Role of alpha-2 adenosine (A2A) receptors in hot and cold cognition: effects of single-dose istradefylline in healthy volunteers

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***Abstract***

**Rationale:** The role of the adenosine neurochemical system in human cognition is under-studied, despite such receptors being distributed throughout the brain.

**Objective:** The aim of this study was to shed light on the role of the alpha-2 adenosine receptors in human cognition using single-dose istradefylline.

**Methods:** Twenty healthy male participants, aged 19-49, received 20mg istradefylline and placebo, in a randomized, double-blind, placebo-controlled cross-over design. Cognition was assessed using computerized cognitive tests, covering both cold (non-emotional) and hot (emotion-laden) domains. Cardiovascular data were recorded serially. Cognitive effects of istradefylline were explored using repeated measures analysis of variance and paired t-tests as appropriate.

**Results:** On theEMOTICOM battery, there was a significant effect of istradefylline versus placebo on the Social Information Preference task(t=2.50, p=0.02, *d*=-0.59), indicating that subjects on istradefylline interpreted social situations more positively.No other significant effects were observed on other cognitive tasks, nor in terms of cardiovascular measures (pulse and blood pressure). De-briefing indicated that blinding was successful, both for participants and the research team.

**Conclusions:** Further exploration of the role of adenosine 2 receptors in emotional processing may be valuable, given that abnormalities in related cognitive functions are implicated in mental health disorders such as ADHD. The role of adenosine systems in human cognition requires further clarification, including with different doses of istradefylline.

**Key words:** Istradefylline, cognition, ADHD,adenosine

***Introduction***

It is widely established that distinct cognitive functions are under the modulatory influence of various neurochemical systems (Kehagia et al., 2010; Ott and Nieder, 2019; Robbins and Roberts, 2007)(Kehagia et al., 2010; Robbins and Roberts, 2007). The role of particular receptors and neurotransmitters in cognition is highly relevant to understanding the neurobiology of prevalent mental disorders, such as attention deficit hyperactivity disorder (ADHD). Using single-dose pharmacological agents to ‘probe’ the role of particular neurochemical systems in human cognition has shed considerable light on the roles of noradrenaline, dopamine, and serotonin (e.g. Chamberlain and Sakakian, 2006; Mehta et al., 2001, 1999). In contrast, the role of the adenosine system in human cognition is relatively understudied, as compared to other neurotransmitter pathways. For example, a PubMed search using the terms “adenosine AND cognition AND humans” yielded 630 results whereas a search for “serotonin AND cognition AND humans” yielded 5294 results.

Adenosine is a key neurotransmitter that is widespread throughout the brain (Fink et al., 1992). It acts through multiple mechanisms that are not well understood and has indirect effects on other neurotransmitter pathways, such as dopaminergic, glutamatergic and noradrenergic systems (Ioannidis et al., 2014).

Perhaps the most widely studied pharmacological agent acting on the adenosine system – and certainly the most widely used in everyday life – is caffeine, whose cognitive effects are substantially mediated via non-specific antagonism of multiple adenosine receptors (Ioannidis et al., 2014; McLellan et al., 2016)(Ioannidis et al., 2014; McLellan et al., 2016). Caffeine is widely used throughout the world for its alerting properties (Ioannidis et al., 2014) but its effects on cognition are mixed and further research is needed. For example, there is consensus that caffeine improves reaction time and vigilance (*Encycl. Diet. Suppl.*, 2010; McLellan et al., 2016), while its effects on memory and executive function are less consistent (McLellan et al., 2016).

It is known that adenosine receptors are highly expressed throughout the brain, and that adenosine plays a role in processes such as sleep and arousal (Lopes et al., 2011), but less is known about the specific functions of A2A receptors. There is some evidence from animal studies for the involvement of A2A receptors in drug addiction (Sebastião and Ribeiro, 2009; Lopes et al., 2011), which warrants further research into the modulation of A2A receptors.

