Vol 6 | Issue 1 | 2016 | 31-34.

e-ISSN 2248 - 9169
Print ISSN 2248 - 9150

International Journal of
Experimental Pharmacology

www.ijepjournal.com

EFFECT OF LITHIUM ION ON RESPONSES INDUCED BY CHOLINERGIC AND ADRENERGIC DRUGS ON ISOLATED SMOOTH MUSCLE PREPARATION

Midala TAS[1], Timothy SY[2*], Mohd AS[1]

[1]Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Gombe State University, Gombe, Nigeria.
[2]Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Maiduguri, Maiduguri, Nigeria.

ABSTRACT

The aim of this study is to find out the effect of lithium on responses induced by cholinergic and adrenergic drugs on isolated smooth muscle preparations. Guinea-pigs, albino rats of either sex and a matured rabbit were used in these experiments. In each experiment, the animal was killed humanely and the throat was cut to bleed. The abdomen was opened and a piece of ileum (3-4 cm long) was removed and mounted in an organ bath of 50 ml capacity containing tyrode solution which was maintained at 37^{o}C and continuously aerated with oxygen throughout the experiment. The tissue was allowed to equilibrate for 30 minutes before adding Lithium chloride, ACh, Methacholine and Noradrenaline. The contraction or relaxation of muscles induced by drugs was recorded isotonically using microdynamometer. The effect of lithium chloride on guinea-pig ileum was observed to be concentration dependent contraction, whereas at concentrations between 200µg/ml to 400µg/ml it exhibited a biphasic action. The contractile activity of ACh at lower concentrations of lithium was not concentration dependent. However, at higher lithium concentrations the activity of Ach on the isolated guinea pig ileum was observed to be concentration dependent. A similar observation was made with methacholine at varying lithium concentrations. The effect of lithium chloride on isolated rabbit jejunum was hyperpolarizing and concentration dependent. Again, it was observed that the higher the lithium concentration the higher the relaxing effect of noradrenaline on the rabbit jejenum. Lithium produced relaxation of the rat duodenum in a dose dependent manner by adrenaline. The relaxation of rat duodenum produced by adrenaline was not concentration dependent. However, as the concentration of lithium chloride increases the hyperpolarizing activity of noradrenaline also increases. Lithium ion was found to alter the depolarizing and hyperpolarizing activities of cholinergic and adrenergic drugs on isolated smooth muscle preparations.

Keywords: Lithium, cholinergic, adrenergic, smooth muscle.

INTRODUCTION

Lithium ion is a member of the group 1a alkali metals and occurs in trace amount in the body but has no known biological role [1]. However, the ion mimics some of the biological properties of both extracellular sodium and. intracellular potassium ions. It can replace sodium in isolated nerve, muscle and erythrocyte preparation though this counterfeit activity is not complete [2]. Ross and Frank reported the therapeutic usefulness of lithium in gout and as a mood stabilizer mainly bipolar disorder. Lithium ions abolished the turbulent endogenous excitement of periodic mania [3]. Prien have shown that lithium is effective in the prevention of both mania and depression [4]. Also, it has been reported by Goodwin that Lithium ion is more effective for the treatment of bipolar than unipolar patients [5]. It has been reported by Watanabe that lithium ion is effective in all sub-types of depression and that even in severe depression. Apart from its clinical use, lithium ion has been associated with certain pharmacological actions. Coppen reported that lithium ion impaired synaptic transmission [6]. Bjegovic and Randic in agreement with Coppen's reported that lithium ion decreased the evoke

Corresponding Author

Timothy Samuel Yerima
Email id: satiye2002@gmail.com

release of acetylcholine from cat cerebral cortex and from nerve terminals of guinea-pig ileum (longitudinal muscle strip). It has also been reported that lithium ion can replace both extracellular and intracellular electrolytes including sodium ions [7]. Busuray and Dutta have reported that acute or continuous infusion of lithium ion into an anaesthesised cat caused partial replacement of sodium ions and thereby decreased the release of acetylcholine on electrical stimulation of vague nerve. Lithium ion has also been reported to impair transmission at the mammalian sympathetic ganglia Coppen and can also decrease the pressor response to exogenous norepinephrine in man. The biochemical application of lithium chloride is in the precipitation of ribonucleic acid (RNA) from cellular extracts [8]. The mechanism of action of lithium ions is not known with certainty. However, it has been postulated that lithium reduces free energy change (F) through replacement of sodium and potassium ions [9, 10]. Another suggestion is that the ion inhibits adenosine triphosphate (A.T.P.) energy production. In mania, the ability of pumping out intracellular sodium ions is defective, such that these ions are constantly releasing the labile neurotransmitter (noradrenaline) from synaptic vesicles. The transmitter then acts on adrenergic receptor sites producing excitement and elation of mania. In lithium therapy, lithium ion displaces sodium from the cell and possibly doesn't have the same capacity to release neurotransmitter substance from the vesicular sites. Therefore, this diverse activity of lithium ion needs to be evaluated autonomically.

