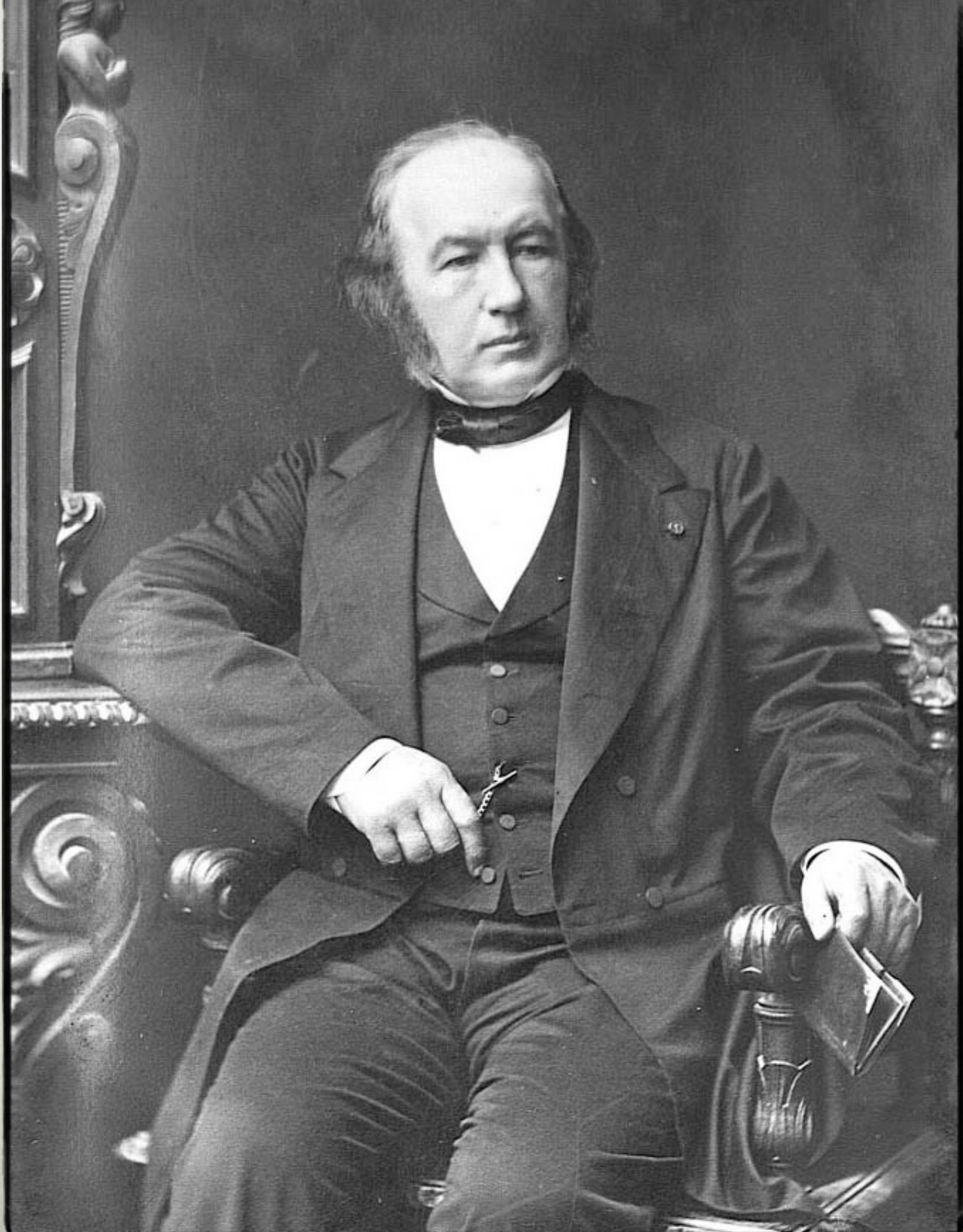
Conceitos básicos de Farmacodinâmica

Prof. Dr. Fernando Silva Carneiro

Claude Bernard
1813-1878



Claude Bernard
1813-1878

Curare

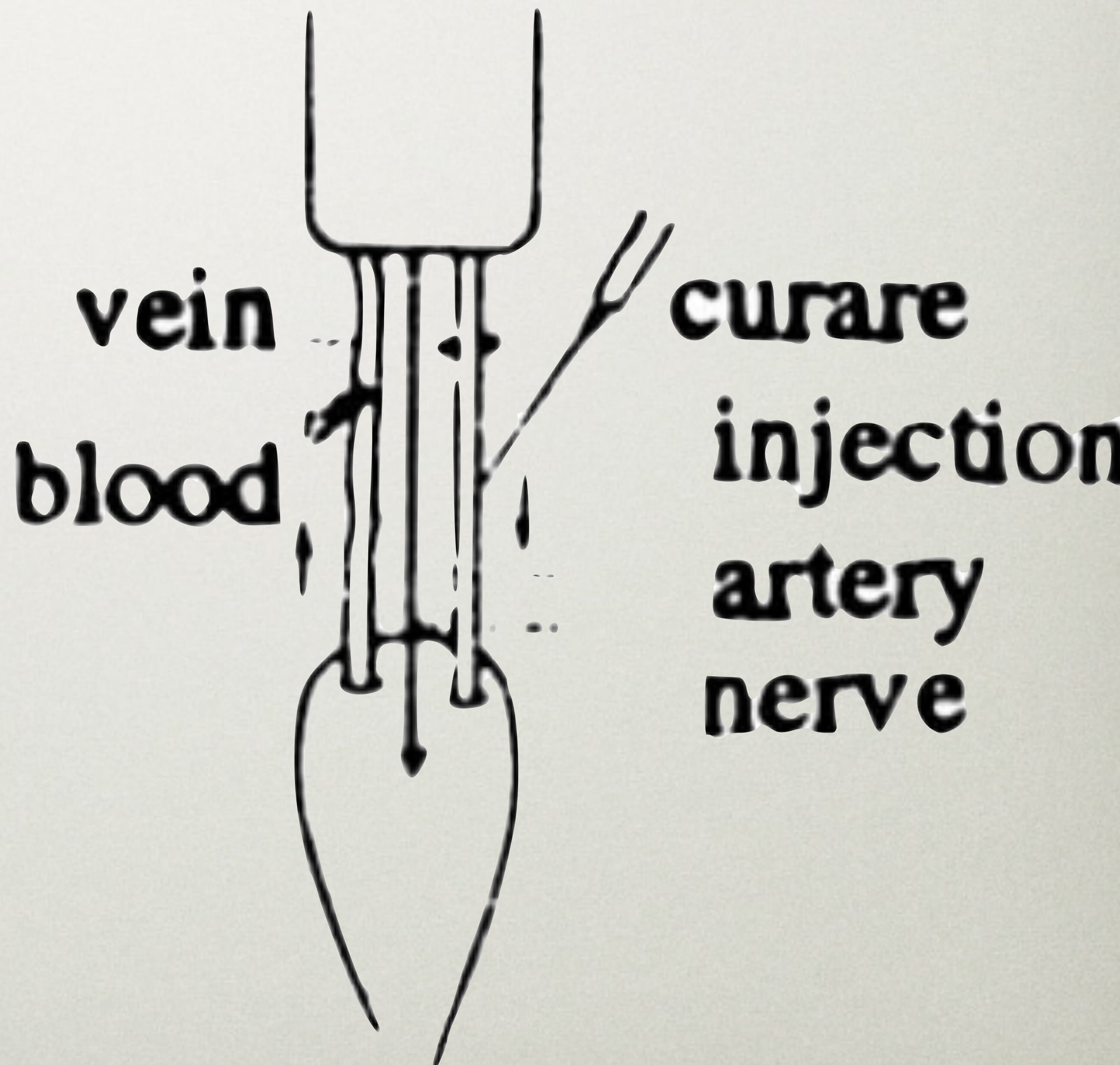
"A poisoned arrow obtained from a friend who had connections with South American natives was thrust into the subcutaneous tissue of a rabbit at the internal part of the thigh and maintained there for 30 seconds. The animal was then observed. At first, nothing happened. But after six minutes it became totally paralysed: no reflex movements were observed on pinching the rabbit, although the heart continued to beat."

