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Mechanism-based assessment on the pharmacodynamics of neuromuscular relaxants and general consideration for receptor blockers

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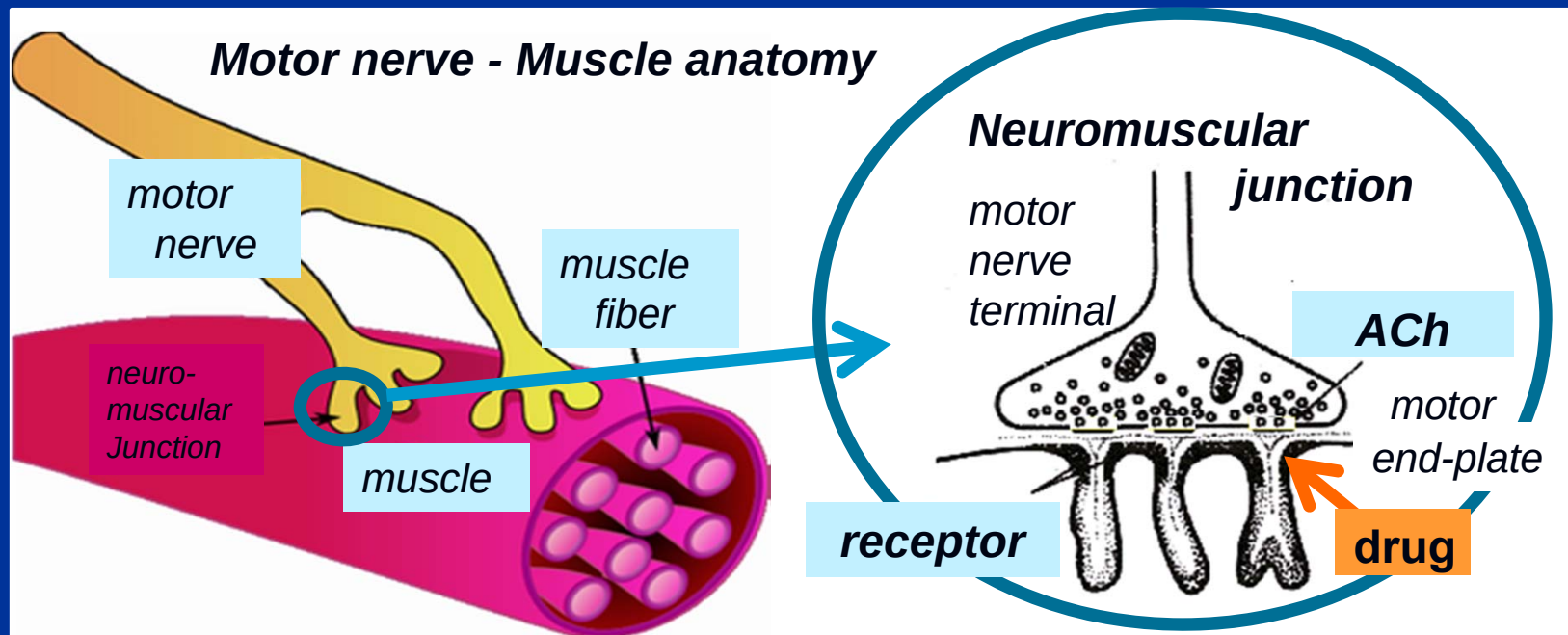
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Background and objective

Physiology and pharmacology for neuromuscular relaxants

- ✓ Transmitter, acetylcholine (ACh) released from motor nerve terminal binds receptor densely located on motor end-plate in neuromuscular junction of a muscle fiber (receptor density: $0.04 - 0.4 \mu\text{M}^{-1}$). A receptor binding by ACh elicits a binominal response of the muscle fiber (i.e., contraction or none).
- ✓ Muscle is fasciculus of muscle fibers. The tension of whole muscle contraction depends on receptor occupancy by ACh.
- ✓ Neuromuscular relaxant competitively inhibits receptor binding of ACh, resulting in the pharmacological effect, depression of tension of muscle contraction.



Background and objective

Pharmacodynamic property for neuromuscular relaxants

- ✓ *In-vitro* affinity for receptor (K_c) and *in-vivo* potency (EC_{50}) are neither in concord nor in a proportional relationship. Rather, even for a high affinity drug, a substantial concentration is needed to evoke the neuromuscular blockade effect.