MATERIALS AND METHODS

Isolated tissue preparation

Guinea-pigs of either sex weighing between 300-500 g, albino rats (200-250 g) and a matured rabbit (1.2 kg) were used in these experiments. In each experiment, the animal was killed by giving a sharp blow on the head and the throat was cut to bleed. The abdomen was opened and a piece of ileum (3-4 cm long) was removed and transferred to a petri dish containing tyrode solution. The mesentry and fatty materials were trimmed away and the tissue was suspended in an organ bath of 50 ml capacity containing tyrode solution which was maintained at 37^{o}C and continuously aerated with oxygen throughout the experiment. The tissue was allowed to equilibrate for 30 minutes before adding the drugs (Li^{+}, ACh, Methacholine and Noradrenaline). The drugs were allowed to act for 15 seconds and the interval between successive additions of drugs was 5 minutes. The time course of action of lithium ion with isolated muscle preparation was 3 minutes. In all the experiments performed each tissue was washed twice with a fresh physiological salt solution in between doses of drugs. The contraction or relaxation of muscles induced by drugs or nerve stimulation was recorded isotonically using microdynamometer.

RESULTS ANALYSIS

Effect of lithium chloride against Ach and Methacholine induced contraction on isolated guinea pig ileum

Lithium chloride induced contraction of the guinea-pig ileum in concentration related manner. The contractile effect was immediate and sustained as long as the lithium chloride was in contact with the tissue. The effect of lithium chloride on guinea-pig ileum was observed to be concentration dependent contraction, whereas at concentrations between 200 µg/ml to 400 µg/ml it exhibited a biphasic action (initial quick relaxation followed by contraction). The contractile activity of ACh at lower concentrations of lithium (0.04 µg/ml to 0.8 µg/ml) was not concentration dependent. However, at higher lithium concentrations (2 µg/ml to 400 µg/ml) the activity of Ach on the isolated guinea pig ileum was observed to be concentration dependent. The maximum depolarising activity of ACh was observed at 200 µg/ml of lithium chloride. A similar observation was made with methacholine at varying lithium concentrations. However, the concentrations of lithium chloride which elicited contraction had a synergistic effect upon the contractions induced by these drugs. Higher doses of lithium chloride from 200 - 400 µg/ml reduced the effect of ACh and methacholine in a concentration related manner (Table 1).

Effect of lithium chloride on noradrenaline induced relaxation of isolated rabbit jejenum

The effect of lithium chloride on isolated rabbit jejunum was hyperpolarizing and concentration dependent. Noradrenaline at 20 ng/ml had no effect on the isolated rabbit jejunum, while at higher concentrations (40 to 160 ng/ml) the relaxing effect of noradrenaline was concentration dependent. Again, it was observed that the higher the lithium concentration the higher the relaxing effect of noradrenaline on the rabbit jejenum (Table 2).

Effect of lithium chloride on noradrenaline induced relaxation of isolated rat duodenum

Lithium chloride at the tested concentrations produced a little or no relaxation of rat duodenum. Concentrations of lithium varying from 0.8 µg/ml to 200 µg/ml produced relaxation of the rat duodenum in a dose dependent manner by noradrenaline. These concentrations produced synergistic effect with the noradrenaline. The relaxation of rat duodenum produced by adrenaline was not concentration dependent. However, as the concentration of lithium chloride increases the hyperpolarizing activity of noradrenaline also increases (Table 3).

Table 1. Effect of lithium chloride against Ach and Methacholine induced contraction on isolated guinea pig ileum

Drugs	Organ bath conc.(ng/ml)	Responses due to Lithium in millimeters				
Lithium (µg/ml)		*0.04*	*0.8*	*2.0*	*200.0*	*400.0*
Lithium		16	33	52	±	±
Ach	2.0	30	34	30	39	20
	4.0	29	34	53	51	43
	8.0	33	33	53	53	44
	16.0	34	34	55	56	45
Methacholine	0.2	32	35	25	37	25
	0.4	28	24	39	48	44
	0.8	24	15	54	55	45
	1.6	20	13	56	57	48

± = biphasic effect (initial quick relaxation followed by contraction)

Table 2. Effect of lithium chloride on noradrenaline induced relaxation of isolated rabbit jejenum

Drugs	Organ bath conc.(ng/ml)	Responses due to Lithium in millimeters				
Lithium (µg/ml)		*0.8*	*20.0*	*40.0*	*80.0*	*200.0*
Lithium		-	18	38	40	45
Noradrenaline	20.0	-	-	-	-	-
	40.0	0.0	9	16	12	22
	80.0	15	20	24	15	30
	160.0	19	25	30	20	35

± = biphasic effect (initial quick relaxation followed by contraction), - = no effect

Table 3. Effect of lithium chloride on noradrenaline induced relaxation of isolated rat duodenum

Drugs	Organ bath conc.(ng/ml)	Responses due to Lithium in millimeters			
Lithium (µg/ml)		*0.8*	*40.0*	*80.0*	*200.0*
Lithium		-	-	-	-
Noradrenaline	100.0	27	37	40	48
	200.0	30	42	45	51
	400.0	15	39	51	49
	800.0	19	35	42	45

