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Drug treatments to reduce excitotoxicity *in vivo*: a potential for α2-adrenoceptor antagonists?

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Summary. It is hypothesized that the locus coeruleus-noradrenergic system controls compensatory and repair mechanisms in the CNS, and that its dysfunction is a critical factor in the progression of central neurodegenerative diseases. Pharmacological activation of locus coeruleus neurons can be achieved with α_2-adrenoceptor antagonists, and such compounds are protective *in vivo* in some models of brain injury where excitotoxicity is thought to be a causative factor. To further explore this neuroprotective potential, the effects of a 7-day treatment with the α_2-antagonists, (+)-efaroxan and (±)-idazoxan, were evaluated in rats undergoing a unilateral lesioning of the striatum with the excitotoxin, quinolinic acid. The α_2-antagonist treatments reduced both the ipsiversive circling response to apomorphine and the deficit of choline acetyltransferase in the lesioned animals. To elucidate the mechanisms underlying this neuroprotective effect, a modulation of the extracellular levels of amino acids within the striatum was investigated using *in vivo* microdialysis. Intrastriatal injection of quinolinic acid increased taurine and tyrosine levels by 2–2.5 fold, while most other amino acids were not significantly altered; the effect of (+)-efaroxan on these changes is being investigated. Further research is required to identify which of several possible mechanisms is involved in the neuroprotective action of α_2-antagonists *in vivo*.

Keywords: Amino acids – Excitotoxicity – Quinolinic acid – Intracerebral microdialysis, – α_2-Adrenoceptor antagonists – Neuroprotection

Introduction

Dysfunction of the noradrenergic system originating in the locus coeruleus (LC-NA) is proposed to be a decisive factor in the pathogenesis and progression of central neurodegenerative disorders, including Parkinson's, Huntington's and Alzheimer's diseases, where neuropathological evidence for LC-NA deficits has been documented (Mavridis et al., 1991; Colpaert,

1994; Hoogendijk et al., 1995). Animal studies show that disruption of the LC-NA can compromise neuronal survival and/or retard recovery in models of neurodegenerative disease states, such as the MPTP monkey (Mavridis et al., 1991) and mouse (Marien et al., 1993; Bing et al., 1994), cerebral ischemia (Blomqvist et al., 1985; Davis et al., 1989) and traumatic brain injury (Feeney, 1998; Kolb et al., 1997). These studies support the notion that normal activity of the LC-NA system is critical in the operation of endogenous protective or compensatory mechanisms which influence recovery and/or slow neurodegenerative processes.

Part of the research aimed at documenting a protective/trophic role of the LC-NA system has focused here on an *in vivo* model of excitotoxicity. Excitotoxicity refers to a cascade of cellular events in which excessive stimulation of excitatory amino acid receptors, particularly the ionotropic N-methyl-D-aspartate (NMDA) type, results in neuronal cell death (Choi, 1992; Olney, 1990; Rothman and Olney, 1995). Excitotoxicity may be implicated in several human neuropathologies including Parkinson's, Alzheimer's and Huntington's disease (Beal, 1992; Olney, 1990; Turski and Turski, 1993), and glutamate receptor antagonists are protective against excitotoxin- and mitochondrial toxin-induced lesions in animal models of these disorders (Beal et al., 1993). Intrastriatal injection of the NMDA receptor agonist quinolinic acid (QUIN) produces neurochemical, neuroanatomical and behavioural changes in animals which reproduce some aspects of Huntington's disease, and this model is frequently used to study excitotoxicity *in vivo* (e.g., Miyamoto and Coyle, 1990; Susel et al., 1989; see review by Stone, 1993). To evaluate the potential protective role of the LC-NA system in the QUIN lesion model, we examined the effects of the α_2-adrenoceptor antagonists (+)-efaroxan and (±)-idazoxan, these drugs being capable of activating the LC-NA via blockade of the inhibitory α_2-adrenergic autoreceptors (e.g. Dennis et al., 1987). Repeated treatments with (+)-efaroxan and (±)-idazoxan were found to significantly reduce the behavioural (apomorphine-induced ipsilateral circling) and biochemical (loss of stiatal ChAT activity) indices of the striatal QUIN lesion. To further investigate the possible mechanisms underlying this protective drug effect, we examined whether (+)-efaroxan affected the extracellular levels of neuroactive amino acids, as measured by intracerebral microdialysis, following the intrastriatal injection of QUIN. The results are discussed in regard to potential mechanisms by which α_2-adrenoceptor blockade might attenuate neurodegenerative processes. Portions of this work have been previously published (Martel et al., 1998).

