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ORIGINAL INVESTIGATION

Effect of aspirin on hypothalamic–pituitary–adrenal function and on neuropsychological performance in healthy adults: a pilot study

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Abstract
Rationale Hypothalamic–pituitary–adrenal axis dysregulation predicts poor clinical and biochemical response to antidepressants. Antiglucocorticoids have therapeutic benefits but most have a troublesome adverse event profile. Aspects of neuropsychological performance, notably working memory, are susceptible to corticosteroid modulation and are impaired in depression. Aspirin has been shown to attenuate the adrenocorticotropic hormone (ACTH) and cortisol response to physiological challenge suggesting its potential to act as an augmenting agent in depression.
Objectives To examine the effect of sub-acute (300 mg daily for 7 days) aspirin pre-treatment on the cortisol awakening response and the effect of acute (600 mg) and sub-acute aspirin on the neuroendocrine and neuropsychological response to the arginine vasopressin analogue, desmopressin.
Results We demonstrated that aspirin pre-treatment did not attenuate the cortisol or ACTH response to desmopressin but, as hypothesised, significantly reduced the cortisol awakening response and improved working memory.
Conclusions Further studies to examine the impact of aspirin on neuropsychological performance and HPA axis function are warranted.

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Introduction

The aim of this study was to investigate whether aspirin has potential as an augmenting agent in major depressive disorder (MDD). MDD is a huge global problem (Murray and Lopez 1997) in part because of the high rates of treatment resistance.

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis is a common concomitant of MDD and is associated with treatment non-response (Young et al. 2004b), most likely via an attenuation of the serotonergic response to antidepressants (Gartside et al. 2003). Normalisation of the HPA axis may precede and be necessary for treatment response (Ising et al. 2007). A recent Cochrane review supports the proposition that agents that reduce HPA axis overactivity have efficacy as augmenting agents in the treatment of MDD (Gallagher et al. 2008).

Working memory impairment has been demonstrated in mood disorders including drug-free depressed patients (Porter et al. 2003) and unipolar and bipolar patients who are in symptomatic recovery (Robinson et al. 2006; Zobel et al. 2004). The severity of the impairment appears to relate to the degree of HPA axis dysregulation (Watson et al. 2006). Corticosteroid administration impacts on neuropsychological performance (Lupien and McEwen 1997; Young et al. 1999) including declarative memory (Newcomer et al. 1994); working memory, however, appears to be particularly sensitive (Lupien et al. 1999). Working memory has utility as an outcome measure of

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treatment trials in mood disorder patients (Venn et al. 2005; Young et al. 2004a).

Aspirin has been shown to reduce the HPA axis response to physiological and pharmacological challenge. For instance Nye and colleagues have shown that acute administration of aspirin reduces the adrenocorticotropic hormone (ACTH) and cortisol response to arginine vasopressin (AVP) (Nye et al. 1997).

We hypothesised that both acute and sub-chronic aspirin treatment would reduce the adrenocorticotropic hormone, cortisol and working memory response to an analogue of arginine vasopressin and would attenuate the cortisol awakening response (CAR).

Materials and methods

The study had Ethics Committee Approval and all subjects gave informed consent.

Subjects were given placebo (for 7 days), acute aspirin (placebo for 6 days then 600 mg aspirin on day 7) and chronic aspirin (300 mg for 7 days) with a washout period of 2 weeks between regimes in a random order (unstratified six block randomisation was used). Medication was taken at 10 am.