- = no effect

DISCUSSION

Lithium ion mimics some of the biological properties of both extracellular sodium and intracellular potassium ions. When introduced into biological systems lithium acts more like sodium than any other ion as observed in the present study. For example, lithium can replace sodium ion in isolated nerve, muscle and erythrocyte preparations. Lithium salts are also used in the treatment of manic depressive psychosis but its mode of action is not yet clear. A variety of actions of lithium on the synthesis, release and metabolism of many biogenic amines have been described which may account for its effectiveness in the treatment of mania [11]. Lithium ions have been reported by Corrodi *et al* to increase intraneuronal inactivation of noradrenaline and to increase the uptake of noradrenaline by synaptosomes [12,13]. Lithium ions have also been reported to inhibit the evoked release of noradrenaline from brain. These actions of lithium ions may reduce the availability of noradrenaline at the receptor sites Coppen resulting in a decrease of the sympathetic activity. Furthermore, lithium ions have been reported to inhibit the synthesis and release of acetylcholine. Lithium also inhibits the release of 5-HT and possibly increases synthesis and the turn-over rate of 5-HT. Lithium also alters the concentration of aminobutyric acid and glutamate. In the present study, lithium chloride produces quite interesting results in the peripheral cholinergic and adrenergic systems. Lithium chloride in lower concentrations evokes contraction of the vascular and nonvascular smooth muscles, such as guinea pig ileum, rat ileum and rabbit intestine. This effect is probably mediated through the depolarization of the membrane of the muscle because it mimics the biological properties of sodium and potassium [5]. Higher concentration of lithium chloride was observed to produce a quick and brief relaxation, followed by a sustained contraction in this study. The quick

relaxation may be due to preventing the entry of calcium ion from extracellular site to intracellular site and probably this effect wears off quickly. The concentration of lithium chloride which produces contraction of the smooth muscles also produced a synergistic effect with acetylcholine and methacholine on nonvascular smooth muscle and with noradrenaline on vascular smooth muscle. preparations. This has demonstrated that the mode of action of lithium chloride being different from those of cholinergic and adrenergic drugs.

CONCLUSION

Lithium ions in lower concentrations evoke contraction of the non-vascular and vascular smooth muscles, whereas in higher concentrations produce a biphasic effect of an initial and brief relaxation followed by a sustained contraction of smooth muscles. In lower concentrations it produces synergistic effect with cholinergic drugs and in higher concentrations reduces their contractile effect.

ACKNOWLEDGEMENT

The authors are sincerely thankful to the technologists in the Pharmacology laboratory of the Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Ahmadu Bello University Zaria, Kaduna State, Nigeria for their technical assistance and support.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Philip M. The periodicity of physical and chemical properties. Advanced chemistry (low price edition), Cambridge university press, 1992, 533-550.
2. Gilman AG. Goodman and Gilman: The pharmacological basis of therapeutics, 5th edition, McGraw-Hill publisher, 5th edition, 1975, 184-187.
3. Gilman GA, Hardman JG, Limbird LF. Goodman and Gilman: The pharmacological basis of therapeutics, 10th edition, McGraw-Hill publisher, 2001, 31-44.
4. Prien RF, Klett CJ, Caffey EM. Lithium carbonate and Imiprarnine in prevention of affective episodes: Arch. *General Psychiat*, 29, 1972, 420-425.
5. Goodwin GM. Recurrence of mania after lithium withdrawal. Implicatios for the use of lithium in the treatment of bipolar affective disorder. *Br J of Psychiatry*, 164, 1994, 149-152.
6. Coppen AJ. The biochemistry of affective disorder. *Br J Psychiatry*, 113, 1967, 1237.
7. Bjergovic M, Randic M. Effects of Lithium ions on the release of acetylcholine from cerebral cortex. *Nature*, 230, 1971, 587-591.
8. Singer I, Rotenberg D. Mechanism of lithium action. *New Eng. J. Med*, 289, 1973, 254-257.
9. Cathala G, Savouret J, Mendez B. A method for isolation of intact, translationally active ribonucleic acid. *DNA*, 2(4), 1983, 329-335.
10. Andreani G, Caselli G, Martellica H. Clinical and electro encephalographic finding during treatment of mental disorders with lithium salts. *A Psichiat Neuropathol*, 86, 1958, 273-275.
11. Ross JB, Frank IT. Drugs and the treatment of psychiatric disorders: psychosis and mania. In: Goodman and Gilman The pharmacological basis of therapeutics, 2001, 485-520.
12. Corrodi H, Fuxe K, Hokfelt T, Schou M. The effect of lithium on cerebral monoamine neurons. *Psychopharmacologia*, 11, 1967, 345-353.
13. Colburn R, Goodwin F, Bunney WE, Davis J. Effect of lithium on the uptake of noradrenaline by synaptosomes. *Naure*, 215, 1967, 1395-1397.