Junho 1844

Bernard, C., 1883. Lecons sur les Effets des Substances Toxiques et Medicamenteuses. Bailliere, Paris.

“Curare does no more than interrupt something motor which puts the nerve and the muscle into electrical relationship for movement”..................

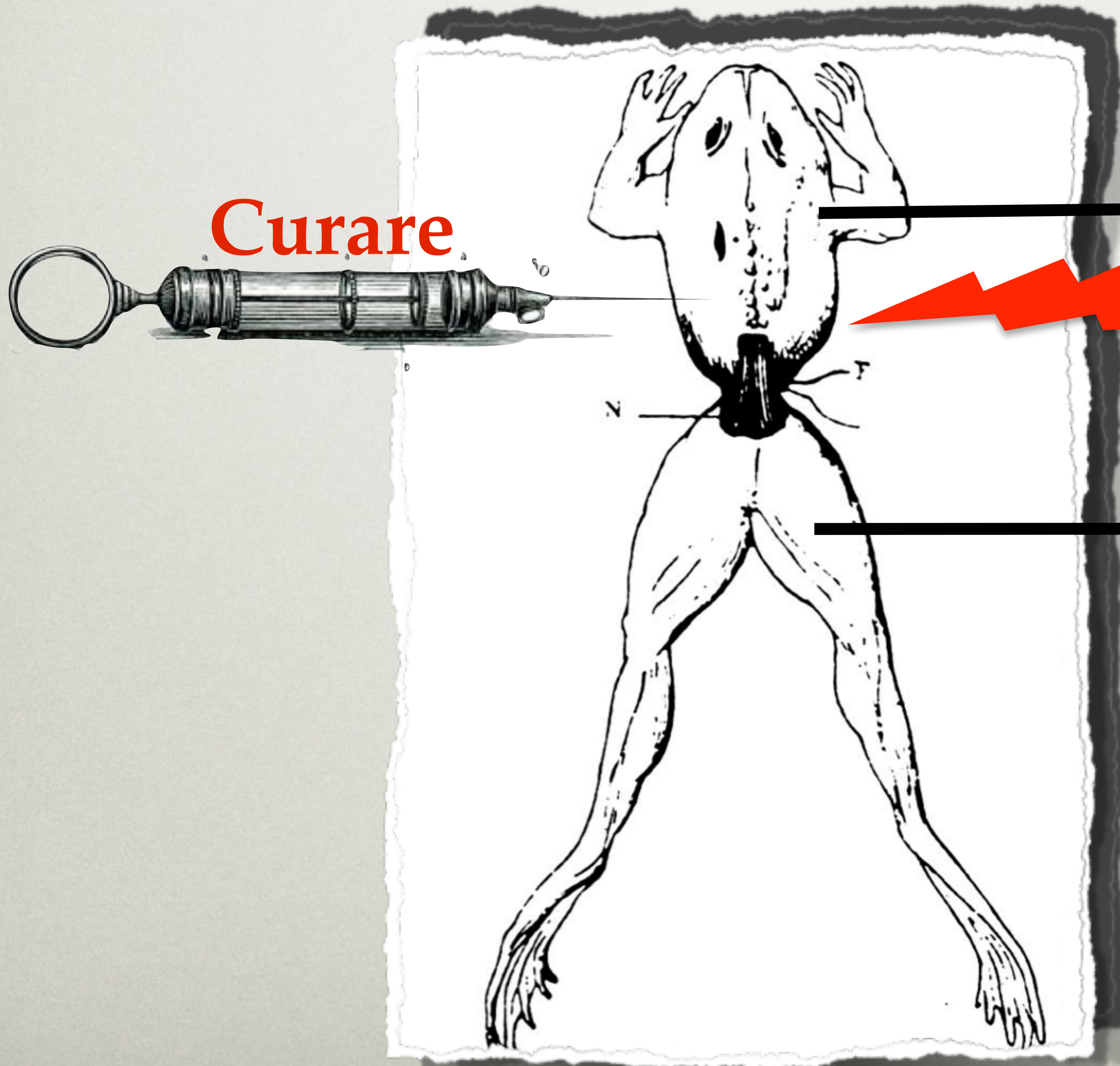
Claude Bernard



Bernard, C., 1883. Lecons sur les Effets des Substances Toxiques et Medicamenteuses. Bailliere, Paris.

“Curare afeta nervos motores, mas não os sensoriais”