Material and methods

Animals

Animals were handled and cared for in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 1996) and the European Directive N° 86/609, and the experimental protocols were was carried out in compliance with the institutional ethical committee guidelines for animal research. Male Sprague-Dawley rats [ICO:OFA-SD (IOPS.Caw); IFFA CREDO, Domaine des Oncins, France) weighing

240–260 g at the beginning of the experiment had free access to water and food, and were housed 4–6 per cage at 20–24°C under a 12 hr light : dark cycle (lights on at 7 hoo).

Drugs

(+)-Efaroxan and (±)-idazoxan were synthesized at the CRPF. (+)-MK-801 was purchased from RBI (Bioblock Scientific, Illkirch, France). Other chemicals including QUIN were obtained from Sigma (Saint Quentin Fallavier, France). Drugs were prepared in physiological saline (pH 7.4) and were injected in a volume of 10 mL/kg. QUIN was prepared for intrastriatal injection as described previously (Martel et al., 1998).

QUIN lesion of striatum

Rats were anaesthetised with a halothane/oxygen mixture and positioned in a stereotaxic apparatus with the incisor bar fixed at −3.3 mm. Body temperature was maintained at 37.5 ± 0.2°C with a thermostated heating pad. A small hole was drilled in the skull at 0.5 mm anterior to and 3.0 mm lateral from bregma. The dura was carefully perforated and a 26 gauge cannula was slowly lowered to 6.0 mm below the skull surface at bregma, these coordinates corresponding to the center of the left caudate-putamen (Paxinos and Watson, 1986). One microliter of QUIN (150 nmoles/μL, lesioned animals) or saline (sham-operated animals) was infused over 2.5 min at a flow rate of 0.4 μL/min. The cannula was left in place for an additional 5 min before withdrawal. For local drug co-injection experiments, a "Y"-shaped injection cannula was fashioned from a CMA/11 microdialysis probe (CMA/Microdialysis AB, Stockholm) as previously described (Martel et al., 1998). Animals were allowed to recuperate from anaesthesia in individual cages under an infrared light, and then housed individually with free access to food and water for the rest of the study.

Drug treatments

Unless otherwise stated, animals received an intraperitoneal (i.p.) injection 30 min before operation (sham or lesion procedure) and at 4 and 8 h later, and were injected i.p. thrice daily thereafter (at 8 hoo, 12 hoo and 16 hoo) for 7 days with either saline (10 ml/kg), (+)-efaroxan (0.63 mg/kg) or (±)-idazoxan (2.5 mg/kg). The drug doses and interdose interval were chosen since they have been shown to be optimal for blocking α_2-adrenoceptor-mediated effects in the rat CNS *in vivo* (e.g. antagonism of the behavioural effects of α_2-adrenoceptor agonists; Colpaert, 1986; Millan et al., 1994; unpublished data). Additional groups of rats received either a single i.p. injection of MK-801 (2.5 mg/kg) 30 min before the intrastriatal injection of QUIN (or vehicle), or a single intrastriatal co-injection of (+)-efaroxan (100 fmoles in 0.5 μL, 100 nM final co-injection concentration) at the time of the QUIN (or vehicle) injection. Doses refer to the free base equivalent of drug.

Behavioural testing

At ten days following the QUIN lesioning procedure, rats were placed in cylindrical cages and the number of rotations, both ipsiversive and contraversive with respect to the side of the lesion, were recorded using an automatic rotometer (RotaCount-8, Columbus Instruments) for a 1 h period immediately following the administration of apomorphine (0.63 mg/kg s.c.). In this animal model, apomorphine induces an ipsiversive rotation (Miyamoto and Coyle, 1990; Susel et al., 1989), presumably due to the lesion-induced loss of striatal targets (i.e. D1 and D2 receptor-bearing neurons) which mediate the motor stimulatory effect of the dopamine agonist.

