ELSEVIER

European Journal of Pharmacology 317 (1996) R1–R2

ejp

Rapid communication

Ibogaine selectively inhibits nicotinic receptor-mediated catecholamine release

Allan S. Schneider *, Jean E. Nagel, Stephanie J. Mah

Department of Pharmacology and Neuroscience, Albany Medical College, Albany, NY 12208, USA

Received 8 October 1996; accepted 11 October 1996

Abstract

The effects of ibogaine, a putative anti-addictive drug, on stimulated catecholamine release were examined in cultured chromaffin cells to clarify its mechanism(s) of action. Low concentrations of ibogaine (1–10 μM) had a selective inhibitory action on nicotinic receptor-mediated catecholamine release, while higher concentrations (100 μM) inhibited additional modes of stimulated catecholamine release. These results suggest a selective inhibitory action of ibogaine at the nicotinic acetylcholine receptor, possibly at the receptor ion channel site.

Keywords: Ibogaine; Catecholamine release; Nicotinic acetylcholine receptor

Ibogaine is an indole alkaloid which has been claimed to interrupt addiction to opiates, alcohol, cocaine and nicotine (reviewed in Popik et al., 1995). The putative anti-addictive action of iboga alkaloids is supported by animal studies demonstrating a reduction in self-administration of opiates and cocaine and a corresponding reduction in dopaminergic responses in nucleus accumbens and striatum (Glick et al., 1994). This latter effect is consistent with an anti-addictive action in that most addictive drugs are thought to enhance mesolimbic catecholamine release. Although several binding studies have shown that ibogaine interacts with a variety of neuronal receptors and ion channels (Deecher et al., 1992; Popik et al., 1995; Sweetman et al., 1995), the cellular mechanism(s) of an anti-addictive action remains unclear. In the present study, the effects of ibogaine on various modes of stimulated catecholamine release in cultured chromaffin cells were examined. Chromaffin cells were used since they exhibit the essential features of catecholaminergic neurons (synthesis, uptake and release) and contain both receptors and cellular sites of action for many addictive drugs. The results of this study indicate that ibogaine has a selective inhibitory action on nicotinic acetylcholine receptor-mediated catecholamine release.

Bovine adrenal chromaffin cells were isolated by a modified collagenase disaggregation procedure and maintained in primary culture (Bullock et al., 1995). Catecholamine secretion was assayed in terms of release of preloaded [^{3}H]norepinephrine as described (Bullock et al., 1995). Cells were incubated with varying concentrations of ibogaine for 10 min and subsequently subjected to a secretory challenge by either acetylcholine (30 μM), a depolarizing concentration of K^+ (70 mM) or the Na^+ channel agonist, veratridine (100 μM). The effects of ibogaine on these different modes of evoked catecholamine release were then compared with parallel controls not previously exposed to ibogaine.

Different modes of stimulating catecholamine release were used in order to determine whether ibogaine had a selective effect at a specific receptor or ion channel site. Ibogaine had no effect on basal catecholamine release from unstimulated chromaffin cells. Low concentrations of ibogaine ($\leq$ 10 μM) had a potent inhibitory effect on acetylcholine-stimulated catecholamine release, with little or no effect on either K^+- or veratridine-evoked release (Fig. 1). Higher concentrations of ibogaine ($\geq$ 100 μM) disrupted catecholamine release stimulated by all three pathways. These results demonstrate a concentration-dependent inhibition by ibogaine of acetylcholine-, veratridine- and K^+-evoked catecholamine release pathways with IC_{50} values of 5 μM, 50 μM and 150 μM, respectively. The results suggest that low concentrations of ibogaine act at the nicotinic acetylcholine receptor.

* Corresponding author. Tel.: (1-518) 262-5837; Fax: (1-518) 262-5799.

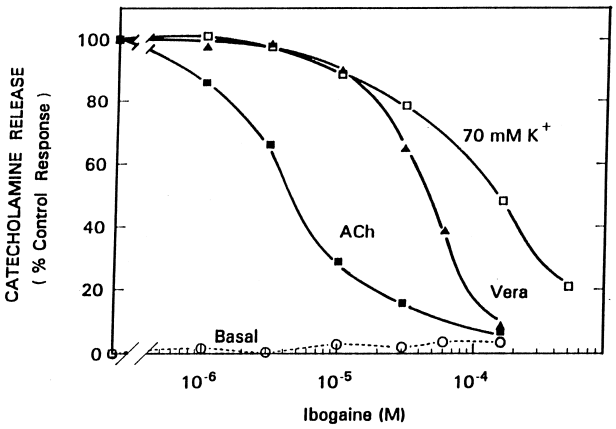

Fig. 1. Concentration dependence of ibogaine effects on basal and stimulated catecholamine release evoked by acetylcholine (30 μM), veratridine (100 μM) or elevated K^+ (70 mM). Cells were preincubated with ibogaine for 10 min and then challenged with stimulant for 10 min at 37°C. Catecholamine release is expressed as % control response for each stimulant in the absence of ibogaine and represents the mean ± S.E. of 4–8 independent experiments, each done in triplicate. Difference between acetylcholine and (acetylcholine + ibogaine) was significant with $P < 0.001$ by paired Student's *t*-test.

