AIMS

Methamphetamine is a highly abused drug with complex pharmacological actions in the brain. Intracerebral microdialysis in freely-moving rats can provide valuable insights in such cases, but it is often limited by the number of neurotransmitters that can be measured in each sample. We have used dual-probe microdialysis to investigate methamphetamine’s effects simultaneously on GABA, glutamate (GLU), dopamine (DA), noradrenaline (NA) and 5-HT in the prefrontal cortex (PFC) and hippocampus (HIP).

METHODS

Five (5) adult male Wistar rats (Charles River, UK) weighing 250-350g were used. Two 4.0 mm microdialysis probes were stereotaxically implanted into the PFC (coordinates relative to bregma: AP +3.4 mm; ML ±0.8 mm; DV -5.0 mm relative to dura) and HIP (coordinates relative to bregma: AP -5.3 mm; ML ±4.8 mm; DV -7.5 mm relative to dura) under gaseous anaesthesia, ie isoflurane (5% to induce, 2% to maintain) in O2 (1 litre/min) delivered via an anaesthetic unit. Dialysate samples were collected at 15 min intervals for 2hr. GABA and GLU were analysed by UHPLC-ECD and DA, NA, 5HT by HPLC-ECD as described by Rowley et al (2014). All analyses were performed using Antec ALEXYS™ systems.

Methamphetamine (3.0 mg/kg) was dosed by intraperitoneal (IP) injection.

RESULTS

• Compared with pre-intervention baseline values, methamphetamine (3.0 mg/kg IP) produced rapid changes in both monoamine and amino acid neurotransmitters that peaked 30-45min after dosing.

• In PFC, methamphetamine (3.0 mg/kg IP) increased the extracellular concentrations of DA (maximum = 533%, p<0.001), NA (maximum = 408%, p<0.001) and 5-HT (maximum = 1500%, p<0.001) (Figure 1). Methamphetamine administration increased extracellular GABA (maximum = 452%, p<0.05) and decreased GLU (-56%, p<0.001) (Figure 2). In hippocampus, the same pattern of effects was observed, but the methamphetamine-induced changes in monoamines were much greater with increases in DA (1781%, p<0.001), NA (765%, p<0.001) and 5-HT (11,058%, p<0.001) (Figure 3). Methamphetamine increased the efflux of GABA (451%, p<0.01) and decreased the efflux of GLU (-31%, p<0.01) (Figure 4).

Table 1. Basal extracellular concentrations of monoamines and amino acid neurotransmitters

<table>
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<tr>
<th>Brain region</th>
<th>DA (fmol/5 μl)</th>
<th>NA (fmol/1.5μl)</th>
<th>5-HT (fmol/5 μl)</th>
<th>GABA (fmol/1.5μl)</th>
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<td>PFC</td>
<td>3.47 ± 1.00</td>
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<td>0.48 ± 0.07</td>
<td>3.6 ± 2.0</td>
<td>496 ± 83</td>
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<td>Hippocampus</td>
<td>1.07 ± 0.12</td>
<td>3.82 ± 0.92</td>
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<td>2.4 ± 0.7</td>
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Results are mean ± SEM, n=5.

REFERENCES


CONCLUSIONS

• The results reveal that methamphetamine produced large increases in DA and NA in PFC and hippocampus, but surprisingly, its greatest effect was to potentiate 5-HT efflux in this region.

• The increases in extracellular monoamines were accompanied by concomitant reductions in GLU and increases in GABA in both regions.

• It is most likely that the decreased excitatory and enhanced inhibitory amino acid neurotransmitter efflux in PFC and hippocampus were homeostatic responses to attenuate the pharmacological effects of methamphetamine.

• The marked increases of 5-HT in both brain regions may also have been part of this response.

Figures 1 – 4: Results are adjusted means; n=5. Vertical arrow indicates time of drug administration. Significant differences versus baseline are denoted by: *p<0.05, **p<0.01, ***p<0.001.

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