On the test day, patients were asked to produce a passive drool saliva sample into a plastic container on waking and at 15-min intervals for a further hour whilst fasting. They then took their final drug treatment at 10 am (in the acute aspirin arm, subjects had therefore taken only placebo for 6 days and the acute aspirin samples were not included in the CAR analysis). Subjects attended the laboratory at noon, where they had a standard light lunch and were cannulated. At 1400 hours (time 0), 10 μg of desmopressin (ddAVP) was injected intravenously over 15 s. Blood samples were taken at −30, −15, 0, 15, 30, 45, 60, 75 and 90 min. Samples were centrifuged, stored at −80 C and assayed for cortisol in-house by using corti-cote radioimmunoassay kits (ICN Pharmaceuticals, CA, USA). For salivary cortisol, the inter-assay and intra-assay coefficients of variation (CV) for the low (4.5 nmol/l), medium (16.2 nmol/l) and high (66.4 nmol/l) quality controls were 10.8%, 10.5% and 7.4% and 16.4%, 10.7% and 13.0%, respectively. The corresponding values for the plasma cortisol analysis were 5.4%, 9.7%, 10.9% and 10.9%, 9.4% and 10.8%. Samples were also assayed in-house for ACTH, intra- and inter-assay CVs were 25.1% and 7.9%.

Neuropsychological performance was determined at 1500 hours. Alternative versions of the following tests were used on each visit:

The Wechsler digit span (Wechsler 1981). In this task, subjects are asked to recall a string of digits, first forwards and then reversed.

The Rey Auditory–Verbal Learning Test (RAVLT) (Rey 1964). This is a test of immediate and delayed verbal learning. Subjects are presented with a list of 15 words a total of five times, with immediate recall tested after each occasion (list A1–A5). A distracter list (list B) is then presented, again with an immediate recall test. Without further presentation, recall of list A is then tested immediately and again after a filled delay of 30 min (list A7). Finally, recognition of both lists is tested from among a series of distracters. For each measure, the number of words correct is recorded.

The Controlled Oral Word Association Test (Benton's FAS) (Benton and Hamsher 1976). This is a verbal fluency test in which subjects generate words beginning with a particular letter following a prescribed set of rules. Total number of words correct is recorded.

Digit Symbol Substitution Test (DSST) (Wechsler 1981). This is a test of attention and psychomotor speed.

Analysis

Thirteen healthy male subjects were recruited by local advertisement for this double-blind placebo-controlled crossover study design. Subjects in the analysis had a mean age of 27.6 (SD=6.2), had spent 17.2 years in full time education (SD=2.3), drank 13.6 (SD=9.7) units of alcohol per week and had a mean national association reading test of 116, (SD=7.6).

Area under the curve was measured by trapezoid integration, with subtraction of baseline cortisol secretion. Statistical analysis employed repeated measures analysis of variance (ANOVA; all within subject factors) and paired *t* tests (two-tailed). All analysis was performed with SPSS version 15. In the ANOVA, significance is reported by Huynh–Feldt corrected *P* values and uncorrected degrees of freedom are reported for clarity.

Results

ddAVP was tolerated and no side effects were reported. For the final data analysis, two subjects were excluded after plasma analysis revealed detectable salicylate during the placebo arm.

The CAR AUC was significantly attenuated after chronic aspirin treatment (mean=22.1, SD=239.8) compared with placebo (mean=171.3 nmol min/l, SD=163.6; mean difference=149.1, SD=154.6; 95% CI of the difference=45.3 to 253.0; t=3.2, df=10, P=0.01 (Fig. 1)). In the acute aspirin arm (in which subjects had received only placebo), the CAR AUC had a mean of 57.5 with a

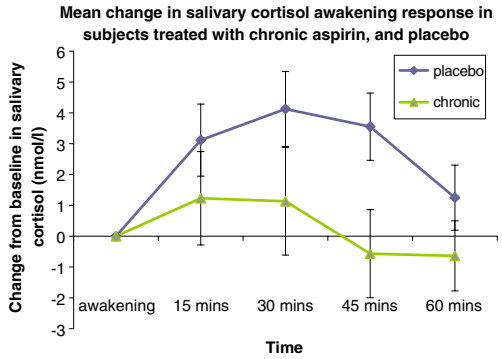

Fig. 1 Mean increase in salivary cortisol awakening response in subjects treated with chronic aspirin compared with those receiving placebo. *Error bars* show standard error of the mean