Claude Bernard



Paralisia

Estímulos dolorosos

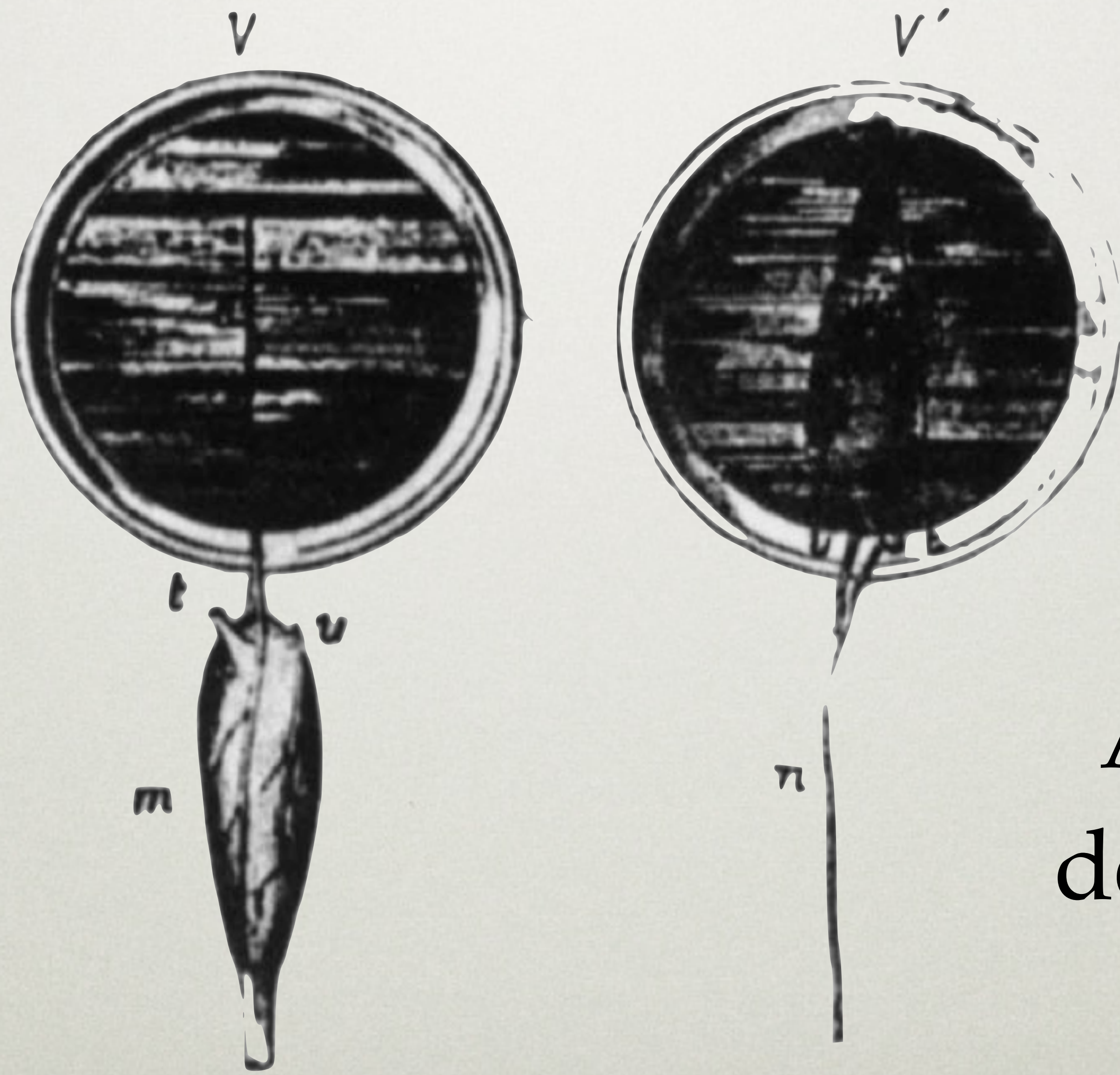
Resposta a estímulos dolorosos

Bernard, C., 1883. Lecons sur les Effets des Substances Toxiques et Medicamenteuses. Bailliere, Paris.

“Curare must act on the terminal plates of motor nerves”.........

Claude Bernard

Curare



Resposta

Ausência de resposta

Bernard, C., 1883. Lecons sur les Effets des Substances Toxiques et Medicamenteuses. Bailliere, Paris.

Antagonismo mútuo entre pilocarpina e atropina

Ano 1878

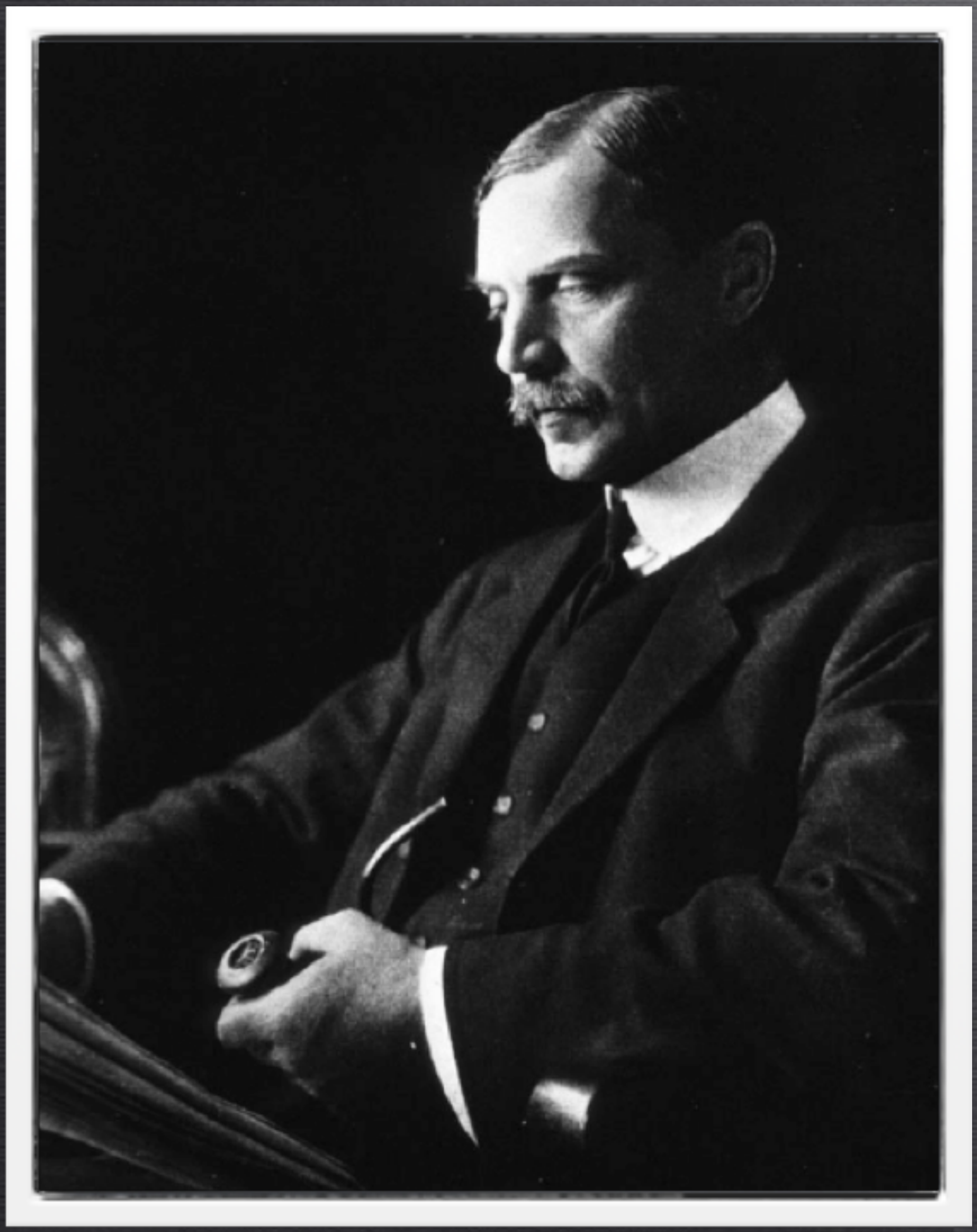
"I think, without much rashness, assume that there is some substance or substances in the nerve endings or gland cells with which both atropin and pilocarpin are capable of forming compounds. On this assumption then the atropin or pilocarpin compounds are formed according to some law of which their relative mass and chemical affinity for the substance are factors."

