local interneurons in the definition of cortical excitability [53]. The interest on this subject is strengthened by the recent observation that adenosine receptor blockade following caffeine administration seems to mainly affect inhibitory rather than excitatory transmission in the Human cortex [54]. Another potential role of A_{2A} receptors in physiological conditions is as coordinator of metabolic activity in brain tissue. Thus, adenosine has long been recognised as a key paracrine modulator in different mammalian tissue, being responsible for function such as cardiac dromotropism, tuberulo-glomerular filtration control, post-prandial vasodilatation and control of excessive immune/inflammatory reactivity [55]. In fact, ATP (one of the most abundant intracellular molecules) and adenosine are released from stressed cells (either suffering insults or upon work overload) and this extracellular adenosine acts on both A_1 and A_{2A} receptors to prompt adaptation and/or restore homeostasis [56,57]. In brain tissues, A_{2A} receptors control capillary vasodilatation [58], the uptake of excitatory amino acids by astrocytes and the pattern of metabolism in astrocytes [59]. This is expected to have a dramatic impact both on the availability and use of metabolic resources that are fundamental to the optimal performance of brain circuits, but the true contribution of A_{2A} receptors for brain metabolism still needs to be thoughtfully tested.

ROLE OF ADENOSINE A_{2A} RECEPTORS IN THE CONTROL OF NEURODEGENERATION

The impact of A_{2A} receptors in the control of neuronal damage was first proposed by John Phillis in a model of cerebral ischemic injury [60]. It was later confirmed that either the pharmacological blockade or the genetic elimination of A_{2A} receptors conferred a robust neuroprotection in animal models of brain ischemia [61,62]. This was later extended to a variety of situations that had in common the deleterious impact of chronic noxious insults to adult brain tissue (reviewed in [20,57]), such as glutamate excitotoxicity [63–65], free radical toxicity [66], epilepsy [67–69], MPTP toxicity [70–72], 6-hydroxydopamine toxicity [70,71], 3-nitropropionic acid toxicity [37,73,74] or β-amyloid toxicity [75,76]. Interestingly, the neuroprotection afforded by A_{2A} receptor blockade is most evident in cortical areas (reviewed in [57]), where the density of A_{2A} receptors is nearly 20 times lower than in the striatum [77]. It is important to note that the neuroprotective effect of A_{2A} receptor antagonists in general correlates with their ability to improve cognitive behaviour in animal models of neurological disorders [20,57,78]. Consequently, A_{2A} receptor activity in brain may achieve the modulation of cognitive function, particularly those associated with degenerative disorders (such as Parkinson's disease, Huntington's disease and Alzheimer's disease), through its control of neuronal cell death.

The mechanism underlying this ability of A_{2A} receptors to impact on brain tissue damage is still a matter of hot debate. The use of tissue-specific transgenic mice fostered by our group in Boston University School of Medicine, indicated that non-neuronal A_{2A} receptors were responsible for the control of brain tissue damage; in ischemic models or models of 3-nitropropionic acid-induced toxicity, it was concluded that the key role was played by A_{2A} receptors from bone marrow-derived cells [37,79], whereas in MPTP-induced neurotoxicity A_{2A} receptors in glial cells were the ones that played the key role in controlling brain tissue damage [28]. This is in agreement with the localization of A_{2A} receptors in microglia cells and their ability to control microglia activation and burst of neuroinflammation [80]. However, there is also robust evidence showing that neuronal A_{2A} receptors can also control the demise of neuronal damage. This was shown in the case of cultured neurons (virtually devoid of microglia or inflammatory cells), where A_{2A} receptor blockade abrogated either β-amyloid- [81] or staurosporine-induced neurotoxicity [82] through a control of mitochondria membrane potential and release of pro-apoptotic factors. These stimuli caused an initial synaptic damage that later evolved into overt loss of neuronal viability, in light of the particular synaptic localization of cortical A_{2A} receptors and with the wide spreading idea that chronic neurodegenerative diseases begin with synaptic dysfunctions that later evolve into different demises of neurodegeneration [83–85]. In agreement with this role of synaptic A_{2A} receptors in the control of brain tissue damage is the observation that A_{2A} receptor antagonists prevented restraint stress-induced synaptic damage in the CA3 area of the rat hippocampus without any apparent involvement of changes in inflammatory-related cells [86]. Clearly, this existence of multiple and apparently conflicting hypothesis illustrate how little we actually know about the different possible demises of brain tissue damage as well as of how little we know on the biology of A_{2A} receptors.

