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Short Communication

The pharmacological studies on intrinsic activities of acetylcholine, methacholine, and carbachol (Homologous Drugs) on isolated rat ileum preparation

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This study investigated the intrinsic activities of equimolar concentrations of three homologous drugs Actylcholine (Ach), Methacholine (Mch) and Carbachol (Cch) on isolated rat ileum preparation. Contractions were monitored on smoked drum fixed on a kymograph. Heights of contractions were measured in (mm) in order to assess their efficacies.In some experiments Ach- induced contractions were measured in the presence of atropine a competitive muscarinic antagonist. The result showed order of potencies, ranked as Cch>Mch>Ach. This result may explain the low intrinsic activities of Ach when compared to Cch, Mch, due to effect of acetylcholinesterase an enzyme which hydrolyze Ach and limit its efficacy in therapeutic use.

Keywords: Intrinsic, homologous drugs, rat ileum, efficacy.

INTRODUCTION

Theoretically, the term intrinsic activity of a drug was first introduced by Ariens and Van Rossum (1957). The term has been used a great deal in their attempt to explain why all drugs do not act in accordance with Clark's theory of drug receptor interaction. Intrinsic activity is a measure for the agonistic potencies of a drug, thus agonists have high intrinsic actives whereas competitive antagonist have zero intrinsic activity, both worker's together with simoni's also introduced another term affinity. The shape of the dose response curve is thought to be a function of both parameters. Efficacy produced by drugs and their antagonist.

The present study was undertaken to use these term by utilizing them in explaining series of dose response curves obtained by using homologous series of drugs and also by using drugs which act on the same receptors but are not members of the homologous series (atropine) and also assess and rank the order of potencies.

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MATERIALS AND METHODS

Rats between (200-305g) were used. The animals were maintained in well ventilated conditions, under constant temperature 37°C and humidity (50%) and exposed to light dark cycle for three weeks before use. The animals were fed on standard livestock pellets with free access to water. The rats were killed by cutting one of the common carotid arteries The Ileum was removed and tied with fine cotton threads and mounted in a 15ml organ bath filled with physiological salt solution maintained at 37°C and aerated with a gas mixture containing 95% O_2 and 5% CO_2. The preparation was equilibrated for 1h in the bathing solution in an unstretched condition and the bathing solution renewed every 20min. After equilibration, the contractile responses were recorded.

Physiological salt solution used was Tyrode physiological salt solution with the following compositions (mM) Nacl 138, Kcl 5.7, Mgcl2 1.1, NaHPo4 0.3, NaHCo3 25, CaCL2 1.8, D-glucose 5.0, PH 7.5. The bath was aerated by means of aerated pump bubble volume of solution up to a constant level in the bath was measured

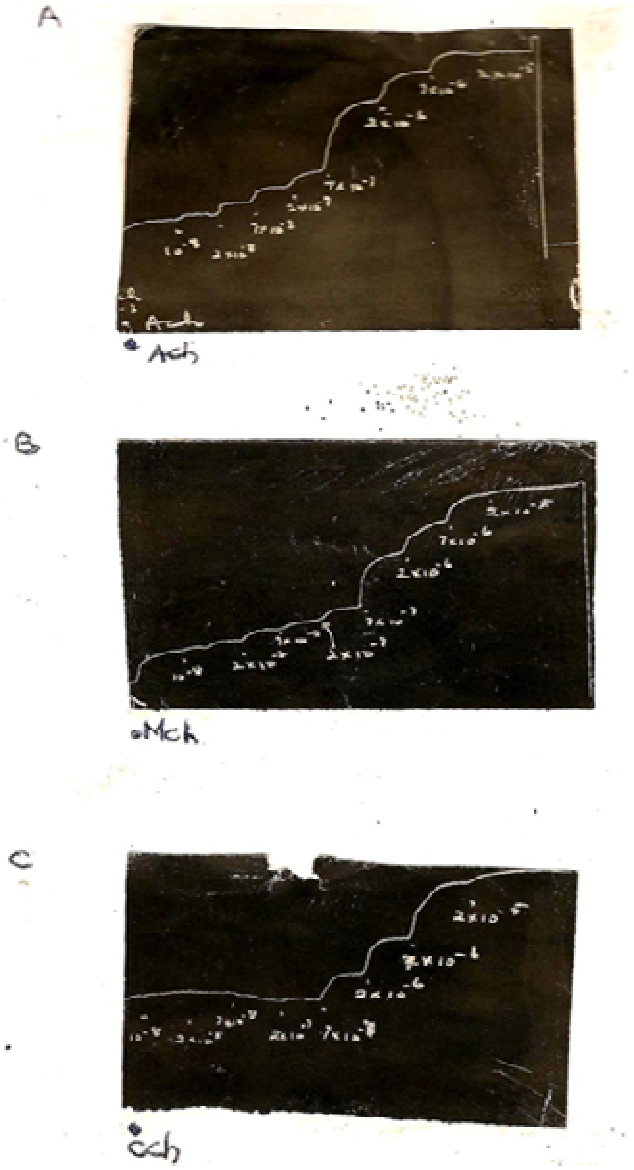

Figure 1: Showing Cummulative Dose Response Relationship Of 3 Homologous Drugs (Ach, Mch, Cch) (1x 10-8M- 2x 10-5M)
Panel A, B, C, show tracings of Cummulative dose response curves to homologous series of (A= Ach 1x10^{-8}M -1x 10^{-5}M 10-) (B= Mch1x10-8M 1x10-5 M and C =Cch 1x10-8M - 1x10-5M)