Choline acetyltransferase (ChAT) assay

Three days after behavioural testing, rats were decapitated and the left and right striata removed for the measurement of ChAT activity (Fonnum, 1975). ChAT activity in the lesioned (left) striatum was expressed as a percentage of ChAT activity in the intact (right) striatum.

Extracellular amino acid levels in the striatum: microdialysis

Rats maintained in a stereotaxic apparatus under constant halothane anesthesia were implanted with a microdialysis probe (CMA/11, 3 mm length; CMA/Microdialysis AB, Stockholm) terminating in the left striatum (AP, 0.5 mm; lat, 3.2 mm; DV, −6.5 mm from dura). Probes were perfused (2 μL/min) with Ringer's solution (NaCl, 147 mM; $CaCl_2$, 1.3 mM; KCl, 4.0 mM), and 20-min dialysate samples were collected. Following a 4 h equilibration period, a 26 gauge cannula was lowered near the zone of dialysis (AP, 0.0 mm; lat, 4.7 mm at a medially directed angle of 14°; DV, −6.0 mm from dura), and 1.0 μL of saline or QUIN (150 mM, pH 7.4) was infused over 2.5 min (0.4 μL/min). The injection cannula was left in place for 5 min and then slowly retracted. Collection of dialysate samples continued over the next 3.5 h. Amino acids were derivatized with ortho-phtaldialdehyde (OPA) and quantified by HPLC with fluorescence detection, similar to the method described by Reynolds and Racz (1987).

Statistics

Statistical analyses were performed using 2-tailed non-parametric tests (GBSTAT, Dynamic Microsystems Inc., Silver Spring, MD). Differences between treatment groups were first examined with a Kruskal-Wallis ANOVA, followed by a Mann-Whitney U-test when the ANOVA revealed significant differences. For microdialysis experiments, changes in amino acid levels over time, in comparison to baseline samples, were analyzed by a repeated measures ANOVA. Differences between saline and QUIN injection treatments were subsequently analyzed by a Mann-Whitney U-test at each corresponding 20-min sample time point.

Results

Within 2–3 h after the intrastriatal injection of QUIN, rats showed a marked barrel rotation and turning behaviour typical of this lesioning procedure. Rats quickly recuperated from this acute phase, and, apart from an initial weight loss, showed no obvious signs of abnormal movements over the 7 day treatment period that followed. Ten days after the lesioning procedure, animals were injected with apomorphine (0.63 mg/kg i.p.) and circling behaviour (ipsiversive and contraversive rotations) was measured over the following 1 h interval (Fig. 1). The number of ipsilateral rotations, as well as the <<behavioural asymmetry>> (i.e., the difference of ipsilateral minus contralateral turns), were considered as indices of the extent of the left striatal lesion. Sham groups consistently failed to show any asymmetry in response to apomorphine. In contrast, saline-treated QUIN-lesioned animals showed a robust ipsiversive rotation (~260 turns/h) in response to the dopamine agonist, and very few rotations in the contraversive direction. The repeated 7 day treatment with (+)-efaroxan resulted in both a significant reduction in the number of ipsiversive rotations and an increase in contraversive rotations,