Adenosine receptors may play a role in ADHD. There is evidence that caffeine can

ameliorate ADHD symptoms, albeit not as effectively as first-line treatments such as psychostimulant medication (Garfinkel et al., 1975; Ioannidis et al., 2014)(Garfinkel et al., 1975; Ioannidis et al., 2014). Psychostimulants are currently the most effective treatment for ADHD (Kollins, 2008) and predominantly affect dopamine transmission by acting as a dopamine reuptake inhibitor (Challman and Lipsky, 2000). Recent research demonstrates that dopamine transmission is also influenced by adenosine receptors (Ferré et al., 2011). Furthermore, caffeine has been shown to modulate impulsive behaviour in a rodent model of ADHD (Leffa et al., 2019), whilst a separate rodent model of ADHD indicated that antagonism of multiple adenosine receptor types could enhance spatial working memory and social recognition, whereas antagonism of a specific adenosine receptor, the A2A receptor was required for improvement of social recognition (Takahashi et al., 2008). Moreover, studies indicate that A2A receptors influence mental tracking (Geiger et al., 2016) and social cognition (Moscoso-Castro et al., 2016), whilst in animal studies, A2A receptors have been implicated in aspects of working memory (Giménez-Llort et al., 2007), reversal learning (Wei et al., 2011) and habit formation (Yu et al., 2009). Therefore, further research into the relationship between A2A receptors and cognition is merited.

 Istradefylline is a selective A2A-R antagonist, developed as an adjunctive treatment in Parkinson’s disease (PD) (Hauser et al., 2008)(Hauser et al., 2008). It has potent selective affinity for A2A receptors (Saki et al., 2013). Some cognitive enhancing effects of istradefylline have been identified in rodents (Kadowaki Horita et al., 2013), as well as in participants with Parkinson’s Disease (Uchida et al., 2014).

The aim of the current study was to use istradefylline as a pharmacological probe to explore the role of A2A receptors in human cognition. This was a randomized, double-blind, cross-over design in healthy volunteers. In light of the above pre-clinical research, we hypothesized that istradefylline would have beneficial effects on classic executive functions but also on social cognition.

***Method***

*Subjects and screening procedures*

Twenty healthy male volunteers were recruited using advertisements in a local newspaper. After a complete description of the study had been provided, and the risks and benefits discussed, participants provided written informed consent. All potential recruits were screened for significant history of psychiatric or medical illnesses using a structured clinical interview supplemented with the Mini International Neuropsychiatric Inventory (MINI) (Sheehan et al., 1998), administered by a trained researcher. Participants provided a urine sample prior to participation in order to exclude recent use of illicit substances (One Step 10 in 1 Drug Testing Kit, Home Health UK). Intelligence Quotient (IQ) was assessed using the National Adult Reading Test (NART) (Nelson, 1982)(Nelson, 1982), and current depressive mood with the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery SA, 1979)(Montgomery and Asberg, 1979). Past week total caffeine intake was quantified using a detailed instrument developed for this study: the Ioannidis Caffeine Questionnaire (ICQ; see Supplement). Trait impulsivity was assessed using the Barratt Impulsiveness Scale (BIS-11) (Patton, J. H., Stanford, M. S., Barratt, 1995; Stanford et al., 2009). We included these measures to examine whether they moderated any observed cognitive effects of istradefylline.

The study was approved by Local Research Ethics Committee (Cambridge, REC reference number: 207190), and was exempted from clinical trials status by the Medicines and Healthcare Products Regulatory Agency (MHRA).

*Inclusion/Exclusion Criteria*

Healthy male participants were recruited, aged 19-49. Exclusion criteria included: taking medication in the past two weeks likely to impact cognition, history of Parkinson’s Disease, history of clinically significant hepatic/cardiac/renal disease (and other major physical health disorders), current depression (as determined by MINI and the Montgomery-Asperg Depression Rating Scale), known substance dependence (including nicotine), recent illicit drug use (determined by self-report and urine illicit drug screen), history or presence of major mental disorders (including bipolar disorder, psychosis, attention-deficit hyperactivity disorder, obsessive-compulsive disorder, or personality disorder), any known contraindication to istradefylline, history of major head injury, baseline cardiovascular parameters outside normal range, insufficient proficiency with English to understand the procedures, involvement in research in the preceding three months that could impact the neurocognitive assessment (such as participation in studies using the same or similar cognitive tasks), age outside the 18-49 bracket and IQ < 80 based on the NART.

