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Research Report

The neuroprotective domains of the amyloid precursor protein, in traumatic brain injury, are located in the two growth factor domains

Frances Corrigan[a,b], *Chi L.L. Pham*[c,d], *Robert Vink*[a,b], *Peter C. Blumbergs*[a,b], *Colin L. Masters*[e], *Corinna van den Heuvel*[a,b,1], *Roberto Cappai*[c,d,*,1]

[a]*Discipline of Anatomy and Pathology, School of Medical Sciences, University of Adelaide, South Australia, Australia*
[b]*Hansen Institute, Institute of Medical and Veterinary Sciences, Adelaide, South Australia, Australia*
[c]*Department of Pathology, The University of Melbourne, Victoria 3010, Australia*
[d]*Bio21 Molecular Science and BioTechnology Institute, The University of Melbourne, Victoria 3010, Australia*
[e]*Mental Health Research Institute, The University of Melbourne, Parkville, Victoria, Australia*

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ABSTRACT

The amyloid precursor protein (APP) is known to increase following traumatic brain injury (TBI). This increase in levels of APP may be deleterious to outcome due to the production of neurotoxic Aβ. Conversely, this upregulation may be beneficial as cleavage of APP via the alternative non-amyloidogenic pathway produces the soluble α form of APP (sAPPα), which is known to have many neuroprotective and neurotrophic functions. Indeed it has previously been shown that treatment with sAPPα following a diffuse injury in rats improves outcome. However, the exact location within the sAPPα molecule which contains this neuroprotective activity has yet to be determined. The sAPPα peptide can consist of up to 6 domains, with the main isoform in the brain missing the 4th and 5th. Of the remaining domains, the D1 and D6a domains seem the most likely as they have been shown to have beneficial actions *in vitro*. This present study examined the effects of *in vivo* posttraumatic administration via an intracerebroventricular injection of the D1, D2 and D6a domains of sAPPα on outcome following moderate-impact acceleration TBI in rats. While treatment with either the D1 or D6a domains was found to significantly improve motor and cognitive outcome, as assessed on the rotarod and Y maze, treatment with the D2 domain had no effect. Furthermore axonal injury was reduced in D1 and D6a domain treated animals, but not those that received the D2 domain. As the D1 and D6a domains contain a heparin binding region while the D2 domain does not, this suggests that sAPPα mediates its neuroprotective response through its ability to bind to heparin sulfate proteoglycans.

* *Corresponding author*. Department of Pathology, The University of Melbourne, Victoria 3010, Australia. Fax: +61 3 8344 4004.
E-mail address: r.cappai@unimelb.edu.au (R. Cappai).
[1] Co-senior authors.

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1. Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality with an estimated 10 million people affected annually by an injury serious enough to result in death or hospitalization (Hyder et al., 2007). Following TBI, cell death is caused by the initial insult and the ongoing contribution of secondary factors such as excitotoxicity, oxidative stress and inflammation (Bramlett and Dietrich, 2004; Enriquez and Bullock, 2004). Although this delayed tissue damage provides a therapeutic window with an opportunity to limit neuronal damage (Vink and Van Den Heuvel, 2004), there are currently no accepted pharmacological interventions available for the treatment of TBI (Maas et al.). As such it seems that the identification of factors within the endogenous neuroprotective and neurotrophic pathways may facilitate the development of novel therapeutic strategies. This is especially important as the upregulation of these pathways appears to be inhibited with more severe injuries (Thompson et al., 2006).

Recent evidence suggests that the amyloid precursor protein (APP) may play a role in these neuroprotective and neurotrophic pathways following TBI, with the metabolite sAPPα shown to improve motor outcome with an associated reduction in axonal injury and apoptotic cell death when administered to rats following TBI (Thornton et al., 2006). Indeed, multiple studies have highlighted the role of sAPPα in providing neuroprotection (Goodman and Mattson, 1994; Masliah et al., 1997), enhancing neurite outgrowth (Ohsawa et al., 1997; Qiu et al., 1995), promoting synaptogenesis (Bell et al., 2006) and increasing neurogenesis (Caille et al., 2004).

