100P ACTIVATION OF GROUP III METABOTROPIC GLUTAMATE RECEPTORS INHIBITS GABA RELEASE IN THE RAT GLOBUS PALLIDUS *IN VIVO*

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Recent electrophysiological evidence supports the idea that group III metabotropic glutamate (mGlu) receptors located on striatopallidal terminals in the globus pallidus (GP) may function as heteroreceptors (Valenti *et al*., 2003). The current study sought to provide more direct evidence for such a role by examining the ability of the selective group III mGlu agonists, L-serine-O-phosphate (L-SOP) and L-(+)-2-amino-4-phopshonobutyric acid (L-AP4) to inhibit depolarisation-evoked GABA release in the GP using *in vivo* microdialysis.

Male, Sprague Dawley rats (270-300g) were anaesthetised with chloral hydrate (bolus dose 130 mg kg^{-1}; maintenance doses 16 mg kg^{-1} as necessary) and a microdialysis probe (2 mm tip, Hospal AN 69 membrane) was implanted into the GP (0.9 mm posterior, 3.0 mm lateral and 0.74 mm ventral to bregma). Probes were perfused with artificial cerebrospinal fluid (aCSF) at a rate of 1 μl min^{-1} and 60 min later collection of 20-min fractions commenced. Following collection of four baseline fractions, animals were perfused for a 40-min period with aCSF containing 0 (control), 3, 30 or 300 μM L-AP4 (n=4-6) or L-SOP (n=4-6). During the last 10-min period of this perfusion, 100 mM KCl was included in the dialysate of all animals and collection of fractions continued for a further 90 min. To establish receptor specificity, in some cases the group III mGlu receptor antagonist, M-serine-O-phosphate (M-SOP; 300 μM) was perfused together with L-SOP (30 μM) using the above protocol. Levels of GABA in collected fractions were analysed by HPLC with electrochemical detection. Basal GABA release was averaged from the first three samples and subsequent fractions were expressed as a % increase over basal release. Data (mean ± S.E.M) were compared by 1-way ANOVA and Student Newman Keuls post-hoc test with $P<0.05$ taken to be significant.

L-AP4 (30 and 300 μM) significantly reduced 100 mM KCl-evoked GABA release from 2281 ± 127 % (n=6) increase over baseline to 1286 ± 288 % (n=6) and 1124 ± 286 % (n=6) increase, respectively. L-SOP (3, 30 and 300 μM) also significantly inhibited KCl-evoked GABA release which reached, at the highest concentration, 794 ± 110 % increase over baseline (n=6) compared to 2125 ± 250 % increase with KCl alone (n=6). M-SOP (300 μM) fully reversed the effects of L-SOP (30 μM). Thus KCl-evoked GABA release in the presence of M-SOP + L-SOP (2189 ± 146 % over baseline; n=5) was not significantly different to that with KCl alone (2433 ± 243 %; n=7).

In conclusion, these data show that direct activation of group III mGlu receptors in the GP can inhibit GABA release from presumed striatopallidal terminals upon which these receptors are known to reside. This action may underlie the ability of group III mGlu agonists to reverse reserpine-induced akinesia in the rat (MacInnes *et al*., 2004), which is characterised by a marked pathological increase in GABA release in the GP.

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MacInnes N. *et al*., (2004). *Br. J. Pharmacol*., 141, 15-22
Valenti S. *et al*., (2003). *J. Neurosci*., 23, 7218-7226