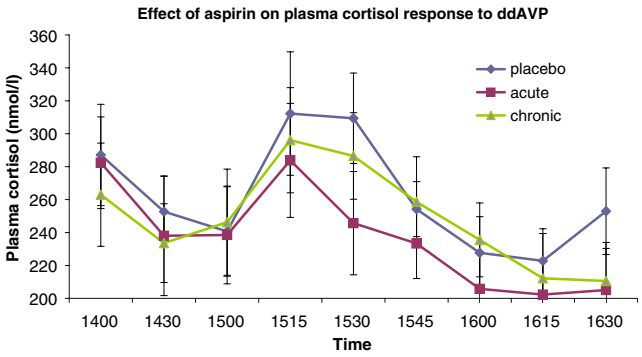

Fig. 3 Effect of aspirin pre-treatment on the cortisol response to desmopressin (administered at 1500 hours). *Error bars* show standard error of the mean

standard deviation of 234.2 and did not differ from the CAR AUC after chronic aspirin treatment (t=0.43, df=10, P=0.67).

Repeated measures ANOVA of the CAR using "drug" (placebo and chronic aspirin) and "time" showed a significant effect of drug (F=8.5, df=1.10; P=0.015) but only an effect of time (F=2.9; df=4.40; P=0.063) and drug by time (F=2.6, df=4.40; P=0.071) at the trend level. Repeating this analysis using three levels of "drug" (placebo, acute and chronic aspirin) revealed an effect of time (F=3.7, df=4.40; P=0.025) but not drug (F=2.1, df=2.20; P=0.15) or drug by time (F=1.4, df=8.80; P=0.23).

Repeated measures ANOVA using three levels of "drug" (placebo, acute and chronic aspirin) and time revealed a significant effect of time (cortisol F=6.9, df=8.80, P< 0.0005; ACTH F=5.3, df=8.80, P=0.001) but no drug by time effect on the plasma cortisol (F=0.57, df=16.160, P= 0.82) or ACTH (F=0.548, df=16.160, P=0.79), response to ddAVP (Figs. 2 and 3). In the placebo arm, there was a significant increase in plasma cortisol (t=2.3, df=10, P= 0.04) and plasma ACTH (t=3.7, df=10, P=0.004) between the 1515 and the 1500 hours sample (taken immediately prior to ddAVP administration).

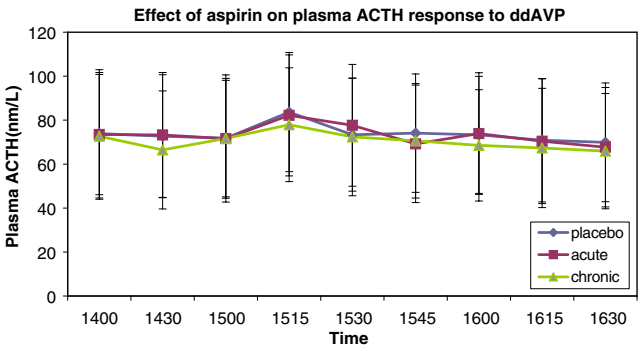

Fig. 2 Effect of aspirin pre-treatment on the ACTH response to desmopressin (administered at 1500 hours). *Error bars* show standard error of the mean

Backwards digit span differed significantly between the three pre-treatment groups (Fig. 4; F=4.5, df=2, 20, P= 0.025). Post hoc analysis revealed that backwards digit span was significantly greater after chronic (t=2.5, df=10, P= 0.03) but not after acute (t=1.5, df=10, P=0.17) aspirin treatment (compared with placebo).

Forward digit span, the RAVLT measures, DSST and verbal fluency did not differ between treatment arms (P>.19; Table 1).

Discussion

The hypothesised attenuation of the cortisol response to ddAVP was not seen; however, the study demonstrated that aspirin treatment over 6 days attenuated CAR AUC.