Langley, JN. On the physiology of salivary secretion. Part II. On the mutual antagonism of atropin and pilocarpin, having especial reference to their relations in the sub-maxillary gland of the cat. *J. Physiol. (Lond) 1, 339-369 (1878).*

Max Lewandowsky
1876-1916

"In 1899 Lewandowsky observed that supra-renal extract in cats causes dilation of the pupil, withdrawal of the nictitating membrane, separation of the eyelids and protrusion of the eyeball. Lewandowsky suggested that the extract acted directly on the smooth muscle and not on the nerve endings in the muscle as he obtained the same results with the extract after excision of the superior cervical ganglion and degeneration of the postganglionic nerves as in the normal animal."

Lewandowsky, M., 1899. Ueber die wirkung des Nebennierenextractes auf die glatten Muskeln, in Besonderen des Auges. Archiv fur Anatomie und Physiologie, 360–366.



"It is equally noteworthy that the effects produced by supra-renal extract are almost all such as are produced by stimulation of some one or other sympathetic nerve. In many cases the effects produced by the extract and by electrical stimulation of the sympathetic nerve correspond exactly."

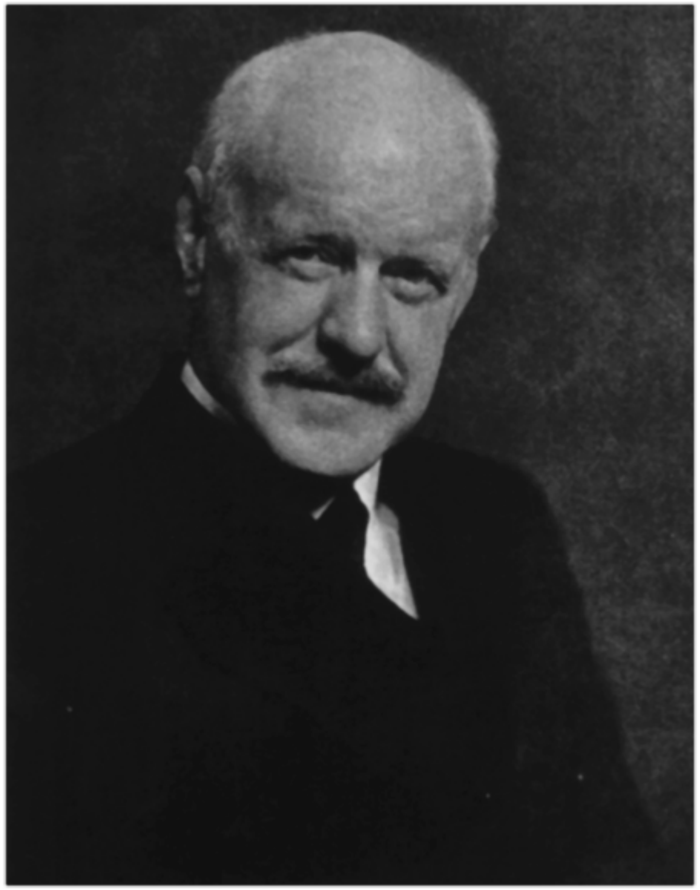
J.N. Langley
1852-1925

Langley, J.N., 1901. Observations on the physiological action of extracts of the supra-renal bodies. Journal of Physiology XXVII, 237–256.

Jokichi Takamine
1854-1922

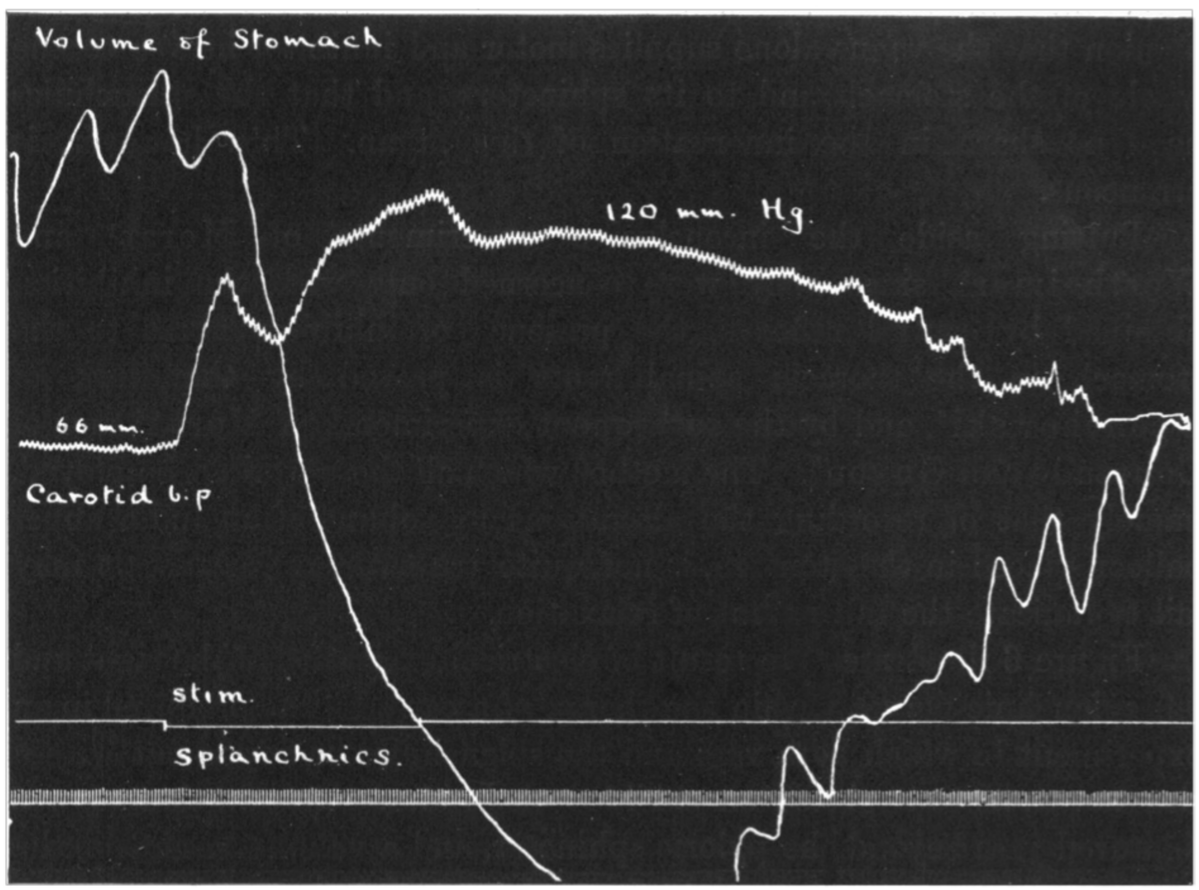
Isola o princípio ativo da glândula supra-renal e nomeia de: "Adrenalina"