*Study Design*

Participants meeting the inclusion criteria attended for two study visits: on one occasion they received a single oral dose of istradefylline (20 mg), and on the other occasion an oral placebo of identical appearance and weight. Medication was over-encapsulated by the supplying pharmacy to ensure visual blinding. The order of drug dosing was randomized and counter-balanced across participants. This was a randomized, within-subject, cross-over, double-blind design. Based on the established pharmacokinetic profile of istradefylline (Hauser et al., 2003), cognitive assessments were undertaken from 1.25 to 2.75 hours after capsule administration. Prior to cognitive assessments, volunteers spent time in a quiet, waiting room, relaxing. Blood pressure and pulse data were collected three times per visit: at baseline, before starting cognitive assessments and after completion of the cognitive tests. At the end of each study visit, we conducted a debriefing to ask participants if they had noticed any effects of the capsule (including ‘side effects’); and they were asked to indicate one of three options: believed they had been on active drug, believe they had been on placebo, or completely unsure. We asked the equivalent question to the member of the research team running the sessions, in order to evaluate study team blinding.

*Neuropsychological Assessment*

Neuropsychological batteries consisted of tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB, v6.0.23, www.camcog.com) for “cold cognition” and EMOTICOM (v1, Bland et al., 2016) for “hot cognition”. Cognitive testing was performed using a touch-screen computer in a quiet room, supervised by a trained test administrator. Cognitive tasks included in this study are described in Table 1.

[TABLE 1 AROUND HERE PLEASE]

*Statistical Analyses*

Analyses were conducted using SPSS v26.0. Effects of drug versus placebo on blood pressure and pulse rate were evaluated using repeated-measures analysis of variance (RM-ANOVA), including effects of time and treatment condition. Effects of istradefylline on cognition versus placebo were quantified using paired t-tests.

The sample size was determined *a priori* based on a power calculation, which indicated that N=20 would yield >80% power to detect a significant effect of drug of effect size d=0.7 or larger, at alpha = 0.05 two-tailed, based on paired t-tests. This was the minimum effect size deemed to be of significant interest. Based on the a priori power calculation, there was no correction for multiplicity, and significance was defined as p<0.05.

***Results***

The characteristics of the study sample are summarized in Table 2. No adverse events were reported during the study.

[TABLE 2 AROUND HERE PLEASE]

Results of neuropsychological test batteries are presented in Tables 3 and 4. No significant effects of istradefylline versus placebo were found for the CANTAB tasks (paired t-tests, all p>0.10). On the EMOTICOM tasks, there was a significant effect of istradefylline versus placebo on the Social Information Preference task (t=-2.50, df=19, p=0.02, *d*=-0.59). This was due to participants on active treatment more positively interpreting social situations than under placebo conditions. No significant effects were detected on the other EMOTICOM tasks (all p>0.10).

Drug-related changes on the Social Information Preference task (affective bias) did not correlate significantly with baseline caffeine intake (r=0.095, p=0.708), nor with baseline impulsivity on the BIS (total scores, r=0.105, p=0.679).

[TABLES 3 AND 4 AROUND HERE PLEASE]

In terms of cardiovascular parameters (Figure 1; in supplementary file), RM-ANOVA indicated no significant effects of time or of treatment, nor were there significant treatment x time interactions (all p > 0.10).

In relation to study blinding, participants and researchers were unable to accurately identify the active medication sessions beyond chance levels (Table 5), indicating that the double-blind was successful.