A consensual idea would be to propose that there might be a successive participation of A_{2A} receptors located in different cells types according to the duration and/or intensity of noxious brain insult: with mild noxious insults, there might be a main role of synaptic A_{2A} receptors; with more prolonged noxious stimuli, microglia A_{2A} receptors would play a predominant role, in view of the importance of microglia in the amplification of early brain damage [87–89]; finally, with more severe damage, causing loss of preservation of the blood-brain barrier, it might be that A_{2A} receptors in inflammatory cells invading the brain parenchyma play the more pronounced role. Clearly, this is a hypothetic scenario that still needs experimental confirmation.

A final topic that deserves consideration is the transducing mechanisms operated by A_{2A} receptors to fulfil their physiological role(s) and to impact on brain tissue damage. There is general agreement in the field that the transducing system operated by adenosine A_{2A} receptors is through the adenylate cyclase/cAMP/protein kinase A pathway [90]. This has received direct experimental confirmation in heterologous expression system (where this was the only pathway that was investigated) and in striatal medium spiny neurons [91–92]. However, it is now clear that A_{2A} receptors can couple to different transducing pathways (reviewed in [23,57]), being a prototypical example of a pleiotropic receptor. At least for its impact on neuroprotection, it is clear and evident that A_{2A} receptors do not act through the cAMP pathway: in fact, it is well known that bursting the cAMP pathway affords neuroprotection [93,94]; in contrast, it is the blockade of A_{2A} receptors (which would trigger but rather prevent accumulations of cAMP) that actually confers neuroprotection. The clarification of the transducing pathways operated by A_{2A} receptors is an issue of particular relevance since “normalisation of signaling” through manipulating A_{2A} receptors is a potential important issue in the realm of psychiatric disorders.

ADENOSINE AND MOOD DISORDERS

Mood disorders are one of the greatest burdens of disease in Europe and the development of effective strategies to manage these conditions should represent a major socio-economic priority [95–97]. The interest in the role of adenosine in mood disorders stems from three concurrent lines of research: first, there is evidence that the consumption of coffee, and particularly of caffeine (an adenosine receptor antagonists, as discussed below) might modify the mood profile both of volunteers as well as of psychiatric patients; secondly, there is evidence that different therapeutic strategies used to control mood disorders cause effects related to the adenosine modulation system; thirdly, there is evidence from animal models that the manipulation of adenosine receptors modifies behavioural responses considered relevant for mood function in Humans. These first two lines of evidence will be discussed in parallel, whereas the last one will be separately discussed since it is the only one that allows directly relating A_{2A} receptors with mood disorders (until data from the use of A_{2A} receptor ligands in Humans becomes publicly available).