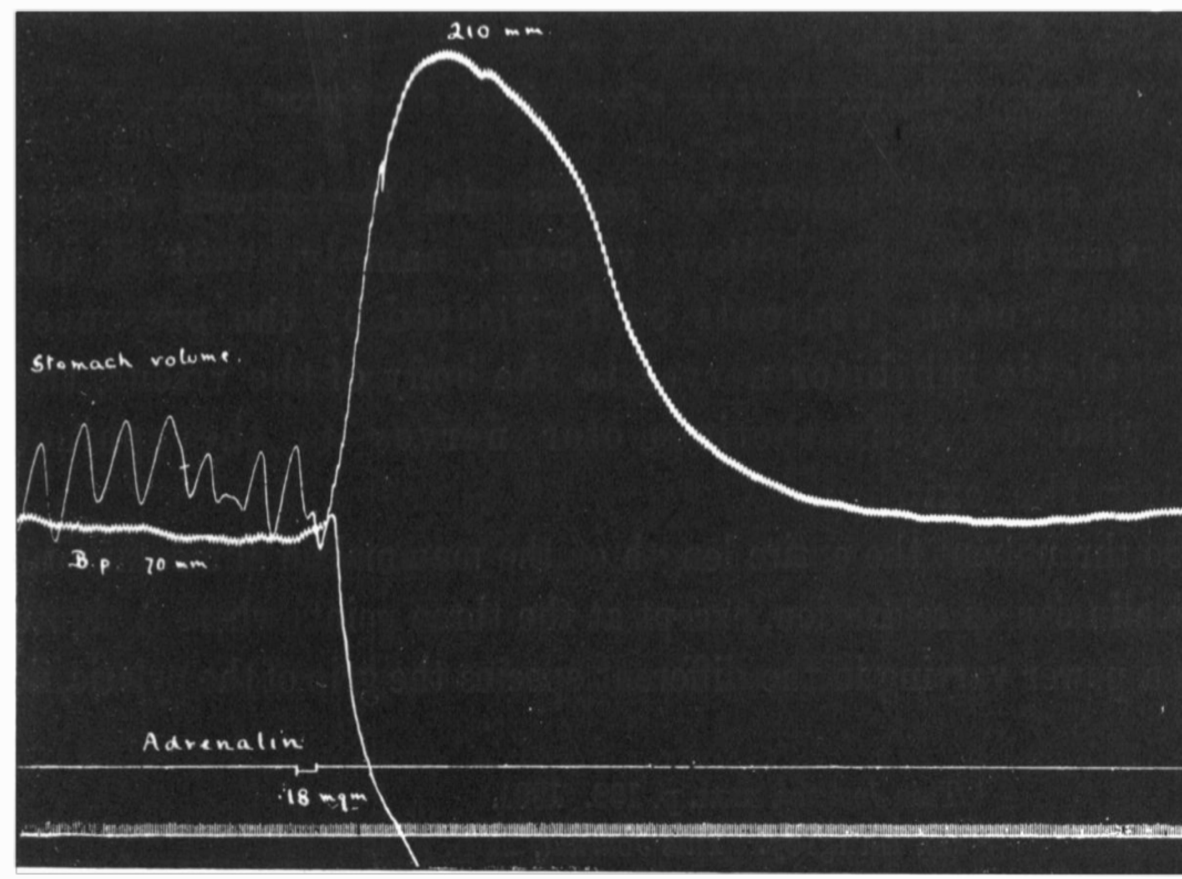
Takamine, J., 1901. The isolation of the active principle of the supra-renal gland. Journal of Physiology XXVII, xxix–xxx.



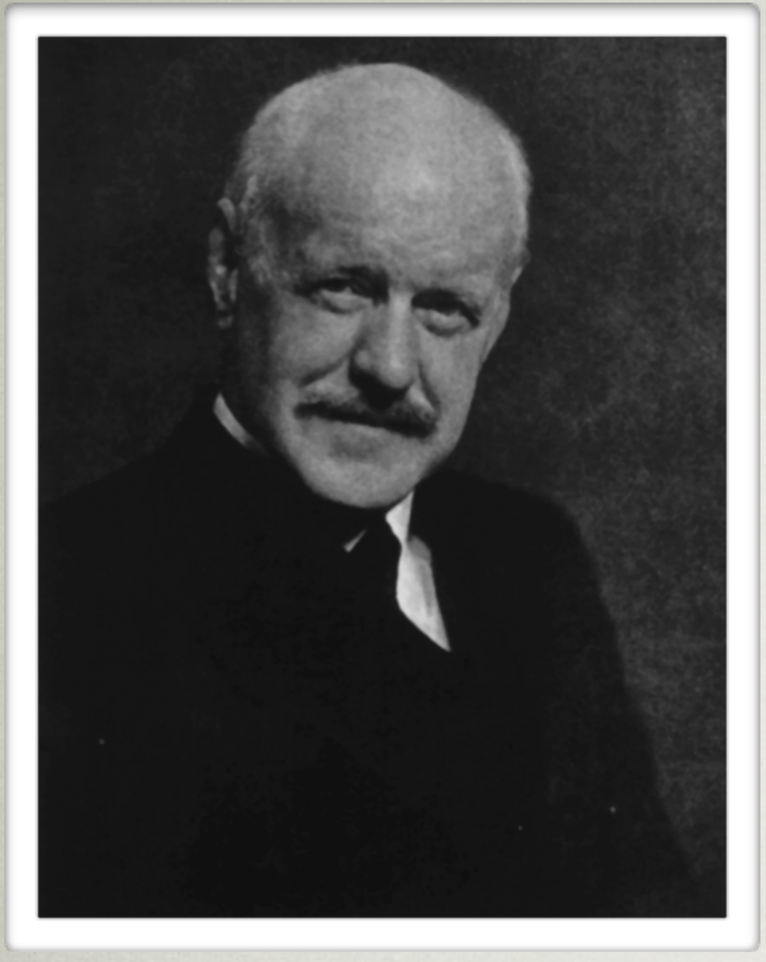
Thomas Renton Elliott
1877-1961

"In all vertebrates the reaction of any plain muscle to adrenalin is of similar character to that following excitation of the sympathetic (thoracico-lumbar) visceral nerves supplying that muscle."





