COMPARISON OF MUSCARINE-LIKE AND NICOTINE-LIKE CHOLINOPOTENTIATING ACTIVITY OF NEOSTIGMINE AND ESERINE

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In minimally acting doses eserine and neostigmine produce excitation of muscarine-like (M) cholinergic systems almost exclusively in isolated organs and in the intact animal. In the intact animal, after administration of neostigmine the ratio between the M and nicotine-like (N) effects is determined mainly by the size of the dose, while in eserine poisoning the effect remains predominantly on M cholinergic structures. Accordingly, M cholinolytics are more effective in the treatment of eserine poisoning, while substances possessing both M and N cholinolytic action simultaneously are more effective in the treatment of neostigmine poisoning.

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Neostigmine and eserine are typical members of the group of anticholinesterase (cholinopotentiating) substances which produce qualitatively different effects on the animal body [1, 3, 5, 6].

In the present investigation the cholinopotentiating (increasing the acetylcholine effect) and cholinomimetic activity of neostigmine and eserine were compared during their action on nicotine-like (N) and muscarine-like (M) cholinergic systems, and the effectiveness of M and N cholinolytics as antidotes for the treatment of neostigmine and eserine poisoning in albino mice was studied.

EXPERIMENTAL METHOD

Experiments were carried out on the isolated rectus abdominis muscle of the frog by the method of Chang and Gaddum [4] at 17-20°. To obtain a control contraction, acetylcholine (AC) was used in concentrations of 3.2×10^{-7} and 1×10^{-6} M. Contractions of the muscle in response to addition of eserine or neostigmine to the bath, like the acetylcholine contractions, were recorded up to two min. An increase in the muscle's response to AC was detected after contact with the anticholinesterase preparation for 20 min. A segment of the terminal ileum of a guinea pig was suspended in aerated Tyrode solution at 30°. The amplitude of the tonic contraction of the segment of ileum in response to the action of cholinopotentiating drugs and the increase in amplitude of its contraction in response to addition of AC in a concentration of 1×10^{-7} M were determined after contact with neostigmine or eserine for 2.5, 5, or 10 min. By plotting dose–effect curves the concentrations of neostigmine and eserine at which a contracture was produced equal to that caused by AC in the control experiment and their concentrations doubling the amplitude of the contracture to AC were found.

TABLE 1. Effectiveness of Neostigmine and Eserine Concentration (in m) When Acting on Isolated Guinea Pig Instestine and Frog Rectus Abdominis Muscle

Time of contact (in min)	Neostigmine		Eserine	
	Potentiation	Contracture	Potentiation	Contracture
Experiments on intestine				
2,5	$1{,}8 \cdot 10^{-7}$	$4 \cdot 10^{-7}$	$1{,}7 \cdot 10^{-7}$	$1 \cdot 10^{-6}$
5	$6{,}5 \cdot 10^{-8}$	$2{,}5 \cdot 10^{-7}$	$7{,}9 \cdot 10^{-8}$	$5 \cdot 10^{-7}$
10	$4{,}0 \cdot 10^{-8}$	$2{,}0 \cdot 10^{-7}$	$1{,}8 \cdot 10^{-8}$	$2{,}6 \cdot 10^{-7}$
Experiments on muscle				
20	$1{,}0 \cdot 10^{-6}$	$1{,}0 \cdot 10^{-6}$	$2{,}5 \cdot 10^{-6}$	$1{,}0 \cdot 10^{-5}$

In experiments on mice the cholinopotentiating drugs were injected intraperitoneally 10 min after subcutaneous injection of cholinolytics. The cholinolytics were used in doses of 1/10 of the minimal toxic dose.

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TABLE 2. $LD_{50} \pm m$ (t 0.05) of Neostigmine and Eserine When Injected Intraperitoneally into Albino Mice Before and 10 min after Subcutaneous Injection of Cholinolytics (in mg/kg)

Cholinolytics	Dose	Cholinopotentiating substance: Neostigmine: Control	Neostigmine: After action of cholinolytic	Neostigmine: CA_n	Eserine: Control	Eserine: After action of cholinolytic	Eserine: CA_e	$CRA = \frac{CA_n}{CA_e}$
Atropine	20	0,61±0,04	0,77±0,13	1,26	0,99±0,25	4,60±0,69	4,90	0,26
	50	0,40±0,05	0,82±0,11	2,05	0,82±0,15	4,85±0,86	5,91	0,34
Metamizil	5	0,61±0,04	1,56±0,53	2,56	0,99±0,25	4,90±0,21	5,00	0,51
Metacin	10	0,61±0,04	1,52±0,52	2,50	0,99±0,25	3,32±0,33	3,35	0,75
Aprophen methylate	6	0,61±0,04	3,31±0,76	5,48	1,10±0,37	3,41±0,53	3,20	1,70
Arpenal	0,5	0,44±0,05	0,45±0,03	1,02	—	—	—	—
	5	0,44±0,05	1,32±0,12	3,00	—	—	—	—
	10	0,36±0,05	3,30±0,47	9,17	1,10±0,37	3,61±0,56	3,28	2,80
Pediphen	15	0,36±0,05	0,56±0,08	1,55	0,99±0,25	1,09±0,10	1,10	1,40
Hexamethonium	10	0,36±0,05	0,65±0,10	1,80	0,99±0,25	1,55±0,44	1,56	1,15
	25	0,36±0,06	0,60±0,08	1,67	—	—	—	—

EXPERIMENTAL RESULTS AND DISCUSSION

The experimental results are given in Tables 1 and 2. Tests of the compounds in vitro (Table 1) showed that the intervals between M and N cholinopotentiating and between M and N cholinomimetic concentrations differed very considerably for the same substance. For instance, whereas neostigmine potentiated the action of AC on N cholinergic systems in a concentration only 25 times greater, in tests of its effect on M cholinergic systems (for 10 min) the eserine concentrations had to be 1400 times greater than during its action of M cholinergic systems. Neostigmine caused contractions of the frog rectus abdominis muscle in a concentration 500 times greater than that required to cause contraction of the intestine, while eserine, even in a concentration 4000 times greater, had no mimetic action [2] on the frog rectus abdominis muscle. The effectiveness of the cholinolytics as antidotes in neostigmine and eserine poisoning was expressed as a coefficient of activity (CA), obtained as the ratio between LD_{50} after preliminary administration of the antidote and LD_{50} in the control. The relative effectiveness of the cholinolytics in the treatment of poisoning by these two substances was expressed by the coefficient of relative activity ($CRA = \frac{CA_n}{CA_e}$).

With weakening of the M cholinolytic properties and the stimultaneous strengthening of the N cholinolytic properties of the cholinolytics used, the value of CRA increased (Table 2).

It may be concluded from these results that qualitative differences in the effects of neostigmine and eserine may largely be attributed to the more marked N cholinopotentiating activity of neostigmine.

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