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Research Report

The modulatory action of harmane on serotonergic neurotransmission in rat brain

Haya Abu Ghazaleh[a,b,*], Maggie D. Lalies[c], David J. Nutt[d], Alan L. Hudson[c]

[a]Psychopharmacology Unit, University of Bristol, Dorothy Hodgkin Building, Whitson Street, Bristol, BS1 3NY, UK
[b]General Education Department, American University of the Middle East, P.O. BOX 220 Dasman, 15453 Kuwait
[c]Pharmacology Department, University of Alberta, Medical Sciences Building, Edmonton, Alberta, T6G 2H7, Canada
[d]Centre for Neuropsychopharmacology, Imperial College London, Burlington Danes Building, London, W12 0NN, UK

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ABSTRACT

The naturally occurring β-carboline, harmane, has been implicated in various physiological and psychological conditions. Some of these effects are attributed to its interaction with monoaminergic systems. Previous literature indicates that certain β-carbolines including harmane modulate central monoamine levels partly through monoamine oxidase (MAO) inhibition. However, this is not always the case and thus additional mechanisms may be involved. This study set to assess the potential modulatory role of harmane on the basal or K^+ stimulated release of preloaded radiolabelled noradrenaline (NA), dopamine (DA) and serotonin (5-HT) in rat brain cortex *in vitro* in the presence of the MAO inhibitor pargyline. Harmane displayed an overt elevation in K^+ -evoked [^{3}H]5-HT release; whilst little and no effect was reported with [^{3}H]DA and [^{3}H]NA respectively. The effect of harmane on [^{3}H]5-HT efflux was partially compensated in K^+-free medium. Further analyses demonstrated that removal of Ca^{2+} ions and addition of 1.2 mM EGTA did not alter the action of harmane on [^{3}H]5-HT release from rat brain cortex. The precise mechanism of action however remains unclear but is unlikely to reflect an involvement of MAO inhibition. The current finding aids our understanding on the modulatory action of harmane on monoamine levels and could potentially be of therapeutic use in psychiatric conditions such as depression and anxiety.

1. Introduction

β-carbolines are ubiquitous in nature found in both plants and mammalian systems (Airaksinen and Kari, 1981a; Airaksinen and Kari, 1981b). These compounds can also be formed endogenously through a Pictet-Spengler cyclization reaction between indolealkylamines and aldehydes (McIsaac et al., 1972). Various β-carbolines have shown to be associated with a number of clinical conditions, including Parkinson's disease, drug dependence and amnesia (Pfau and Skog, 2004).

*Corresponding author at: Psychopharmacology Unit, University of Bristol, Dorothy Hodgkin Building, Whitson Street, Bristol, BS1 3NY, UK.
E-mail address: Haya.Abu-Ghazaleh@aum.edu.kw (H. Abu Ghazaleh).

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Numerous β-carbolines have been shown to interact with different classes of receptors: 5-hydroxytryptamine (5-HT), dopamine (DA), benzodiazepine and opioid (Airaksinen and Mikkonen, 1980; Glennon et al., 2000). In more recent years, a number of publications arose reporting the interaction of β-carbolines, including harmane, to a novel class of binding sites termed the imidazoline binding sites (I-BS) (Hudson et al., 1999). To date, three types of I-BS have been classified (I_1, I_2 and I_3) in accordance to their drug selectivity and physiological function (Eglen et al., 1998).

The aromatic β-carboline, harmane, has been proposed to be a potential endogenous ligand at I-BS exhibiting high affinity and functional activity at these sites (Adell and Myers, 1994; Cooper et al., 2003; Finn et al., 2003; Hudson et al., 1999; Husbands et al., 2001; Musgrave and Badoer, 2000). In the central nervous system (CNS), harmane has been shown to modulate monoamine release and turnover similarly to I_2-BS gated ligands (Adell et al., 1996; Baum et al., 1996). However, the mechanism by which I_2-BS selective ligands and harmane alter brain extrasynaptic levels of monoamines remain enigmatic.

Previous literature proposed that I_2-BS selective compounds and harmane modulate brain monoamine concentrations through inhibition of monoamine oxidase (MAO) (Glover et al., 1982; Lalies et al., 1999), a mitochondrial enzyme involved in the degradation of biogenic amines. A subpopulation of I_2-BS is reported to be associated at a domain on MAO; although their binding sites are distinct from the enzyme's catalytic domain (Paterson et al., 2003; Tesson et al., 1995). Furthermore, functional studies demonstrated that I_2-BS selective compounds as well as harmane inhibit the activity of MAO (Lalies et al., 1999). Although, some studies suggested that I_2-BS compounds modulate brain monoamine levels independently of MAO inhibition (Baum et al., 1996; Sastre-Coll et al., 2001). In 1995, Nutt et al. reported that the I_2-BS selective ligand 2-(2-benzofuranyl)-quinoline (2-BFI) augmented the potassium-evoked [^{3}H]NA release from hippocampal slices (Nutt et al., 1995); suggesting that 2-BFI elevate brain NA levels through increase in neuronal release. Several other β-carbolines have been shown to alter brain monoamine levels through modulation of exocytotic release (Dolzhenko and Komissarov, 1987; Melchior et al., 1978; Rommelspacher and Subramanian, 1979). Although harmane was previously reported to enhance the electrical – evoked release of monoamines in rat brain there has been no reported action of harmane on monoamine release elicited by depolarizing concentration of K^+ ions in rat brain cortex. Thus, the current study was set to examine the modulatory role of harmane on the efflux of radiolabelled monoamines in rat brain cortex *in vitro*.