There was an effect of aspirin treatment on the task of working memory (digit span backwards) that was not seen on the control measures of executive function (verbal fluency) or declarative memory (RAVLT).

The demonstration of salicylates in the blood of two subjects in the placebo arm reduced the effective sample size to 11, limiting the power of the study.

The impact of salicylates on ACTH and cortisol release in previous studies varies depending on a number of factors, including dose. For example, levels of over 25 μg/mL but not 10 μg/mL attenuated the cortisol

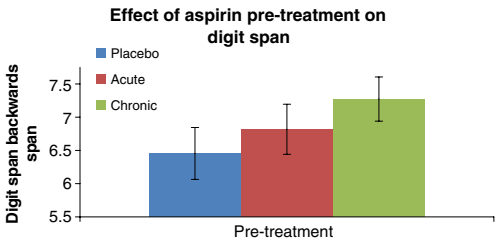

Fig. 4 Effect of aspirin pre-treatment on digit span backwards span. *Error bars* show standard error of the mean

Table 1 Neuropsychological data

Neuropsychological variables	***Acute aspirin*** *Mean (SD)*	***Chronic aspirin*** *Mean (SD)*	***Placebo*** *Mean (SD)*
Digit span			
Forward span	7.8 (1.2)	7.7 (1.3)	8.0 (1.3)
Backwards span	6.8 (1.3)	7.3 (1.1)	6.5 (1.3)
Rey-AVLT			
Learning (total A1 to 5)	52.6 (9.2)	53.4 (12.8)	56.4 (13.0)
Long-term recall (A7, % retained)	82.7 (18.0)	82.2 (18.9)	93.1 (33.5)
Long-term recognition (list A)	13.2 (2.1)	12.9 (2.2)	13.8 (1.8)
Verbal fluency (FAS)			
Number correct	48.6 (7.0)	46.4 (8.4)	49.9 (11.2)
DSST			
Number correct in 90 s	66.2	66.4	63.8

response to castration in calves (Coetzee et al. 2007). The nature of the challenge also appeared relevant, in studies using hypoglycaemic and naloxone stimulation, salicylates tended not to reduce cortisol release (Cavagnini et al. 1979; Halter and Metz 1982; Hockings et al. 1993). Duration of treatment also appears important, 10 days treatment with 1.6 g of aspirin daily reduced the cortisol response to exercise (Di Luigi et al. 2001), whereas in a different study, 1.5 g daily over 2 days did not (Przybyłowski et al. 2003).

The effect of aspirin on CAR but not on the cortisol or ACTH response to ddAVP is intriguing, particularly given the previously demonstrated impact of aspirin on the ACTH and cortisol response to AVP (Nye et al. 1997). The absence of a ddAVP effect may be a type II error consequent on a lack of power. Pharmacological differences between ddAVP and AVP may also be important. ddAVP is an analogue of AVP used in this study because of its better safety and tolerability profile but limited by its comparatively reduced affinity for the AVP1b receptor. There was a cortisol and ACTH response to ddAVP; however, had we used AVP instead, the response may have been greater allowing any influence of aspirin on the HPA axis to be revealed.

Aspirin may have exerted the effect on CAR by chronic lowering of inflammatory cytokines (von Känel et al. 2008) thereby enhancing GR function (Pace et al. 2007) and hence negative feedback control of cortisol release. AVP treatment has been shown to synergise the effect of CRH on pituitary corticotrophs and overcome the suppressant effects of GR activation on ACTH release (von Bardeleben et al. 1985). Administration of ddAVP may have therefore minimised the influence of GR function on ACTH release and hence negated the aspirin effect.

The results are promising and suggest that further studies to evaluate the effect of aspirin on HPA axis function and neuropsychological performance are warranted. These will allow examination of the potential for a therapeutic trial of aspirin in patients with MDD or mild cognitive impairment.

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