Several studies in Humans have explored the relation between coffee intake and the mood changes. These studies are likely to be relevant to the understanding of the putative role of the adenosine modulation system in the control of mood for two reasons: first because it is becoming evident that most of the effects of caffeine on brain related functions are mostly due to the effects of caffeine, since they are not mimicked by decaffeinated coffee or other drinks such as fruit juice (reviewed in [98]); secondly, the only known molecular target of caffeine at physiological (i.e. nontoxic) doses are the A_1 and A_{2A} adenosine receptors, where caffeine acts as a competitive antagonist [99,100]. The consumption of coffee is well documented to increase alertness (reviewed in [98,101]) and there is a trend to consider that caffeine improves performance and cognition, especially in situations decreasing performance of cognition (reviewed in [20,57,78]). There is also a general perception that caffeine consumption may render individuals more anxious. Actually, large consumption of coffee (or caffeine) has been argued to trigger a constellation of behavioural modifications that has led to coining the term ‘caffeinism’ [102–104]. In this situation, there are both anxiety disorders as well as greater incidence of depressive-like conditions [103,105]. Another situation where there is a strong link between caffeine intake and modifications of mood is upon withdrawal of caffeine [106, 107]. Apart from headache, fatigue and decreased alertness [108–109], withdrawal from regular consumption of caffeine triggers a variety of anxiety-like symptoms, such as irritability, sleepiness, dysphoria, nervousness or restlessness [106,107,110–112]. It is interesting to note that some of these same withdrawal symptoms are similar to those described to occur upon ‘caffeinism’. This leads to two inter-twinned ideas that should be kept in mind when evaluating the putative role(s) of adenosine and its receptors in the control of mood. The first idea is that adenosine (and in an inverse manner caffeine) act on two receptors with globally opposite function, namely inhibitory A_1 and facilitatory A_{2A} receptors. Hence, it is possible that different concentrations (or doses) of caffeine and adenosine may cause opposite effects operated by different receptors. The second idea is a re-phrasal of the previous idea, i.e. that the adenosine neuromodulation system should be viewed as a paracrine system designed to maintain homeostasis or promote adaptation of neuronal systems. This means that the fundamental role of this adenosine modulation system is to narrow the window of functioning of biological systems, curtailing its edges of extremes of functioning. Adhering to these ideas will make it obvious that two much or too little adenosine in a system will cause its failure to properly adapt to its environment. This might be a possible underlying cause to explain the similarity between withdrawn of caffeine and ‘caffeinism’

A second line of evidence that is suggestive of a role of adenosine receptors in the control of mood is the observations that different therapeutic strategies used to control mood disorders have effects related to the adenosine modulation system [113]. In fact, both electroconvulsive

therapy and sleep deprivation are two types of treatments of mood disorders, both of which causing short term and long term adaptations of the adenosine neuromodulation system. Thus, there are short term adaptive neuronal responses that are operated through inhibitory A_1 receptors, namely in terms of the slow wave sleep [114] and cerebral metabolic activity [115, 116]. There are also more long term adaptive changes, such as up-regulation of A_1 receptors [117,119] and possibly of A_{2A} receptors (reviewed in [57]) the former being a strong candidate to mediate the reduction of cerebral blood flow [116,120–122], which is observed after these treatments. It should be made clear that at this stage there is a tentative parallel between the effects operated by these mood disorder treatments and the adenosine modulation system in the brain, but it still remain to be directly shown that the mood beneficial effects of these treatments is hampered by manipulation of adenosine receptors.

ADENOSINE A_{2A} RECEPTORS AND ANXIETY

The role of adenosine A_{2A} receptors in anxiety is still to be defined. In fact, whereas higher doses of caffeine tend to increase [103,123–127] and lower doses of caffeine tend to reduce anxiety levels in Humans [128,129], it is currently difficult to ascribe these opposite effects to the a putative differential manipulation of A_1 and A_{2A} receptors. In animal models aimed at measuring spontaneous anxiety-like responses (such as the light/dark box or the elevated plus maze), there is an anxiogenic-like behaviour in both A_1 receptor knockout mice [130,131] as well as in A_{2A} receptor knockout mice [132–134]. In contrast, careful studies by our group in CNRS showed that the anxiogenic-like effect of caffeine in rodents is not shared by selective A_{2A} receptor antagonists [135].