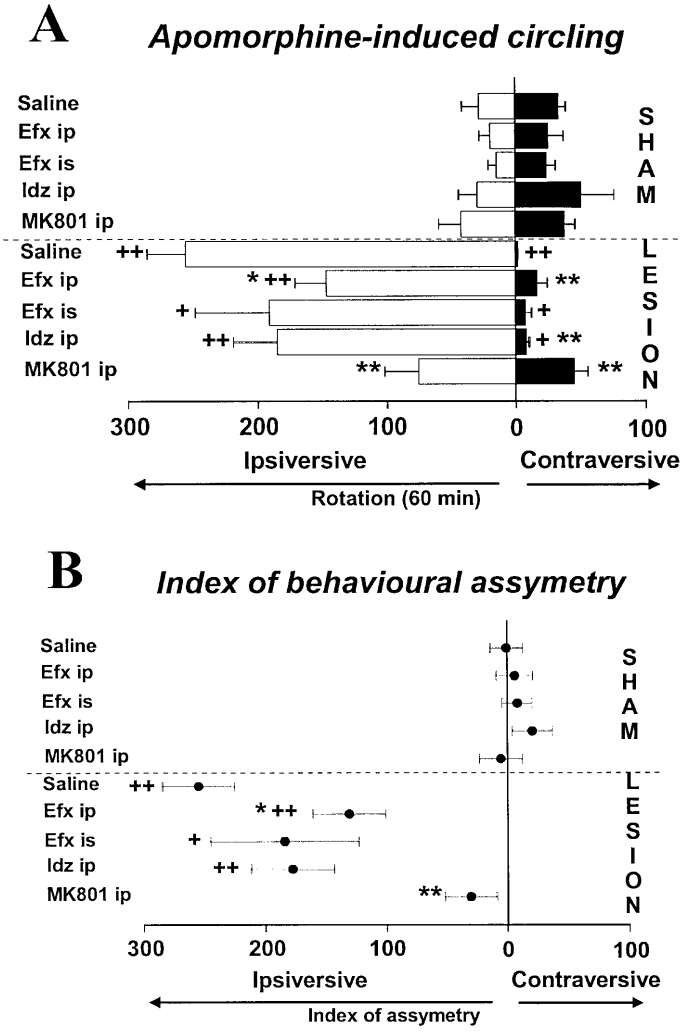

Fig. 1. **A** Apomorphine-induced rotations in sham-operated and QUIN-lesioned rats. **B** Index of behavioural assymetry, calculated as the difference of ipsiversive minus contraversive turns. Treatments with systemically-administered saline, (+)-efaroxan (*Efx*), (±)-idazoxan (*Idz*), MK-801 or intrastriatal (+)-efaroxan (*Efx i.s.*) are as described in the Methods. The number of ipsiversive and contraversive rotations (abscissa) was measured for 60 min immediately following subcutaneous injection of apomorphine (0.63 mg/kg). Values are means ± SEM for each treatment group, 5–14 rats per group. $^{+}$, $^{++}P < 0.05$, 0.01 *vs.* equivalent drug treatment group of sham-operated animals. *, **$P < 0.05$, 0.01 *vs.* saline-treated QUIN-lesioned group (Mann-Whitney U-test)

thus resulting in a reduce behavioural asymmetry score. The repeated (±)-idazoxan treatment also tended to reduce behavioural asymmetry (increased contraversive rotation). On the other hand, the intrastriatal co-injection of (+)-efaroxan together with QUIN did not result in any significant reduction in either ipsilateral or contralateral rotations induced by apomorphine. As a validation of the QUIN lesion model, rats treated on the day of the lesioning procedure with the NMDA antagonist MK-801 (2.5 mg/kg i.p.) showed no significant behavioural assymetry in response to apomorphine,

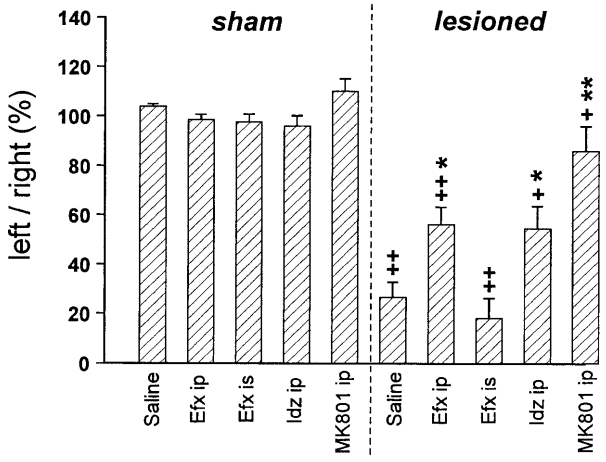

Fig. 2. Striatal choline acetyltransferase (ChAT) activity in sham-operated and QUIN-lesioned rats. ChAT activity was measured in striatal homogenates obtained from the same rats evaluated in the apomorphine-induced rotation test (Fig. 1). ChAT activity is expressed as % of enzyme activity in the left (lesioned) relative to the right (intact) striatum. Values are means ± SEM. Drug treatments, abbreviations, statistics and number of animals per group are as indicated in the legend to Fig. 1

both ipsiversive and contraversive rotations being equivalent and not significantly different from sham animals.