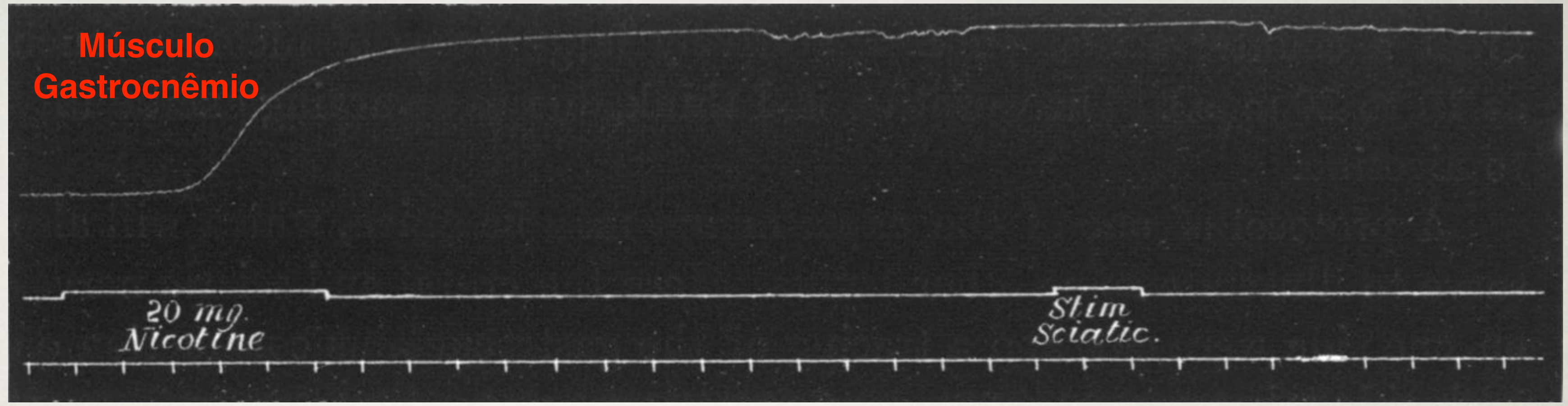
Elliott, T.R., 1905. The action of adrenaline. Journal of Physiology XXXII, 401–467

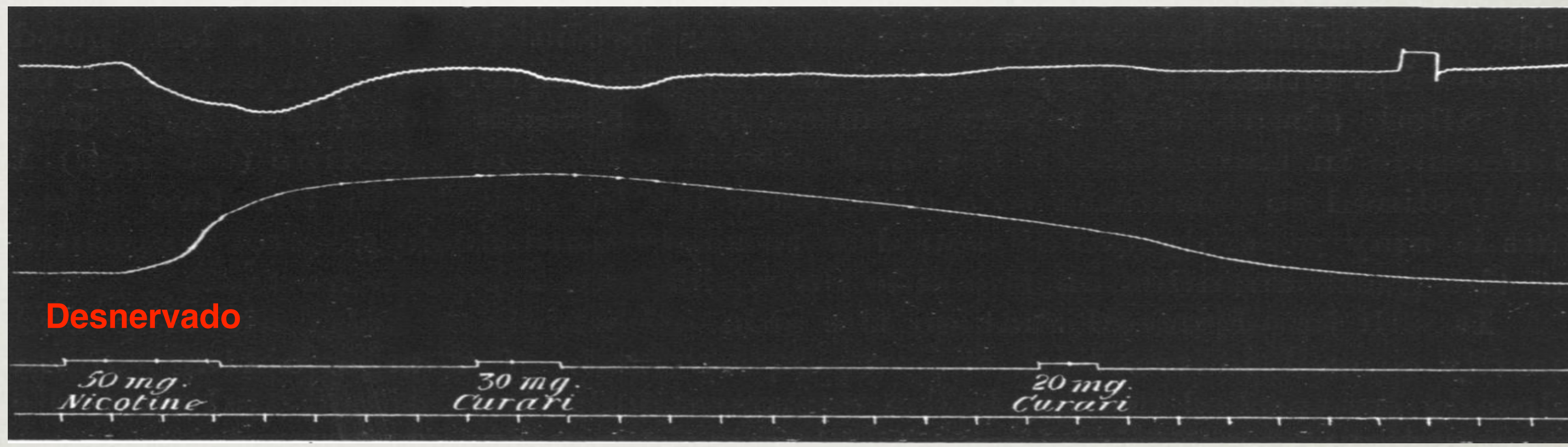


Thomas Renton Elliott
1877-1961

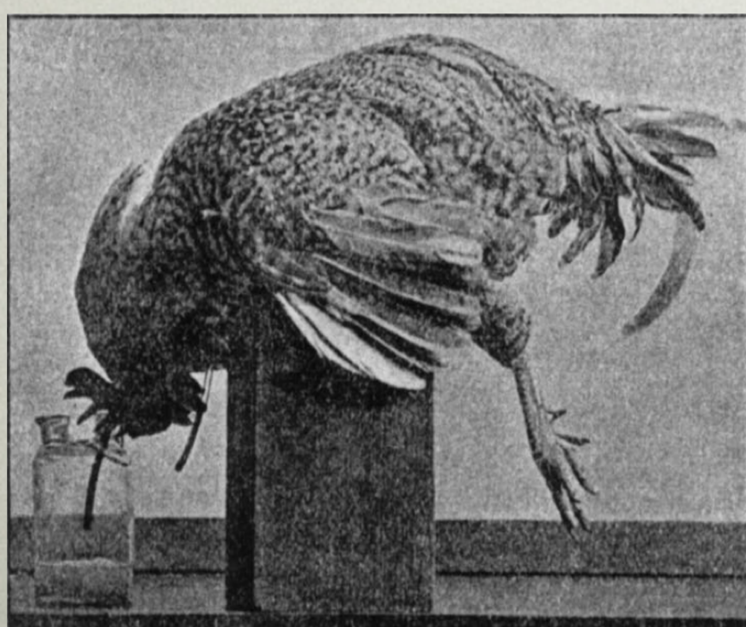
"But since adrenalin does not evoke any reaction from muscle that has at no time of its life been innervated by the sympathetic, the point at which the stimulus of the chemical excitant is received, and transformed into what may cause the change of tension of the muscle fibre, is perhaps a mechanism developed out of the muscle cell in response to its union with the synapsing sympathetic fibre, the function of which is to receive and transform the nervous impulse. Adrenalin might then be the chemical stimulant liberated on each occasion when the impulse arrives at the periphery."