Another line of evidence that indicates a possible role of A_{2A} receptors in anxiety-related conditions derives from polymorphism analysis of the A_{2A} receptor gene. Thus, it was observed that there is a significant association between self-reported anxiety after caffeine administration and two linked polymorphisms on the A_{2A} receptor gene, the 1976C>T and 2592C>T polymorphisms [137]. Likewise this same polymorphism in the A_{2A} receptor gene was also observed to be associated with the incidence of panic disorder [137,138], which can be envisage as a situation of anticipatory anxiety. Finally, another polymorphism of the A_{2A} receptor gene (1083TT genotype) is inversely correlated with caffeine consumption [139] and is related with the inter-individual sensitivity to caffeine [140]. This is reminiscent of the idea that there is little evidence for a correlation between the consumption of caffeine and anxiety in volunteers [141,142], but there seems to be an anxiogenic effect of caffeine in a sub-group of patients with different psychiatric disorders [143–147]. It remains to be studied if this differential effect of caffeine on anxiety in psychiatric patients may be related to the presence of polymorphisms in the A_{2A} receptor gene [148].

ADENOSINE A_{2A} RECEPTORS AND DEPRESSION

Whether caffeine affects the evolution of depression-like conditions is currently not clear from the epidemiological point of view. In fact, in non-hospitalised cohorts, there is no difference in the consumption of caffeine between control and depressed subjects, albeit there is a trend for greater caffeine-induced anxiety effects in depressed patients [145–147]. Likewise, an analysis of life-long caffeine consumption in twin pairs failed to note any evident relation between caffeine intake and the risk for common psychiatric disorders [142].

The association of the adenosine modulation system with depression has been initially developed based on observations showing that adenosine and its analogues caused depressant-like behavioural effects in two widely used animal models of depression. Thus, elevating the adenosine levels increased the time of immobilization in rats submitted to inescapable shocks as well as in the forced swimming test [149–151]. Further arguing for an ability of the adenosine system to control depression is the observation that classical antidepressants reverse the

adenosine-induced immobility in these tests [152]. Interestingly, classical tricyclic antidepressants such as nortriptiline, chlorimipramine or desipramine can bind to adenosine receptors [153] and dose-dependently reduce the activity of ectonucleotidases in cortical nerve terminals [154], a key controller of the extracellular formation of adenosine from released adenine nucleotides [56]. Accordingly, these tricyclic antidepressants modify the outflow of adenosine from cortical cups [155–156] and the glucose and ATP levels in healthy volunteers [157–160].

The most direct evidence to implicate adenosine receptors in the control of depression was obtained by our group in CNRS. In a series of careful studies, we found that A_{2A} receptor antagonists prolong escape directed behaviour in two screening tests for antidepressants, the tail suspension and forced swim tests [161]. Further support for a potential role of A_{2A} receptor antagonists as novel anti-depressants was provided by the observation that A_{2A} receptor antagonists also displayed an attenuated 'behavioural despair' in these two screening tests [162]. The observation that a dopamine D_2 receptor-like antagonist (haloperidol) prevented the antidepressant effects resulting from A_{2A} receptor blockade or inactivation led to the hypothesis these effects of A_{2A} receptors might involve adenosine-dopamine interactions [161,162], in view of the effectiveness of drugs acting on dopaminergic signalling to manage mood disorders. However, additional mechanisms such as the A_{2A} receptor interaction with other neurotransmitter systems in forebrain regions (but outside the striatum) or the ability to control glial metabolism and neuroinflammation should also be explored by future studies.

This putative deleterious role of A_{2A} receptors in depression [162] is in notable agreement with other observations showing that the blockade of A_{2A} receptors relieves the early stress-induced hippocampal modifications [86]. One of the consequences of chronic stress is favouring the implementation of a state of depression in susceptible individuals [163]. Interestingly, adenosine controls the release of corticotrophin and cortisol/corticosterone release [164–167] and the ability of adenosine receptor activation to modulate hippocampal excitability [23], a key region in the control of HPA [168], and control memory and cognition, mostly through A_{2A} receptors [20,57,78,169,170]. Finally, adenosine receptors can also control the release of serotonin through A_1 and A_{2A} receptors [171] and it has been shown that the ability of caffeine to reduce restraint-induced stress correlates with a striking ability of caffeine to reduce the levels of serotonin in the hippocampus, an effect attributed to A_{2A} receptors [172]. This is particularly relevant since depression as well as the early stress-induced re-modelling of hippocampal circuits are under the control of serotonin (e.g. [173–174]) and several novel antidepressant drugs target the serotoninergic system [175].