At the end of the study (3 days after behavioural testing), ChAT activity was measured by radioenzymatic assay in the left (injected) and right (non-injected) striata of all animals (Fig. 2). ChAT activity in the non-injected striata of sham-operated vehicle control animals was 164 ± 24 and 187 ± 12 nmoles ACh/mg protein/h (means ± SEM of 2 separate studies). All sham groups failed to show a significant change in ChAT activity in the left striatum, in comparison to the right. On the other hand, the QUIN injection resulted in a clearcut decrease in ChAT activity, down to 27 ± 8% of that in the corresponding contralateral (non-injected) striatum. The (+)-efaroxan and (±)-idazoxan treatments partially and significantly reduced the QUIN-induced ChAT deficit to 56 ± 7% and 55 ± 11% of control levels, respectively. However, the local co-injection of (+)-efaroxan at the time of QUIN injection had no significant effect on the QUIN-induced ChAT loss. Finally, MK-801, administered i.p. at the time of the intrastriatal QUIN injection, afforded an almost complete protection against the ChAT loss (i.e. to 86 ± 10% of control).

In microdialysis experiments in halothane-anesthetized animals, QUIN injection into the striatum resulted in significant changes over time in the extracellular levels of glutamate, glycine, GABA, alanine, taurine and tyrosine (repeated measures ANOVA; Table 1). However, these changes were significantly different from control (intrastriatal saline injection) only for taurine and tyrosine (Mann-Whitney U-test at corresponding time points; Fig. 3). Taurine levels were increased to 225% of baseline levels, this effect being transient and maximal at 1–2 h following QUIN injection (Fig. 3).

Table 1. Changes in striatal extracellular amino acid levels over time, as measured by in vivo microdialysis, following instrastriatal injection of QUIN or vehicle (saline) (repeated measures ANOVA)

Treatment group	Taurine	Tyrosine	Glutamate	Glycine	GABA	Alanine
Saline						
F	4.8593	1.6791	1.3752	1.1367	11.7604	1.8543
P	<0.01	NS (p = 0.08)	NS (p = 0.19)	NS (p = 0.34)	<0.01	<0.05 (p = 0.0472)
QUIN						
F	4.1873	5.4941	2.3329	2.7585	5.4616	6.4200
P	<0.01	<0.01	<0.05 (p = 0.0105)	<0.01	<0.01	<0.01

NS not significant.

Tyrosine levels were increased by 2.0–2.5 fold during the second and third hour following QUIN injection (Fig. 3). Levels of glutamate, glycine, alanine and GABA showed some increases but these changes were not significantly different from saline-injected controls (Fig. 3). Extracellular levels of other amino acids, including aspartate, arginine, asparagine, glutamine and serine (not shown) were not significantly affected during the 3.5 h post-injection period.

Discussion

The present findings demonstrate that a one-week repeated administration of (+)-efaroxan or (±)-idazoxan, starting on the day of the lesioning procedure, reduced both the behavioural and biochemical indices of a QUIN-induced striatal lesion in the rat. These results complement other *in vivo* studies using models of cerebral ischemia (Gustafson, 1991) or traumatic brain injury (Feeney, 1998; Goldstein, 1998) where α_2-adrenoceptor antagonists such as yohimbine and idazoxan have been found either to be neuroprotective or to improve functional (motor) recovery following brain damage. QUIN neurotoxicity is presumably mediated through a cascade of events initiated by the activation of NMDA receptors, consistent with the protective effect of NMDA receptor antagonists such as MK-801 in QUIN lesion models (Stone, 1993; this study). The negligible affinity of (±)-idazoxan and (+)-efaroxan for [^{3}H]MK-801 binding sites *in vitro* ($IC_{50} \geq 190\,\mu M$; Olmos et al., 1996) argues against a direct antagonism of QUIN at this level. Both (+)-efaroxan and (±)-idazoxan are potent and selective antagonists at α_2-adrenoceptors showing good central bioavailibility upon systemic administration (Doxey et al., 1983; French, 1995; Hudson et al., 1992; Millan et al., 1994; Renouard et al., 1994), and have negligible affinities for most other receptor sites including those that may be involved in mediating neuroprotection in the QUIN lesion model, e.g. MK-801, dopamine, adenosine, sigma, opioid, calcium or potassium channel sites (Garside et al., 1996; Stone, 1993). Both compounds are imidazoline derivatives, but only (±)-idazoxan possesses appreciable affinity for I_1- and