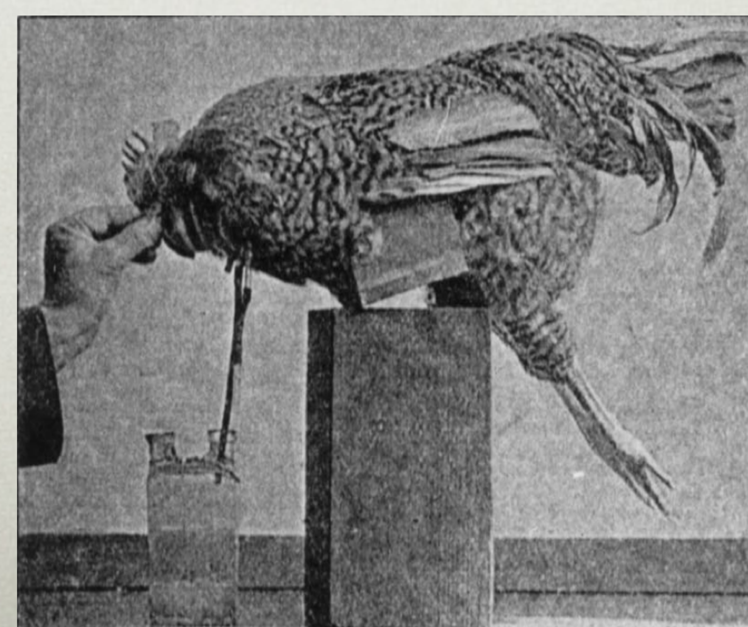
Elliott, T.R., 1904. On the action of adrenaline. Journal of Physiology XXXI, xx–xxi.





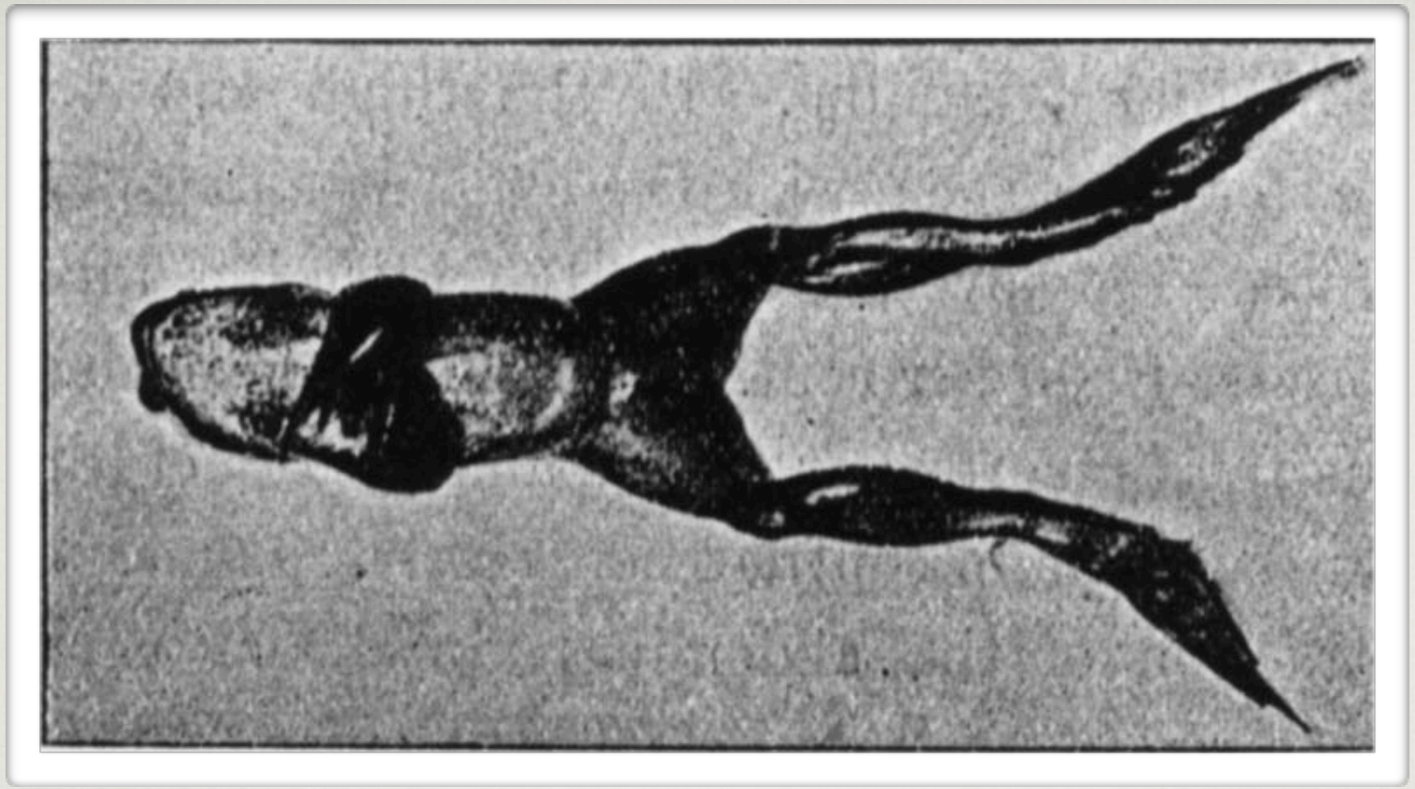
Langley, J.N., 1905. On the reaction of cells and of nerve endings to certain poisons, chiefly as regards the reaction of striated muscle to nicotine and to curari. Journal of Physiology XXXIII, 374–413.