Drug		K_c (μM) ^{2,3}	EC_{50} (μM) ^{4,5}
Pancuronium	(Affinity) 	0.001	0.4
d-Tubocurarine		0.015	0.8
Gallamine		0.4	6.0

K_c : dissociation constant of receptor-drug complex

- ✓ Slope of concentration-effect or dose-effect curves vary with drugs, and drugs with higher potency tend to have steeper slopes ^{4,6-8}).



The purpose of this study is to investigate the underlying mechanism on the pharmacodynamic properties using a physiologically and pharmacologically based dynamic model.

Methods

Dynamic model for receptor binding by the law of the mass action

$$RA = R_T \cdot A / \{A + K_a (1 + K_c/C)\} \quad \dots \text{Eq.1}$$

$$RC = R_T \cdot C / \{C + K_c (1 + K_a/A)\} \quad \dots \text{Eq.2}$$

$$A_T = RA + A \quad \dots \text{Eq.3}$$

$$C_T = RC + C \quad \dots \text{Eq.4}$$

Simultaneous equations (Eqs. 1-4) were numerically solved for RA and RC using a Newton iterative method.

RA: receptor-ACh complex

RC: receptor-drug complex

R_T : receptor ($0.205 \mu\text{M}$)⁹⁾

A_T and A : total and free ACh (A_T : $0.866 \mu\text{M}$)⁹⁾

C_T and C : total and free drug

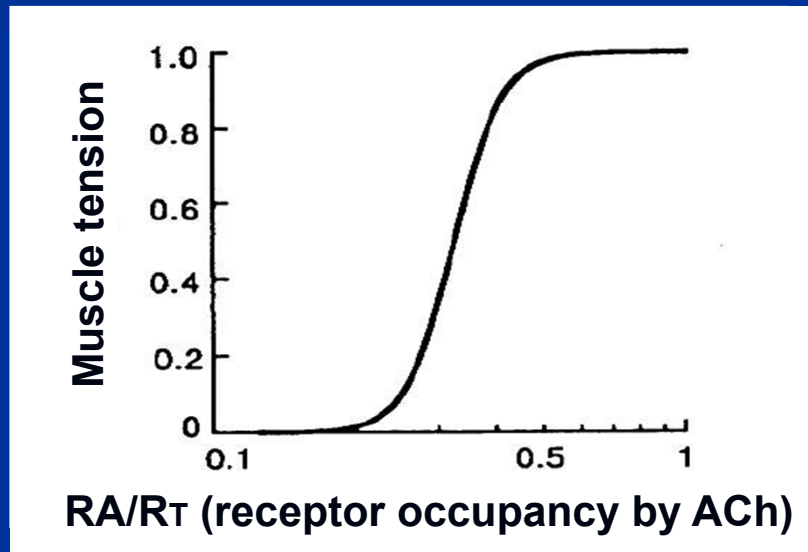
K_a : dissociation constant for receptor-ACh complex ($0.100 \mu\text{M}$)²⁾

K_c : dissociation constant for receptor-drug complex ($0.001, 0.01, 0.1, 1.0 \mu\text{M}$)

Methods

Dynamic model for transduction of receptor binding of ACh to tension of muscle contraction using a Hill's equation

$$\text{Muscle tension} = \frac{RA^S}{(RA^S + RA_{50}^S)} \quad \dots \text{Eq.5}$$



Hill's equation is similar to normal distribution¹⁰⁾, which is probabilistically derived for fasciculus of muscle fibers with binominal response to receptor binding of ACh