 [TABLE 5 AROUND HERE PLEASE]

***Discussion***

Despite istradefylline being used as an add on treatment for Parkinson’s Disease in some global jurisdictions, very little is known about its cognitive effects. More broadly, we sought to use istradefylline to probe the role of adenosine 2a receptors in human cognition. We found a significant effect of istradefylline on affective bias on the Social Information Preference (SIP) task, which measures the difference in the proportion of selected positive and negative scenario outcomes. This result indicated that participants interpreted social situations more positively in the istradefylline condition compared to placebo. However, there were no significant effects on the other cognitive tasks that were examined although there was a non-significant trend effect of istradefylline on risk adjustment loss on the Cambridge Gamble Task (CGT), indicating possible risky behaviour in the loss condition. Some caution is needed however, as this study did not correct for multiple comparisons due to the limited sample size.

The SIP task assesses a participant’s preference for selecting different types of information (facial expression, 'theory of mind' related, and fact-related), to interpret ambiguous or incomplete scenarios, and is from a battery of tasks designed to assess hot cognition (EMOTICOM). Hot cognition refers to the cognitive processing of emotionally salient information (Roiser and Sahakian, 2013) and disruptions in these processes have been implicated in neuropsychiatric disorders, including ADHD (Dam et al., 2019), as well as psychosis (Berry et al., 2015). Interestingly, a previous study indicated that paranoia was associated with a negative interpretation of ambiguous social information (Savulich et al., 2015). Given that istradefylline was associated with more positive interpretation of social situations on the SIP task in the current study, it would be potentially interesting to explore effects of adenosine receptor manipulation in clinical populations characterised by abnormalities of social information processing.

Contrary to our expectations, given pre-clinical findings, and the distribution of adenosine 2a receptors throughout the brain, we did not detect any other effects across a variety of hot and cold cognitive domains. However, it should be noted that this study was designed to detect only drug effects of large size or greater, and so it would have been underpowered to detect subtler cognitive effects. Nonetheless, the current data suggest acute doses of 20mg istradefylline did not have any untoward (e.g. sedative) deficits using cognitive tests with established sensitivities to such effects, nor were any cardiovascular effects noted, which is reassuring in terms of the use of this medication as an add-on treatment for Parkinson’s Disease in some jurisdictions, at least at this dose level.

Though we believe this to be the first study to comprehensively assess cognitive effects of istradefylline in humans using a range of tests, several limitations should be considered. This was a single-dose study; as such, we do not yet know if istradefylline given in higher doses and/or with repeated dosing could impact cognition. Our sample size, while adequate to detect large effects, was underpowered to detect subtler effects. It should be noted that this sample had an above average IQ. Future work could examine whether these findings generalize to a wider population. Though subjects had higher than population average IQs, we feel it unlikely that ceiling effects contributed to the negative findings reported herein. For example, on the CANTAB SWM, there were an average of 51 errors across placebo and drug conditions, while on the CANTAB RVP, the probability of identifying the correct box was 84% across placebo and drug conditions, suggesting there would be ample scope for improvement in task performance through a cognitive enhancing manipulation. While we cannot rule out the possibility that differences in participants’ caffeine intake could have affected the study results, however we feel this is unlikely: the study used a cross-over design with each participant acting as their own control to minimize inter-individual differences. Lastly, we did not correct for multiple comparisons because this was an exploratory study with a sample size inappropriate for statistical correction due to power. This may provide a potential alternative explanation for the significant result on the SIP.

Future work could include electrophysiological measures to help determine if the effect of istradefylline on cognition reflects central rather than peripheral effects. The significant result in the current cannot conclusively be determined to be the result of central effects, however we believe it is unlikely to be resulting from peripheral effects as we found no effects of medication on cardiovascular perimeters.

 In conclusion, we found initial novel evidence of a role for adenosine 2a receptors in emotional processing on the Social Information Preference test, biasing towards positive. This may be relevant to conditions such as ADHD, which are often characterized by emotional dysregulation (Hirsch et al., 2018). The study highlights the need for more research into the role different adenosine receptors in human cognition, both in healthy controls and patient groups.