Another avenue of research that can link A_{2A} receptors with the aetiology of depression resides in the tight interaction between A_{2A} receptors and Trk-B receptors [176], which signal the presence of neurotrophins such as brain-derived neurotrophic factor (BDNF). Thus, there is a continuous build-up and strengthening of the 'neurotrophin hypothesis of depression' (reviewed in [177,178]) and evidence is accumulating to suggest that A_{2A} receptors are tight controllers of the actions of BDNF, either through transactivation in an acute manner [179–181] or normalization of its signalling in more chronic situations [182]

Furthermore, it is important to keep in mind that the effect of the adenosine modulation system on depressive-like conditions might be more complex. In fact, the group of Ana Lúcia Rodrigues has consistently shown that the administration of adenosine, either peripherally or intracerebroventricularly has an antidepressant effect. This involves the recruitment of A_1 and A_{2A} receptors [183] and involves systems such as NO/cGMP [184] or the opioid system [185].

ADENOSINE A_{2A} RECEPTORS AND SCHIZOPHRENIA

Another psychiatric condition where several studies suggest a role for the adenosine modulation system is schizophrenia. Comparing the features of schizophrenia with some physiological roles of adenosine or with the effects of caffeine and theophylline that are used to probe the role of endogenous adenosine, Diogo Lara has championed the idea that adenosinergic activity might be deficient in schizophrenia [186,187]. Thus, caffeine might exacerbate positive symptoms ([188–190]; but see [191]) and conversely dipyridamole and allopurinol may be beneficial for schizophrenia [192–195]; this provides compelling direct evidence since caffeine blocks adenosine A_1 and A_{2A} receptors and both dipyridamole and allopurinol prevent purine degradation by inhibiting adenosine transporters and xanthine oxidase. Furthermore, the expected deficiency of sensorimotor gating, evaluated as a disturbed prepulse inhibition or P50 evoked potential, which is characteristic of schizophrenic individuals [196], is mimicked by theophylline in healthy volunteers [197]. Furthermore, there are co-morbidity relations, namely with insomnia (particularly with delta activity, see [198]), which is mimicked by caffeine consumption [199] and prevented by activation of adenosine receptors [117], and after seizures [200], which is also mimicked by xanthenes and prevented by adenosine A_1 receptor activation [201]. Altogether these observations support a putative role for deficient levels of adenosine in the brain of schizophrenic patients and are supportive of the adenosine hypofunction hypothesis of schizophrenia. This hypothesis has been further refined to better match the two-hit hypothesis of schizophrenia, to account for the neuro-developmental aspect of this disorder [186,187]. Thus, A_1 receptors have a profound effect of brain development [202], possibly through the control of the function of oligodendrocytes [203–206], which would correspond to the first-hit phase. Furthermore, the role of A_1 receptors in neuroprotection is only fully implemented during adolescence in rodents [207–209], which is compatible with the second hit phase modelling schizophrenia.

In spite of these tempting scenario mainly implying A_1 receptors as a candidate system in the aetiology of schizophrenia, there is also compelling observations that suggest a possible role for A_{2A} receptors. Thus, it was observed that the startle (a measure of sensorimotor function) habituation was reduced by A_{2A} receptor antagonists [210] as well as in A_{2A} receptor knockout mice [211]. Furthermore, A_{2A} receptors can also act as ‘go-between’ normalizing (or re-balancing) an impaired glutamatergic-dopaminergic communication that seems to be crucial importance for proper function of the ventral striatum and prefrontal cortex. A recent study with a transgenic model selectively altering the activity of adenosine kinase in forebrain region has provided some direct evidence in supporting the notion that subtle changes in adenosine level can lead to the emergence of behavioural endophenotypes implicated in schizophrenia [212]. Thus, transgenic mice with over-expression of adenosine kinase in the forebrain (to increase adenosine levels) display severe but selective deficits across different learning paradigms, indicating the cognitive function deficient [212]. In addition, altered adenosine level in forebrain also produces abnormal response to psychostimulants, such as amphetamine and MK-801 [212].