Muscle tension: ratio to the maximum

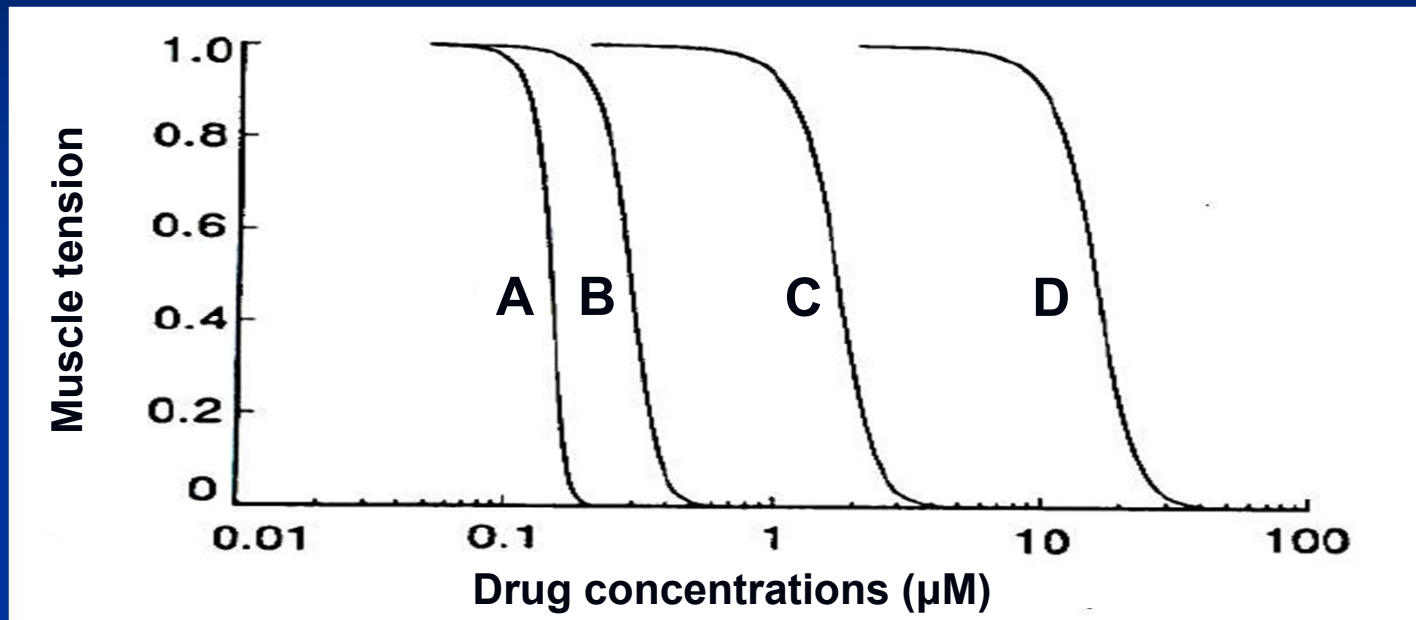
RA₅₀: receptor-ACh complex evoking 50% muscle tension (0.0665 μM)⁹⁾

S: Hill's coefficient (8.56)⁹⁾

Using Eqs. 1-5, concentration-effect (muscle tension) relationships were calculated for drugs with various affinities for receptor ($K_c = 0.001, 0.01, 0.1$ and $1.0 \mu\text{M}$)

Results and discussion

Simulated concentration-effect relationships



		Kc (μM)	EC ₅₀ (μM)	Slop (γ)*
A	(Affinity) ↑	0.001	0.146	11.8
B		0.01	0.285	6.84
C		0.1	1.70	5.19
D		1.0	15.8	5.00

*: $\gamma = (0.8 - 0.2)/\ln(C1/C2)$, C1 and C2 are drug concentrations corresponding to muscle tension of 0.2 and 0.8, respectively.

Results and discussion

- ✓ For low or moderately potent drugs with $K_c=0.1$ and $1.0 \mu\text{M}$, the difference of K_c are almost proportionally reflected in EC_{50} (1.70 and $15.8 \mu\text{M}$) and has little impact on slope γ (5.19 and 5.00).
- ✓ Increasing affinity ($K_c=0.001$ or $0.01 \mu\text{M}$), K_c is under-proportionally reflected in EC_{50} (0.146 and $0.285 \mu\text{M}$) and γ increases (11.8 and 6.84).



EC_{50}

- Drug needs to occlude receptor to exert the effect. Therefore, even a drug with a high affinity needs concentrations close to receptor density ($0.205 \mu\text{M}$). As a result, EC_{50} of a drug with high affinity dose not become so small as expected proportionally from the difference in K_c .

Slop (γ)

- For a drug with a low affinity, free concentration of drug is almost the same as total concentration, because the amount of drug binding to receptors is negligible relative to the total amount of drug.
- On the other hand, for a drug with a high affinity, the amount of drug binding to receptors is non-negligible. Free concentration dose not approximate total concentration. The discrepancy of free and total concentration changes the slop.

Conclusion

- A physiologically and pharmacologically based dynamic model can provide explanations for the apparent pharmacodynamic properties of neuromuscular relaxants.
- On the basis of this study, for not only neuromuscular relaxants but also other therapeutic drugs blocking relevant receptors, pharmacodynamics might be affected by affinity for receptor and also by receptor density when receptors densely locate in the action sites.

References

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