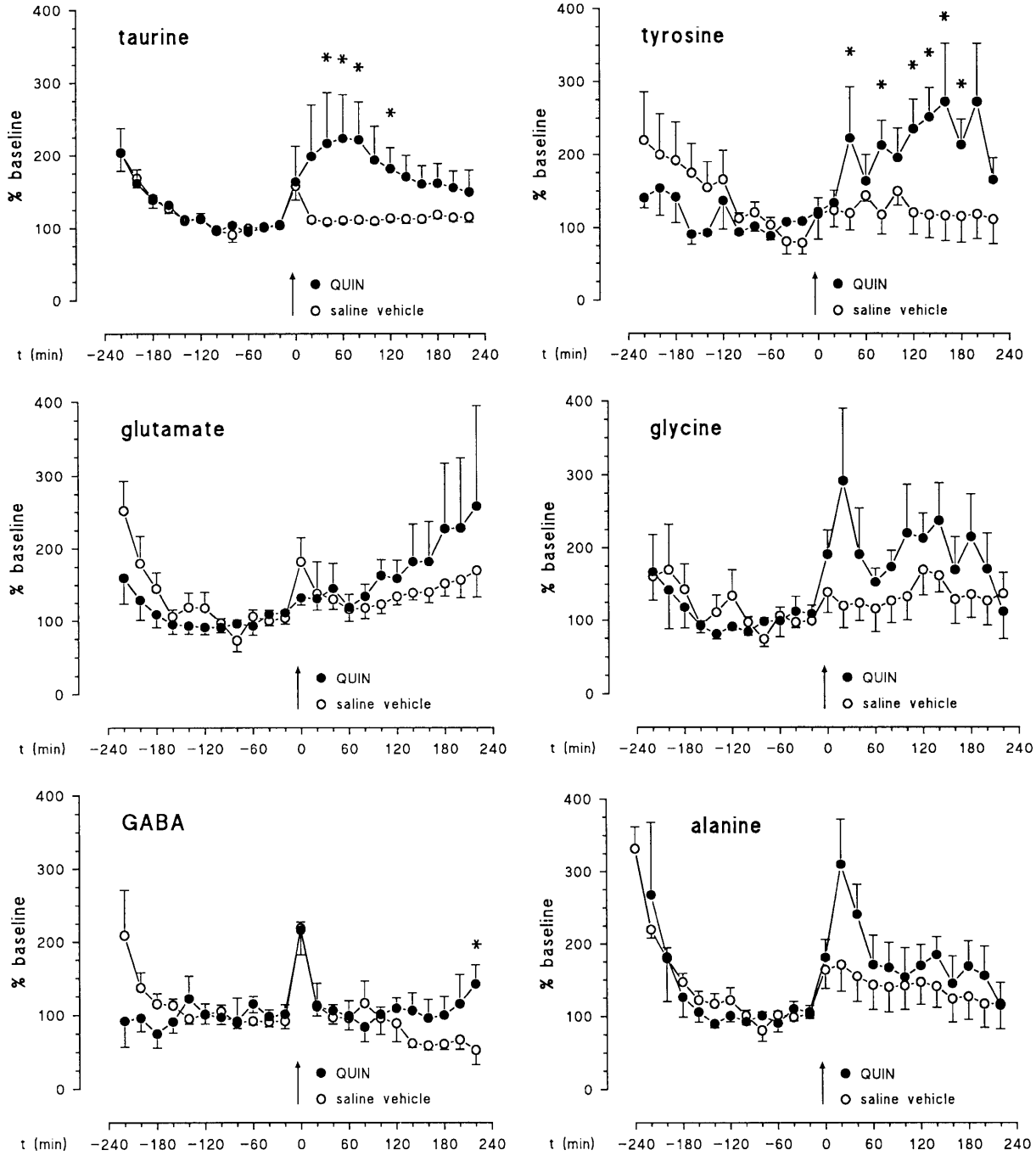

Fig. 3. Effect of intrastriatal injection of QUIN (150 nmoles) or vehicle (saline) on extracellular levels of amino acids in the striatum of halothane-anesthetized rats, as measured by microdialysis. QUIN or vehicle was injected after a 4 h equilibration period following implantation of the dialysis probe. Amino acid levels are expressed as % of the levels measured in the three 20-min <<baseline>> samples immediately preceding the intrastriatal injection (arrow). Values are means ± SEM, 5–6 rats per group. $^*P < 0.05$ *vs.* corresponding samples in the saline-injected group (Mann-Whitney U-test)

I_2-imidazoline sites (Flamez et al., 1997; French, 1995), suggesting that these receptors are not involved in the neuroprotective effect observed in the present study. α_2-Adrenoceptor antagonists increase noradrenaline release *in vivo* by blocking inhibitory α_2 autoreceptors on LC-NA neurons (e.g. Dennis et al., 1987), the expected consequence of this action being an increased activation of postsynaptic α_1- and β-adrenergic receptors. Concomitantly, the α_2 antagonist drug treatment could relieve the inhibitory influence that noradrenaline exerts via α_2-adrenergic heteroceptors on non-adrenergic neurons (e.g., serotonergic, dopaminergic, cholinergic) and glia cells. Thus, a recruitment of diverse adrenergic (and non-adrenergic) receptor-mediated events downstream from α_2-adrenoceptor blockade could conceivably participate in the neuroprotective drug effect observed in the present study; this may include a noradernergic modulation of intracellular events initiated by NMDA receptor activation, such as evoked depolarisation (Zhang et al., 1998), cGMP production (Carter et al., 1988), or intracellular increases of calcium (Bickler and Hansen, 1996). Whether α_2-adrenoceptor antagonists can attenuate these or other intracellular processes initiated *in vivo* by striatal QUIN injection requires further study.