sAPPα can consist of up to 6 different domains, although predominant isoform of APP which is present in the central nervous system, APP695, does not contain the 4th (KPI) or 5th (OX-2) domains (Sandbrink et al., 1996). Thus sAPPα from APP695 can be divided into a growth factor like domain (D1), a copper binding region (D2), an acidic region (D3), and a carbohydrate domain (D6), with the carbohydrate domain further divided into an E2 domain (D6a) and a juxtamembrane region (D6b) (Reinhard et al., 2005; Storey and Cappai, 1999). It should also be noted that the combination of the D1 and D2 domains is sometimes referred to as the E1 domain (Soba et al., 2005). Only the D1, D2 and D6a domains participate in secondary structure formation with the D3 and D6b domains providing flexible linkers to connect the individual folding units (Reinhard et al., 2005). The beneficial actions of sAPPα have previously been linked to the D1 and D6a domains (Jin et al., 1994; Ohsawa et al., 1997; Qiu et al., 1995). However, their efficacy *in vivo*, and their ability to improve outcome following TBI, is yet to be determined. As such the present study examined the effects of *in vivo* post-traumatic administration of the D1, D2 and D6a domains of sAPPα on functional outcome following severe impact acceleration TBI compared to that of animals treated with the full length sAPPα.

2. Results

2.1. *The D1 and D6a domains of sAPPα are as effective as the full length peptide at improving motor outcome post-injury*

Following TBI, motor outcome was determined using the rotarod (Figs. 1A–C), with sham rats performing at close to the maximum time of 120 s, ranging from 111.5 s to 118.7 s over the testing period. The vehicle animals were significantly impaired on all days following injury ($p<0.01$), and although they did improve from 45 s on day 1 to 85.5 s on day 7 post-injury, they never returned to sham level. Similarly, the D2 treated rats (Fig. 1C) were significantly worse than sham rats

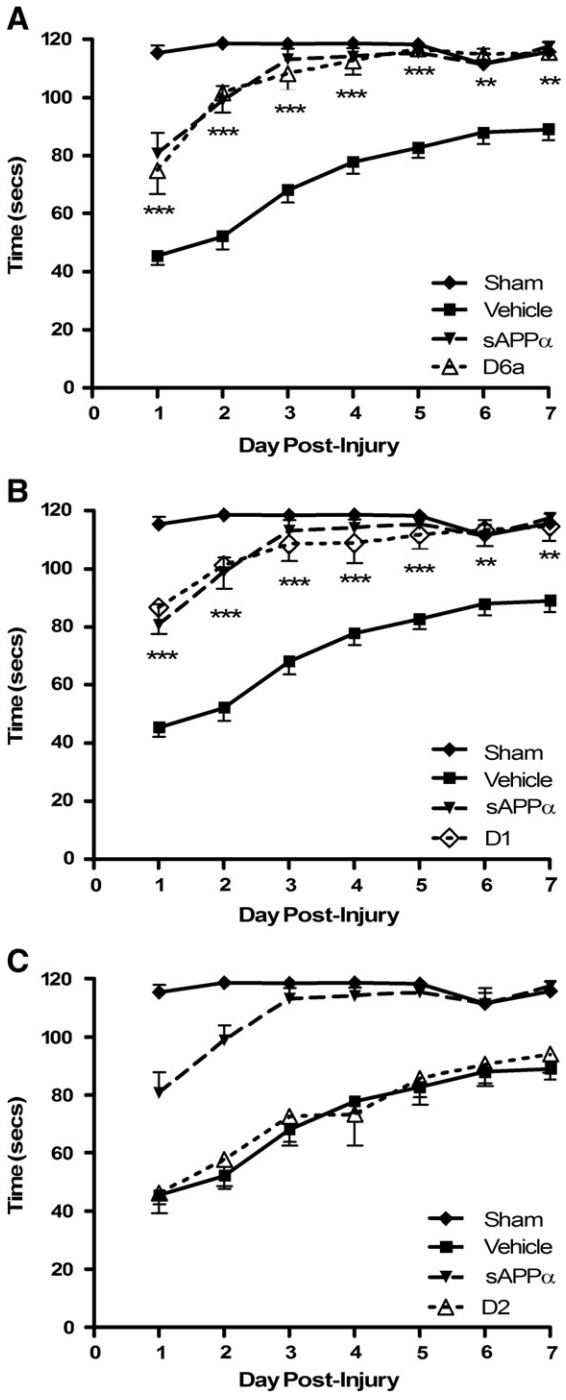

Fig. 1 – Motor (rotarod) scores for rats following TBI. The D1 (1A), D6a (1B) and D2 (1C) treated groups are compared to the performance of the sham, sAPPα and vehicle control groups. Results are expressed as means ± SEM (n = 10 per group) (*$p<0.001$, **$p<0.01$ compared to vehicle controls).**