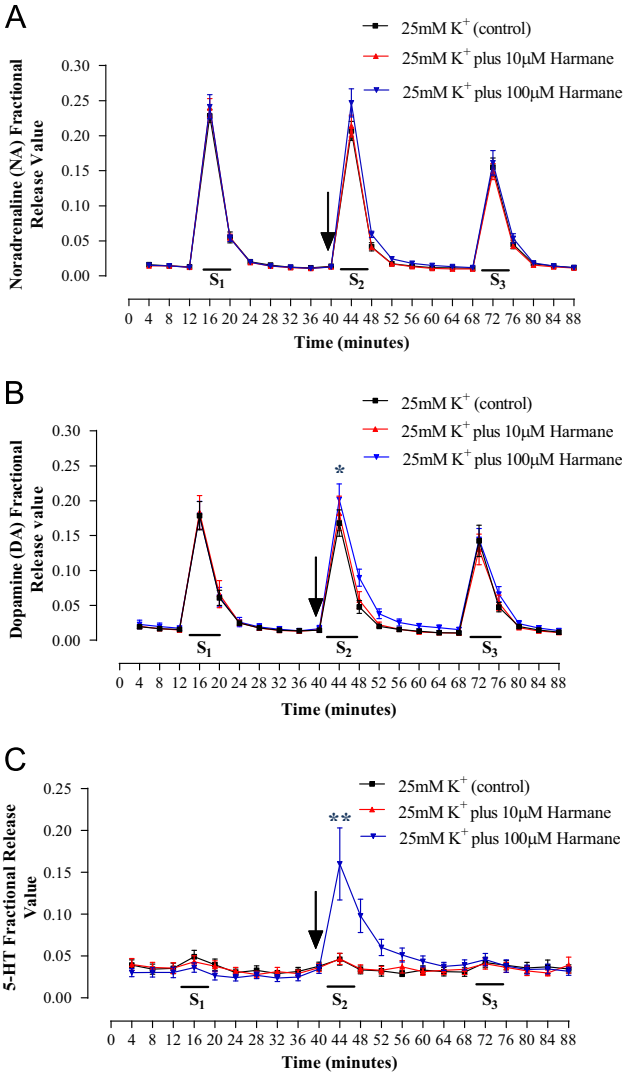

Fig. 1 – The effect of harmane on the fractional release of tritiated (A) Noradrenaline, (B) Dopamine (C) and 5-HT from rat cortical tissue slices *in vitro*. Tritium efflux was evoked at $t=12$, 40 and 68 min for 2 min using depolarising concentrations of K^+ ions in the absence and presence of 10 μM or 100 μM harmane (*application point indicated by arrow*). Data points are expressed as mean ± s.e.mean (vertical bars) of 3–8 independent experiments each performed in duplicate. *$P<0.05$ indicates statistical significance between S_2/S_1 fractional release ratios of control versus 100 μM harmane for DA, and ** $P<0.001$ indicates statistical significance between S_2/S_1 fractional release ratios of control versus 100 μM harmane for 5-HT.

2. Results

2.1. *Effect of harmane on monoamine release in rat brain*

The efflux of [^{3}H]NA (100 nM), in rat cortical tissue slices, was evoked by 25 mM K^+ at $t=12$, 40 and 68 min for a 2 min perfusion period (Fig. 1A). Application of 10 μM or 100 μM harmane, in the presence of 25 mM K^+ at $t=40$ min, did not significantly alter the S_2 phase of stimulated release of [^{3}H]NA relative to control (Table 1). Further investigations demonstrated that application of 25 mM K^+ at $t=12$, 40 and 68 induced the release of preloaded [^{3}H]DA (100 nM) from rat cortical tissue slices (Fig. 1B). At $t=40$ min, single application of 10 μM harmane, in the presence of 25 mM K^+ did not significantly alter [^{3}H]DA release evoked by 25 mM K^+ from rat brain slices (Fig. 1B). However, administration of 100 μM harmane, in the presence of 25 mM K^+, caused a significant