Regarding the dopaminergic involvement in schizophrenia, it is noteworthy that activation of adenosine A_{2A} receptors reduces the affinity of dopaminergic D_2 receptors for dopamine, being the probable mechanism underlying the antipsychotic-like profile of adenosine agonists [213], the hyperdopaminergic effect of caffeine [100,213] and the exacerbation of psychotic symptoms by caffeine in schizophrenic patients [195]. The recent finding of increased basal D_2 receptors occupancy by dopamine in schizophrenic patients [214,215] is compatible with a decreased adenosinergic tone, which via A_{2A}-D_2 receptor interaction would increase the affinity of D_2 receptors for dopamine [27,213]. Moreover, striatal dopamine release is under tonic inhibition by adenosine acting on presynaptic A_1 receptors [216,217], which is also in line with the increased release of dopamine in schizophrenia [218]. Finally, it was observed

that the ability of clozapine (an atypical anti-psychotic, an and to a lesser extent haloperidol) to induced *c-fos* expression is blocked by A_{2A} receptor antagonists [219] and this anti-psychotic also affected key pathways of formation of ATP-derived adenosine acting on A_{2A} receptors, the ecto-nucleotidase pathway [220]. Altogether, these observations are consistent with the possibility that the manipulation of A_{2A} receptor might help restore an adequate dopaminergic signalling.

Concerning the NMDA hypofunction model of schizophrenia [221], adenosine A_1 and A_{2A} receptor agonists have been shown to prevent behavioural and EEG effects of NMDA antagonists [222,223]. This effect is in agreement with several lines of evidence: i) activation of NMDA receptors releases adenosine [224–228] and ATP [229,230]; ii) administration of NMDA antagonists reduces the basal outflow of adenosine [225,226,228]; iii) the effects of NMDA antagonists may result from increased glutamate release [231–233], and both A_1 and A_{2A} receptors control the evoked release of glutamate namely in the striatum [35,42,43]; iv) the psychostimulant effects of NMDA receptor antagonists are largely abrogated by genetic or pharmacological blockade of A_{2A} receptors [39,234]; v) NMDA receptor function is modulated both by A_1 and by A_{2A} receptors [44,235–239]. Taken together, these results suggest that the NMDA hypofunction model may also be corrected by manipulating A_{2A} receptors.

Despite indirect data indicating a potential role for adenosine in the aetiopathology of schizophrenia, direct investigation of the adenosine system in patients is lacking. Acute administration of high doses of caffeine to schizophrenic patients exacerbates positive symptoms but, interestingly, fails to produce anxiety [195,240]. Also, the subtype of adenosine receptor (A_1 or A_{2A}) eventually involved in schizophrenia remains undefined. The only post-mortem study of adenosine receptors in schizophrenia reported an increase in striatal A_{2A} receptors [241,242], with no difference between patients on and off medication before death. Also, the A_{2A} receptor gene, located in the 22q12–13 region, is a candidate gene for susceptibility to schizophrenia [243–245].

