Adrenoceptor Subtype-Dependent Regulation of Rat Cerebral Cortex Astrocyte Glycogen Concentration

The glycogen store within astrocytes represents an important local energy reserve within the central nervous system, however, only relatively recently has it been appreciated that this glycogen reserve is extremely dynamic and likely to contribute physiologically, as well as pathologically, to constantly fluctuating local energy requirements (Benarroch, 2010). Here we have examined the ability of the neurotransmitter noradrenaline to regulate glycogen turnover in primary rat cerebral cortex astrocytes and provide evidence for a complex interplay between adrenoceptor subtypes in the control of this important metabolic process.

Astrocytes were prepared from neonatal (P1-2) Wistar rat cerebral cortex as described previously (Bradley & Challiss, 2011). Stimulation of adrenoceptors in astrocytes by noradrenaline (NA) caused a rapid, concentration-dependent decrease in glycogen levels, which was maximal after 60 min of stimulation (basal, 13.7 ± 1.5; +NA, 5.9 ± 0.8 μg glycogen/mg protein; $p<0.001$; pIC_{50} (-log M) 7.77 ± 0.06; n=5 separate cultures). Selective β-adrenoceptor stimulation with isoprenaline (ISO) caused a similar maximal decrease in glycogen levels (basal, 13.0 ± 2.1; +ISO, 5.8 ± 0.7 μg glycogen/mg protein; $p<0.001$; pIC_{50} (-log M) 8.14 ± 0.08; n=4 separate cultures) and further profiling of the glycogen and cyclic AMP responses using the subtype-selective antagonists ICI118,551 and CGP20712A revealed that the β_1-adrenoceptor is predominant.

Maximally-effective concentrations of isoprenaline caused a 3-4 fold greater accumulation of cyclic AMP compared to that stimulated by noradrenaline. This effect was shown to be caused primarily by the activation of α_2-adrenoceptors. Thus, noradrenaline stimulated a substantially greater cyclic AMP response in the presence of phentolamine, while the α_2-adrenoceptor-selective agonist, dexmedetomidine, could concentration-dependently suppress isoprenaline-stimulated cyclic AMP accumulation (pIC_{50} (-log M) 8.71 ± 0.12). Interestingly, selective α_2-adrenoceptor stimulation appears to increase astrocytic glycogen reserves, although this effect was somewhat variable in our hands. Using fluorescence Ca^{2+} imaging of cerebral cortex astrocytes we could demonstrate robust responses to noradrenaline that could be blocked by the α_1 adrenoceptor antagonist doxazosin and recapitulated by the α_1 adrenoceptor-selective agonist A61603. Perhaps surprisingly, selective α_1 adrenoceptor activation failed to cause a significant glycogenolytic response.

We conclude that the glycogenolytic response to noradrenaline in rat cerebral cortex astrocytes is regulated by functionally opposing actions at β_1 and α_2 adrenoceptors with little evidence for α_1 adrenoceptor involvement despite this receptor subtype causing robust increases in astrocytic intracellular Ca^{2+} concentration.

Benarroch EE (2010) *Neurology* **74**, 919–923.
Bradley SJ & Challiss RAJ (2011) *Br J Pharmacol* **164**, 755–771.