In the intrastriatal co-injection experiments, (+)-efaroxan was applied at a concentration of 100 nM, i.e. 10 times its affinity at rat α_2-adrenoceptor binding sites *in vitro* (Renouard et al., 1994). The lack of significant protective effect in this co-injection protocol suggests that protection is not due to a direct antagonism of QUIN action within the striatum, but might be mediated through one or more extrastriatal sites, e.g. reduction of corticostriatal pathway activity by an action at the level of the cortex (see below). Alternatively, intrastriatal injection of a higher concentration of (+)-efaroxan may be required to observe protection, or the drug exerts its protective effect at later times following the QUIN injection, and may require a prolonged post-treatment as was the case with the systemic drug administration protocol. These hypotheses remain to be tested experimentally, by examining the effects of (+)-efaroxan at different doses, treatment times and locations of injection.

Protection against intrastriatal QUIN neurotoxicity is afforded by prior destruction of the overlying cortex (Schwarcz et al., 1984; Stone, 1993), suggesting that an intact corticostriatal input is a requirement for the striatal lesion, e.g. some factor(s) provided by this pathway, possibly glutamate as the main transmitter candidate, is critical in promoting striatal QUIN toxicity. Thus, one hypothesis to account for the protective effect of α_2-adrenoceptor antagonists in the QUIN lesion model is a reduction in corticostriatal glutamatergic input, either by inhibition of neuronal activity at the level of the cortex, or by presynaptic modulation of glutamate released from corticostriatal terminals. However, our preliminary microdialysis study revealed that the QUIN injection was not associated with any immediate or obvious changes in glutamate outflow, at least not during the 3 h post-injection interval, when intrastriatal QUIN levels are estimated to be maximal (Bakker and Foster, 1991). A very similar finding was reported in the microdialysis study by Vezzani et al. (1985) where no changes in extracellular levels of

glutamate, aspartate or glycine were observed immediately following an injection of QUIN (156 nmoles) into the hippocampus of awake rats. Whether changes in glutamate or other amino acids occur at later times following QUIN injection cannot be totally excluded at this time. While QUIN by itself does not appear to acutely alter striatal glutamate output under the experimental conditions used here, current studies are nevertheless examining whether this is also the case when an α_2-antagonist is present.