ADENOSINE A_{2A} RECEPTORS AND ADHD

Attention deficit/hyperactivity disorder (ADHD) is a heterogeneous phenotypically complex disorder, whose exact aetiology is unknown. Most probably it does not have a unique cause and represents the final result of different factors that interact with each other, with every factor having a small contribution and increasing the vulnerability to the disorder through their cumulative effects [246,247]. Without underscoring the importance of environmental and psychosocial factors, a substantial genetic component has been detected in the appearance of ADHD, mostly due to data obtained from family, twin and adoption studies [246,248]. Thus, the heritability of ADHD has been estimated to be between 0.5 and 0.9, which makes it the most heritable mental disorder among children. The search for the most probable genetic traits associated with ADHD has mainly targeted genes involved with catecholaminergic transmission, with a special focus on dopamine [249]. Evidence supporting dopaminergic dysfunction in ADHD derives from different research areas: i) first the psychostimulant medication used to counteract ADHD mostly interferes with dopamine transmission [246, 250]; ii) behavioural studies in animals indicate a prominent role of dopaminergic transmission in motor control and attention processes [251], which dysfunction are hallmarks of ADHD; iii) neuroimaging studies in ADHD patients demonstrate abnormalities (smaller volumes, hypofunction, decrease blood flow) in brain areas with predominant dopaminergic innervation such as the prefrontal cortex, cingulate gyrus and anterior basal ganglia [252]; iv) case-control and family-based allele frequency studies clearly identified different genes related to dopaminergic transmission (e.g. dopamine receptors and transporter) among the genes associated with higher risk of ADHD [246,248]. In particular, a clear association between

ADHD patients and the presence of a particular isoform of the dopamine D_4 receptor, the 7R allele (see below), has been extensively replicated (e.g. [253,254]. The fact that this $D_{4–7}$ receptor allele has a two-fold higher incidence in ADHD probands suggests that it is associated with a significant fraction of the genetic risk for ADHD, which is in accordance with meta-analysis confirming that $D_{4–7}$ receptor is a susceptibility gene for ADHD [255,256].

This evidence clearly indicates that the $D_{4–7}$ receptor should be a potential target for the development of novel effective therapeutic strategies to manage ADHD. The D_4 receptor belongs to the family of dopamine D_2 receptor and displays a number of polymorphisms in Humans, mainly consisting of different repeats in its third exon which encodes the third intracellular loop of D_4 receptors; the most common variants have 2, 4 and 7 repeats, which represent more than 90% of the observed allelic diversity [257]. This region is involved in the G protein coupling of D_4 receptors and it is interesting to note that the allelic variant that represents a risk factor for ADHD displays a reduced efficacy. Therefore, the therapeutic aim would be to design selective D_4 receptor agonists to bolster this defective signalling associated with $D_{4–7}$ receptor. However, in spite of considerable effort by different research groups, no single compound has yet proven sufficiently potent and selective to activate D_4 receptors (e.g. we have found that Ro 10–5824, the most potent and selective D_4 receptor agonist available has hitherto unrecognised non- D_4 receptor targets in native rodent tissue; unpublished observations). Since D_4 receptors belong to the same family as D_2 receptors, there is a growing interest in exploring the possibility that A_{2A} receptors may physically interact, not only with D_2 receptors (see above), but also with D_4 receptors.

The hypothesis that the manipulation of A_{2A} receptors may be a novel therapeutic strategy to manage ADHD is particular compelling in view of the use of caffeine administration to treat this condition [258,259]. In fact, the evidence supporting a dopaminergic dysfunction in ADHD justifies the psychostimulant medication used to counteract ADHD [246,250,260]. Caffeine is the most widely consumed psycho-stimulant drug worldwide and its only known molecular target at non-pathological doses is the antagonism of adenosine receptors, mainly adenosine A_1 and A_{2A} receptors [99]. However, the use of caffeine in ADHD is not widespread nor a first choice because it was reported to be less efficient to manage ADHD when compared with other psychostimulant drugs [261]. This contention merits to be revisited in view of the dosage of caffeine used in these studies, which is inadequate to sustain a prolonged blockade of A_{2A} receptors as expected from the pharmacokinetic profile of caffeine [99]. In fact, given that the pharmacokinetic profile of caffeine in children and adolescents indicates a considerably faster elimination of the drug [262–265], this once-a-day schedule of caffeine administration is clearly inadequate to provide a plasma level of caffeine sufficient to antagonise A_{2A} receptors throughout the day (in fact, it only allows a 4–6 hours effective antagonism of A_{2A} receptors). Certainly, an adequate use of a novel drug (caffeine), which is innocuous for children [266, 267], if effective, would represent a qualitative increment over the traditional repeated use of psychostimulants, which can have severe side effects if repeatedly used in children.