The ibogaine concentrations used in this study are comparable to brain concentrations observed in animal studies. Pharmacokinetic studies indicate that following i.v. administration of 10 mg/kg of ibogaine to rodents, maximal brain concentrations of ibogaine of the order of 100 μM are reached in 10 s and subsequently decline with a half-life of 1 h (reviewed in Popik et al., 1995). The initial transient high brain concentrations of ibogaine may trigger longer term actions and we have indeed found evidence of persistent inhibitory actions of 100 μM ibogaine at 19 h following washout.

The present findings provide new insight into mechanisms of action of ibogaine. Our results point to an action of ibogaine (1–10 μM) at the nicotinic acetylcholine receptor and combined with earlier findings suggest an interaction with the receptor ion channel site. The fact that a low concentration of ibogaine inhibited nicotinic receptor-mediated release but not release evoked by veratridine or depolarization with K^+, would support an action at the nicotinic receptor. Our results are consistent with recent studies demonstrating that ibogaine inhibits nicotine-stimulated catecholamine release in the nucleus accumbens (Benwell et al., 1996). We have previously demonstrated by radiolabelled histrionicotoxin binding competition that compounds containing an iboga ring within their structures, e.g., the vinca alkaloids, interact with the nicotinic receptor channel site (McKay et al., 1985). Ibogaine has also been reported to interact with NMDA receptor channels (Popik et al., 1995). Other drugs which interact with NMDA channels, e.g., phencyclidine, are also known to interact with nicotinic receptor channels. Since nicotinic receptors are known to influence mesolimbic dopamine release and ibogaine has now been shown to affect nicotinic receptor mediated catecholamine release, it is plausible that an anti-addictive action of ibogaine could be mediated in part by mesolimbic nicotinic receptors.

The higher concentration effects of ibogaine on high K^+- and veratridine-evoked release would be consistent with previous evidence for an interaction of ibogaine and iboga alkaloids with Ca^{2+} and Na^+ channels (Miller and Godfraind, 1983; Deecher et al., 1992; Popik et al., 1995). The combined results would argue for multiple sites of early action of ibogaine at high brain concentrations ($\approx$ 100 μM) and a selective inhibitory action at neuronal nicotinic receptors persisting during ibogaine metabolism to lower brain concentrations ($\leq$ 10 μM).

Acknowledgements

We wish to thank Dr. S.D. Glick for stimulating our interest in ibogaine mechanisms. This work was supported in part by NIH grants: DA06787, Subcontract A10165(b) and DA03817.

References

Benwell, M.E.M., P.E. Hotlom, R.J. Moran and D.J.K. Balfour, 1996, Neurochemical and behavioural interactions between ibogaine and nicotine inthe rat, Br. J. Pharmacol. 117, 743.

Bullock, A.E., K.E. Barke and A.S. Schneider, 1995, Nicotine tolerance in chromaffin cell cultures: acute and chronic exposure to smoking related nicotine doses, J. Neurochem. 62, 1863.

Deecher, D.C., M. Teitler, D.M. Soderlund, W.G. Bornmann, M.E. Kuehne and S.D. Glick, 1992, Mechanisms of action of ibogaine and harmaline congeners based on radioligand binding studies, Brain Res. 571, 242.

Glick, S.D., M.E. Kuehne, J. Raucci, T.E. Wilson, D. Larson, R.W. Keller and J.N. Carlson, 1994, Effects of *iboga* alkaloids on morphine and cocaine self administration in rats: relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum, Brain Res. 657, 14.

McKay, D.B., R.S. Aronstam and A.S. Schneider, 1985, Interactions of microtubule-active agents with nicotinic acetylcholine receptors, Mol. Pharmacol. 28, 10.

Miller, R.C. and T. Godfraind, 1983, The action of tabernanthine on noradrenaline-stimulated contractions and ^{45}Ca movements in rat isolated vascular smooth muscle, Eur. J. Pharmacol. 96, 251.

Popik, P., R.T. Layer and P. Skolnick, 1995, 100 years of ibogaine: neurochemical and pharmacological actions of a putative anti-addictive drug, Pharmacol. Rev. 47, 235.

Sweetman, P.M., J. Lancaster, A. Snowman, J.L. Collins, S. Perschke, C. Bauer and J. Ferkany, 1995, Receptor binding profile suggests multiple mechanisms of action are responsible for ibogaine's putative anti-addictive activity, Psychopharmacology 118, 369.