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**Table 1: Descriptions of cognitive tasks included in this study**

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| --- | --- |
| **Task** | **Task Description** |
| CANTAB Spatial Working Memory (SWM) | A measure of working memory. Participants are asked to search a number of coloured squares in order to find a yellow token (Chamberlain et al., 2005). The number of boxes can be gradually increased to 12 in order to increase the difficulty. Outcome measures include strategy and errors (revisiting boxes already found to be empty).  |
| CANTAB Rapid Visual Processing (RVP) | A measure of sustained attention in which participants are required to detect a target sequence of digits (Soar et al., 2012). Outcome measures include speed of response, probability of false alarms and sensitivity.  |
| CANTAB Intra-Extra Dimensional Set Shift (IED) | Measures set-shifting by testing rule acquisition and reversal. Participants are asked to use feedback to work out a rule to determine which of two stimuli are correct (García-Villamisar and Dattilo, 2015).  |
| EMOTICOM Reinforcement Learning (RL) | An assessment of learning through reward and punishment. Participants must choose from a series of paired coloured circles, each with a high or low chance of monetary reward/monetary loss (Bland et al., 2016). |
| EMOTICOM Cambridge Gambling Tast (CGT) | Assesses decision making and risk-taking behaviour. During the task participants are shown a roulette wheel divided into two colours, with the proportions of each colour changing on every trial. Participants are required to choose the colour they wish to bet on and the size of the bet (Bland et al., 2016; Dam et al., 2019). |
| EMOTICOM Social Information Preference (“Theory of Mind; SIP) | A task designed to assess information preference by hiding nine pieces of information in a socially ambiguous situation. Participants are instructed to pick four pieces of information to help them decide whether the situation is positive, neutral or negative (Dam et al., 2019; Skandali et al., 2018).  |
| Delay Discounting task (DD) | Participants are offered choices between monetary awards available immediately and larger rewards available following a delay (Ainslie, 1975). |

Table 2. Demographic data and results of self-administered psychological tests

|  |  |  |
| --- | --- | --- |
|  | Mean (SD) | Range |
| Age (years) | 30.2 (7.9) | 19-49 |
| Caffeine Consumption(mg per week) | 1670 (1246) | 0-4122 |
| NART | 121.0 (4.5) | 111-126 |
| BIS-11 total score | 59.2 (9.3) | 42-77 |
|  Motor | 22.7 (4.2) | 13-29 |
|  Non-Planning | 21.1 (4.5) | 11-30 |
|  Attentional | 15.5 (3.9) | 8-23 |
| SOC | 116.6 (6.5) | 104-128 |
| SDS | 17.9 (7.2) | 5-29 |
| NEO-FFI-3 total score | 137.2 (16.9) | 115-171 |
|  Neuroticism | 16.4 (7.7) | 2-30 |
|  Extraversion | 28.5 (6.8) | 15-43 |
|  Openness to experience | 30.9 (5.9) | 20-42 |
|  Agreeableness | 29.6 (7.0) | 13-41 |
|  Conscientiousness | 31.7 (6.9) | 21-46 |

Abbreviations. SD: standard deviation, NART: National Adult Reading Test, BIS-11:

Barratt Impulsiveness Scale 11 (BIS-11), MADRS: Montgomery-Asberg Depression Rating Scale

