Profound suppression of noradrenaline, dopamine and 5-HT turnover in various regions of rat brain evoked by the \( \alpha_2 \)-adrenoceptor agonist, clonidine

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INTRODUCTION

3-Methoxy-4-hydroxyphenylethylglycol (MHPG) is a noradrenaline (NA) metabolite that has been validated as a marker of NA turnover in mouse brain (Heal et al, 1989), but not in rat brain where it exists predominantly as the sulphate conjugate. Recently, we have developed “neurochemical fingerprinting” in the mouse as a rapid ex vivo screen to identify compounds with different presynaptic dopaminergic mechanisms (Heal et al, 2009, 2010). We have now used, clonidine to determine (a) whether unconjugated MHPG can be used as an indicator of NA turnover in the rat and (b) the “neurochemical fingerprint” of this \( \alpha_2 \)-adrenoceptor (\( \alpha_2 \)AR) agonist in the striatum (STR) and prefrontal cortex (PFC).

METHODS

Groups of adult, male Wistar rats (n=8/group) and C57BL/6JAX mice (n=8/group) were dosed with clonidine (100 µg/kg, ip) or saline and killed 60 min later.

Rat and mouse brains were rapidly dissected into PFC, STR and rest of brain minus cerebellum (RoB) and tissue samples were snap-frozen in liquid N2. PFC and STR from rat brains were analysed for monoamines (NA, dopamine [DA] and 5-HT) and metabolites (3-MT [3-methoxytyramine], DOPAC [dihydroxyphenylacetic acid], HVA [homovanillic acid], 5-HIAA [5-hydroxyindoleacetic acid]) by HPLC-ECD (Heal et al, 1990, 2009, 2010). RoB samples from rat and mouse were used to quantify unconjugated MHPG concentrations (Heal et al, 1989).

RESULTS

- Clonidine (100 µg/kg, ip) decreased the concentration of unconjugated MHPG in the brains of both rats and mice. The decreases in RoB were 49.8% (p<0.001) in the rat and 35.3% (p<0.001) in the mouse (Fig. 1). The percentage reduction of MHPG produced by clonidine (100 µg/kg, ip) was similar to that reported previously for mouse whole brain minus cerebellum (Heal et al, 1989).
- In the “neurochemical fingerprinting” experiment, clonidine decreased DA turnover in rat STR as shown by falls in DOPAC (-21.5%), and 3MT (-79.3%) and by an increase in the DA/DOPAC ratio (38.7%) (Fig. 2).
- Clonidine administration decreased DA and 5-HT turnover in rat PFC as shown by increases in the ratios of DA/DOPAC (89.1%) and 5HT/5HIAA (22.1%) and a decrease in 5-HIAA (16%), respectively (Fig 3).
- Clonidine also increased the concentration of NA in the PFC by 17.3% (p<0.001) and DA by 67.5% (p<0.01) providing further indirect evidence of a reduction in the turnover of these monoamines (Fig 3).

CONCLUSIONS

- Clonidine produced similar reductions in the concentration of unconjugated MHPG in the brains of rats and mice indicating that this metabolite can be used as a viable index of NA turnover in rat brain.
- The “neurochemical fingerprinting” experiment revealed that clonidine markedly suppressed the turnover of DA in PFC and STR and 5-HT in PFC. The observed increases in DA and NA in PFC are consistent with a decrease in the turnover of these catecholamines.

REFERENCES

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