In the microdialysis experiments, an immediate and transient doubling in the extracellular levels of taurine was observed following the intrastriatal injection of QUIN. Similarly, Vezzani et al. (1985) reported a 2.24-fold increase in extracellular taurine in the rat hippocampus, as measured by microdialysis, following local injection of QUIN. Since the majority of intracerebrally-injected QUIN is cleared from brain tissue within 2 h (Bakker and Foster, 1991; Vezzani et al., 1985), the taurine response appears to correlate with the presence of QUIN in the striatum. Taurine has osmoregulatory and neuroinhibitory functions in the brain; its release from neural tissue can be evoked by glutamate agonists, neuronal excitation, cell swelling and cell-damaging conditions such as hypoxia and ischemia, and it has neuroprotective effects which are proposed to be due to its potent inhibitory actions, e.g. it increases chloride ion conductance in excitable membranes, leading to hyperpolarization and a reduction in neuronal calcium influx (see Huxtable, 1992; Oja and Saransaari, 1996). In this context, the increase in extracellular taurine may be a protective or enantiostatic cellular response to the excitototoxic event(s) initiated by QUIN. The ability of the α_2-antagonist (+)efaroxan to modulate the taurine response to QUIN is currently being investigated.

Excitotoxicity is promoted and potentiated by cellular energy impairment (Novelli et al., 1988; Albin and Greenamyre, 1992; Beal et al., 1993; Turski and Turski, 1993). Glial cells possess α_2- and β-adrenoceptors (Aoki et al., 1987; Bockaert et al., 1990; Salm and McCarthy, 1992; Stone and Ariano, 1989). By regulating the critical "housekeeping" functions of glia which influence energy metabolism and the composition of the extracellular milieu (e.g. regulation of glutamate uptake), these glial adrenoceptors may indirectly modify the excitability of neighbouring neurons (Feinstein et al., 1993; Hanson and Ronnback, 1992; Hertz, 1992; Stone and Ariano, 1989; Tsacopoulos and Magistretti, 1996). Lesioning of the LC-NA exacerbates metabolic deficiency and hippocampal neuronal losses following cerebral ischemia (Davis et al., 1989), while idazoxan can mitigate ischemia-induced neuronal damage in the rat brain and restore cerebral glucose metabolism from post-ischemic depression (Gustafson, 1991; Gustafson et al., 1989, 1990). Noradrenaline may also modify regenerative processes by stimulating nerve growth factor (NGF) production through activation of β-adrenoceptors on glial cells (Schwartz and Mishler, 1990; Stone and Ariano, 1989); NGF has been shown to protect striatal cholinergic interneurons from QUIN excitotoxicity in rats (Pérez-Navarro et al., 1994). Systemic administration of the α_2-adrenoceptor antagonist yohimbine increases hippocampal tissue

levels of NGF mRNA in rat (Stone et al., 1994) and leads to rapid and dramatic increases in cortical TrkB autophosphorylation, presumably as a consequence of activity-dependent anterograde transport and release of BDNF from LC-NA afferents (Fawcett et al., 1998). In addition, noradrenergic axons regulate reactive astrocyte formation in response to CNS injury (Griffith and Sutin, 1996) and as such may be important for cellular repair *via* an amplification of neurotrophin production and transmitter reuptake by glia in their reactive state (Eddleston and Mucke, 1993). Together, these findings indicate that pharmacological modulation of the LC-NA system can influence glial cell function, neurotrophin synthesis, CNS energy utilization and extracellular homeostasis, factors that may all participate in determining nerve cell fate following injury.

In conclusion, the α_2-adrenoceptor antagonists (+)-efaroxan and (±)-idazoxan reduced the behavioural and biochemical deficits induced by striatal QUIN lesions in rats. The precise mechanisms underlying this effect are not known for certain, but several testable hypotheses do exist for further study. Neuroprotection afforded by α_2-adrenoceptor antagonists may have important therapeutic implications for those neuropathologies where excitotoxic mechanisms may be involved.

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