Table 3. Neuropsychiatric data of CANTAB

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Batteries | Measures | Drug Conditions (SD)(20 participants each) | Statistic (t value) | p value | Cohen’s *d* |
| Istradefylline | Placebo |  |
| IED | Adjusted total error | 11.3 (7.9) | 12.2 (11.7) | 0.42 | 0.68 | 0.09 |
|   | Extra dimensional error | 2.7 (3.0) | 3.5 (5.2) | 0.81 | 0.43 | 0.18 |
| RVP | Median latency | 358.1 (59.3) | 344.3 (39.5) | 1.73 | 0.10 | -0.39 |
|   | Probability of hit | 0.80 (0.14) | 0.77 (0.17) | 1.02 | 0.32 | -0.23 |
|   | Probability of false alarm (\*102) | 0.30 (0.38) | 0.34 (0.49) | 0.24 | 0.81 | 0.05 |
| SWM | Between-search errors | 54.9 (46.3) | 44.3 (44.4) | 1.44 | 0.17 | -0.32 |
|  | Double errors | 2.0 (2.7) | 2.8 (5.2) | 0.57 | 0.57 | -0.13 |
|  | Total errors | 56.0 (47.3) | 45.2 (44.7) | 1.37 | 0.19 | -0.31 |
|  | Within errors | 3.9 (8.0) | 2.8 (3.6) | 0.50 | 0.62 | -0.11 |

Abbreviations. SD: standard deviation, IED: Intra-Extra Dimensional Set Shift, RVP: Rapid Visual Processing, SWM: Spatial Working Memory

Table 4. Neuropsychiatric data of delay discounting and EMOTICOM

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Batteries | Measures | Drug Conditions (SD)(20 participants each) | Statistic(t value) | p value | Cohen’s *d* |
| Istradefylline | Placebo |  |
| DD | Log of overall k\* | -2.33 (0.81) | -2.22 (0.83) | 1.14 | 0.27 | 0.07 |
|  | Log of small k | -2.16 (0.91) | -2.08 (0.88) | 0.76 | 0.46 | 0.06 |
|  | Log of medium k | -2.29 (0.83) | -2.29 (0.89) | 0.01 | 1.00 | -0.0005 |
|  | Log of large k  | -2.46 (0.75) | -2.35 (0.82) | 1.08 | 0.30 | 0.09 |
| RL | Learning rate in win condition | 0.12 (0.29) | 0.23 (0.34) | 1.24 | 0.23 | 0.26 |
|  | Temperature in win condition | 0.91 (1.68) | 0.47 (0.82) | 1.30 | 0.21 | -0.29 |
|  | Learning rate in loss condition | 0.39 (0.36) | 0.28 (0.30) | 1.00 | 0.33 | -0.21 |
|  | Temperature in loss condition | 0.87 (0.80) | 0.78 (1.26) | 0.27 | 0.79 | -0.05 |
| CGT | Risk adjustment loss | 2.5 (0.7) | 2.2 (1.0) | 1.99 | 0.06 | -0.46 |
|  | Risk adjustment win | 2.1 (0.8) | 1.8 (0.9) | 0.94 | 0.36 | -0.22 |
| SIP | Faces  | 5.7 (5.6) | 8.2 (7.1) | 1.38 | 0.19 | 0.33 |
|  | Thoughts  | 39.9 (7.4) | 39.7 (8.4) | 0.08 | 0.94 | -0.02 |
|  | Facts  | 26.4 (5.3) | 24.1 (4.8) | 1.52 | 0.15 | -0.36 |
|  | Affective bias | 3.7 (4.0) | 1.5 (3.9) | 2.50 | 0.02 | -0.59 |

\*k = coefficient of delay discounting

Abbreviation. DD: delay discounting, RL: Reinforcement Learning Task, CGT: Cambridge Gambling Task, SIP: Social Information Preference (“Theory of Mind”)

Table 5. Blinding results from debriefing sessions pertaining to active treatment visits. Top row shows the N and percentage of participants correctly guessing the were on active treatment, incorrectly guessing they were on active treatment, and indicating they were completely unsure. The bottom row indicates the equivalent responses for what the Researcher running each visit thought about the participant (i.e. study team blinding).

|  |  |  |  |
| --- | --- | --- | --- |
|  | Correct  | Incorrect  | Unsure |
| Study participants | 20% (4/20) | 35% (7/20) | 45% (9/20) |
| Researcher | 5% (1/20) | 5% (1/20) | 90% (18/20) |