The putative interest of A2A receptors in ADHD has been emphasised by the group of Reinaldo Takahashi, based on the beneficial effects of A_{2A} receptor antagonists in Spontaneous Hypertensive Rats (reviewed in [78]). In fact, it has been shown that these animals have attention deficits that may underlie their poorer memory performance [268–270]. Furthermore, these cognitive dysfunctions in SHR are prevented by methylphenidate, which is effective in ADHD [271]. It was observed that caffeine and A_{2A} receptor antagonists are also effective to prevent memory deficits in SHR, while essentially devoid of effects in normal rats [78,272].

CONCLUDING REMARKS

As stressed in the beginning of the review, the lack of clear end–points and of animal models of psychiatric diseases has seriously hampers the ability to critically evaluate the potential of any particular molecule as a relevant target to develop novel drugs to manage psychiatric disorders. The interest in the adenosine system mostly stems from the recognition that its main function is to assist maintaining homeostasis in biological systems. Hence, it should be considered a system of choice to manipulate brain circuits to restore their proper function.

In the particular case of mood disorders, A_{2A} receptors emerge as a promising candidate target since these receptors tightly interact physically and functionally with D_2 receptors, which are major targets of psychoactive drugs. The interest on A_{2A} receptors is further emphasised by their prominent role in controlling synaptic plasticity in glutamatergic synapses: thus, a major role of A_{2A} receptors is to normalize the functioning of glutamatergic synapses which dysfunction seems a common feature of many chronic brain diseases. In accordance with this view, A_{2A} receptor blockade affords a robust neuroprotection against different chronic insults to the brain. This neuroprotection afforded by A_{2A} receptor blockade not only depends on the normalization of glutamatergic synapses but also on the ability of A_{2A} receptors to control mitochondria-induced apoptosis as well as to the effectiveness of A_{2A} receptors to control neuro-inflammation. Thus, A_{2A} receptors might not only control the trigger of neuronal dysfunction of brain circuits (glutamate excitotoxicity) but also its main system of amplification (neuroinflammation and metabolic imbalance) as well as its main effector system (apoptotic-induced neuronal damage).

Some caution needs to be introduced in this idyllic scenario. First, there is the need to understand the time window of opportunity to manipulate A_{2A} receptors in brain diseases. There is also an emerging awareness that there are different populations of A_{2A} receptors located in different cellular (and/or sub-cellular) populations that play different and often opposite roles in the control of the function (and dysfunction) of neuronal circuits. In this respect, considerable work still needs to be achieved to allow understanding the molecular mechanisms by which A_{2A} receptors affect brain function. There is growing evidence that A_{2A} receptors are pleiotropic, coupling to different transducing systems, possibly as a function of their heteromerization with different receptors. This opens a thrilling opportunity to manipulate A_{2A} receptors as a novel strategy of “normalisation of signaling” to manage mood disorders.

Finally, there is still an obvious need to validate this potential of A_{2A} receptors where it is in fact relevant, i.e. in patients. This is currently largely restricted to the use of caffeine. Caffeine is known to be a selective adenosine receptor antagonists in rodents (especially in mice), but it might have other hitherto unknown molecular targets in humans. Furthermore, caffeine is not selective for A_{2A} receptors and also antagonises A_1 receptors, making it difficult to unambiguously ascribe effects of caffeine as being mediated by A_{2A} receptors. This is hoped to change dramatically in the near future since A_{2A} receptor antagonists have already been approved as novel anti-parkinsonian drugs, which is hoped to bolster our knowledge on the role of A_{2A} receptors in the control of psychiatric disorders.

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