and noted, previous to setting up the ileum series of dilution 1,3, 10 100 are given, preparing drugs Acetylcholine, Carbachol, Methacholine in such dilutions. Responses were obtained for the 3 cholinomimetic agonists.

A dose response trace was also obtained for the first compounds of the series in the presence of antagonist, cumulative doses were given without emptying the bath until maximum response were obtained for each drug. Log dose-response curves and plots of response as percentage of maximum agonist log dose were made.

Table 1: Responses of tissue to cholinomimetics drug (Carbachol (Ccb),Methacholine (Mch),and acetylcholine (Ach),and responses in millimeter (mm) heights of Contractions

Doses in Molar Conc.	Ach	Cch	Mch
1x10^{-8} M	-	-	-
3x10^{-8} M	6 +0.5	10 + 0.2	8 + 0.1
1x10^{-7} M	15 +0.2	25 + 0.3	16 + 0.1
3x10^{-7} M	25 +0.1	36 + 0.4	29 + 0.1
1'x10^{-6} M	28 +0.5	45 + 0.2	33 + 0.2
3x10^{-6} M	38 +0.4	52 + 0.1	42 + 0.5

Table 2: Responses of homologous series drugs showing Ach in the presence of Atropine, heights of contractions measured in (mm) (n=6).

Doses of Ach in Molar Concentration	Responses in Presence of 10-^{4}m, And 10-^{3}m (mm)		
1x10^{-8} M	4.5 +0.1	3 + 0.1	5 + 0.2
3x10^{-8} M	14 + 0.5	11.5+0.2	7 + 0.1
1x10^{-7} M	24 + 0.2	19 + 0.3	9.5 +0.5
3x10^{-7} M	33 + 0.2	22.5+0.5	13 + 0.4
1X10^{-6} M	35 + 0.1	31 + 0.5	25 + 0.2

RESULTS

The results obtained using equimolar concentrations (1x10^{-8}M-----2x10^{-5}M) of drugs used (homologous drugs) Ach, Mch, Cch, show a cumulative dose dependent responses to all the drugs in this study (See tracing Figure 1 a, b, c and tables 1 and 2 above).

DISCUSSION

The above result was based on the fundamental and theoretical considerations; the primary step involved in the action of drugs upon tissue is the interaction of drugs molecules with receptor in tissue represented by the following equation

R+A $\rightarrow$ RA where R is the concentration of free receptors A the drug concentration and RA the concentration of receptor complex, the total concentration of the drug receptor is unknown, while the effect may be a complex fraction of the amount of receptor occupied, nevertheless some magnitude has been postulated which by definition is directly proportional to the fraction of receptor occupied Sa/sm&RA/r=&1/1+Ka/A, where SA is stimulus expressed as a fraction of the maximum stimulus (Sm) which is possible. The drug is effective in

concentration of the order magnitude of KA such a concentration may be called the effective drug concentration. The effect is a function of the stimulus Ea/Em=f(Sa/Sm) where EA is the effect obtainable with the biological object. Experimentally the parameters can only be determined in relation to a reference compound. The stimulus effect relationship is often included in the intrinsic activity. This is directly proportional to the stimulus. However if the effect is not linearly related to stimulus the intrinsic activity can still be calculated as the ratio between maximum effect of a drug and maximum effect of reference agonist. The relative intrinsic activity then varies from zero to unity agonist have and intrinsic activity of a real value though that value may be low if drug is combined with another drug with higher intrinsic activity, the former may behave as competitive antagonist. The relative value of and therefore determine whether drugs acts as a stimulant or as an inhibitor.

The affinity (1/km) or its logarithm (PD2=log K2) is a measure for the potency of the (Arien's 1957). The intrinsic activity is the ability to produce effect once the receptors are occupied.

In homologous series of drug which have affinity for the same receptor, it is found that agonistic activity diminishes as the series is ascended. This variation in agonistic activity may be due to variation in intrinsic activity alone. Log dose response procedure will be expected theoretically. The highest members of the series may have very low or zero intrinsic activity. These members then act as competitive antagonist to members which have high intrinsic activity. The result further indicated that Carbachol, Methacholine have higher intrinsic activities than Acetylcholine, this is so because Acetylcholine is a substrate to cholinesterases an enzyme which hydrolyzes it to choline and acetyl group thereby inhibiting its potency, this also explain why acetylcholine does not find a wider application in therapy.(Aziba ,2007).The potency of intrinsic activities decreases in this order Cch>Mch>achin this study.

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