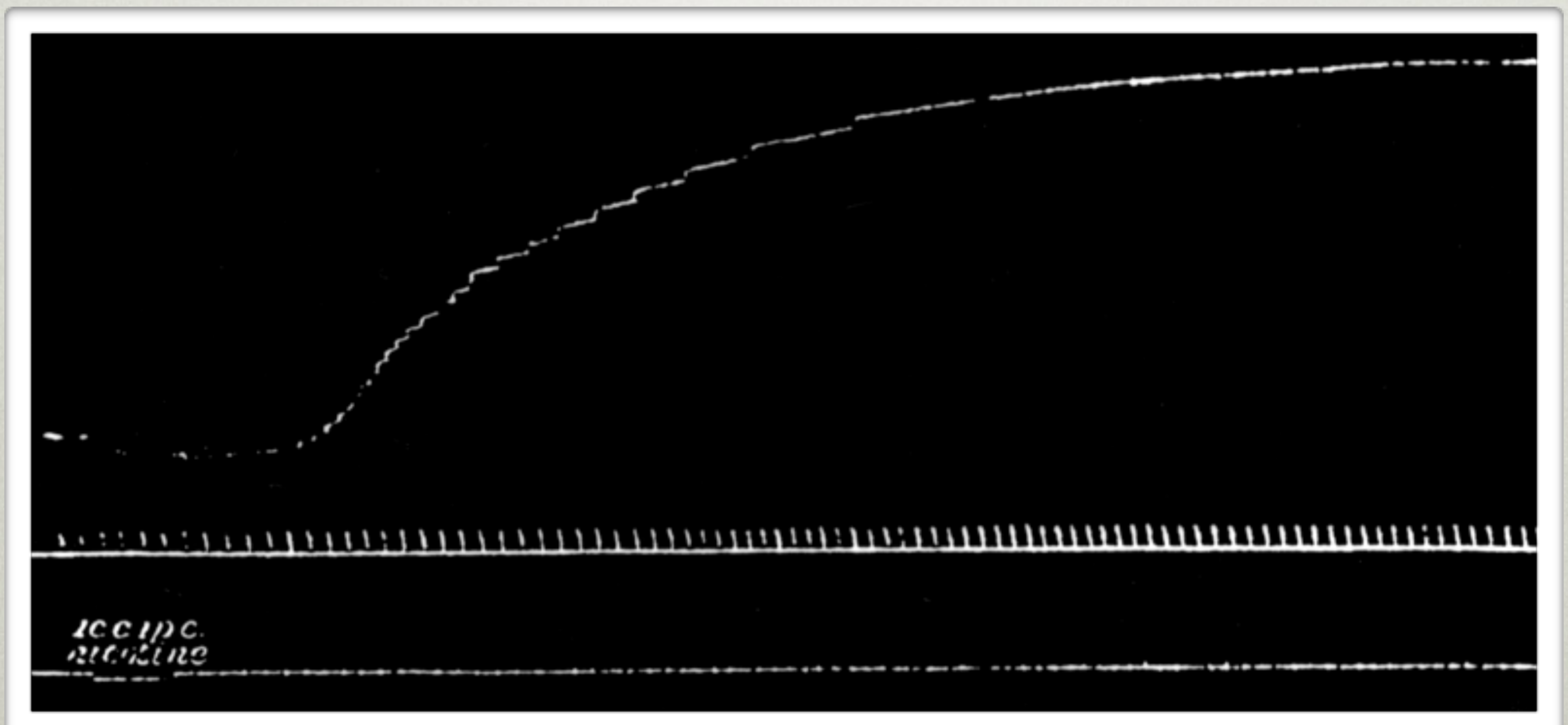




Langley, J.N., 1906. On nerve endings and on special excitable substances in cells. Proceedings of the Royal Society of London B. LXXVIII, 170–194.

Animal decerebrado





Langley, J.N., 1906. On nerve endings and on special excitable substances in cells. Proceedings of the Royal Society of London B. LXXVIII, 170–194.

Conclusões do Langley

“**I conclude then that nicotine acts upon the muscle substance, and not upon the axon-endings…**

…both nicotine and curari abolish the effect of nerve stimulation, but do not prevent contraction from being obtained by **direct stimulation of the muscle…**

…it may be inferred that **neither the poisons nor the nervous impulse act directly on the contractile substance of the muscle** but on **some accessory substance.**

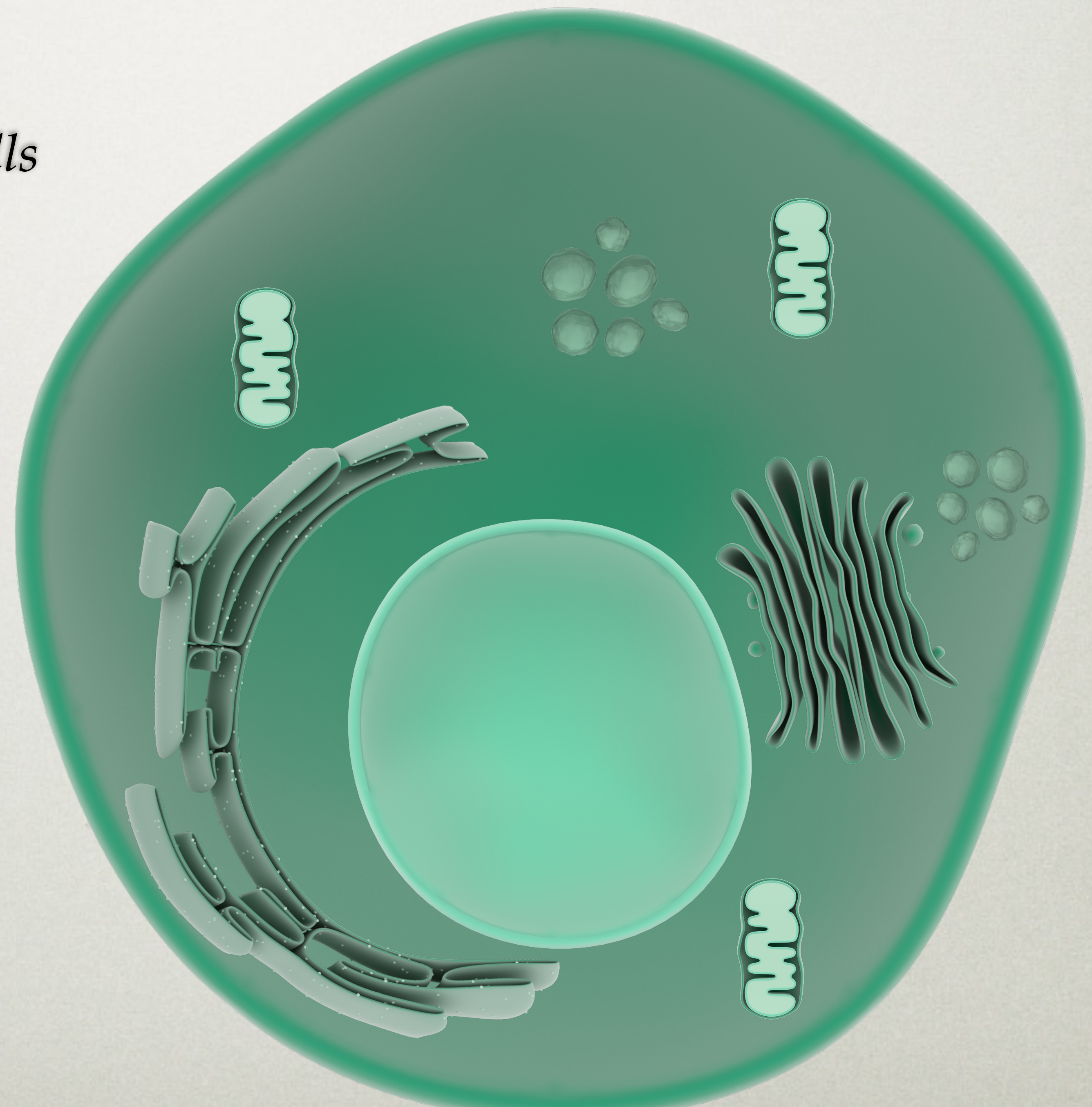
Since this accessory substance is the recipient of stimuli which it transfers to the contractile material, we may speak of it as the **receptive substance** of the muscle.”

Langley, J.N., 1906. On nerve endings and on special excitable substances in cells. Proceedings of the Royal Society of London B. LXXVIII, 170–194.

Superfície celular vs diâmetro molecular

Alfred J. Clark

1933 - *The Mode of action of drugs on cells*



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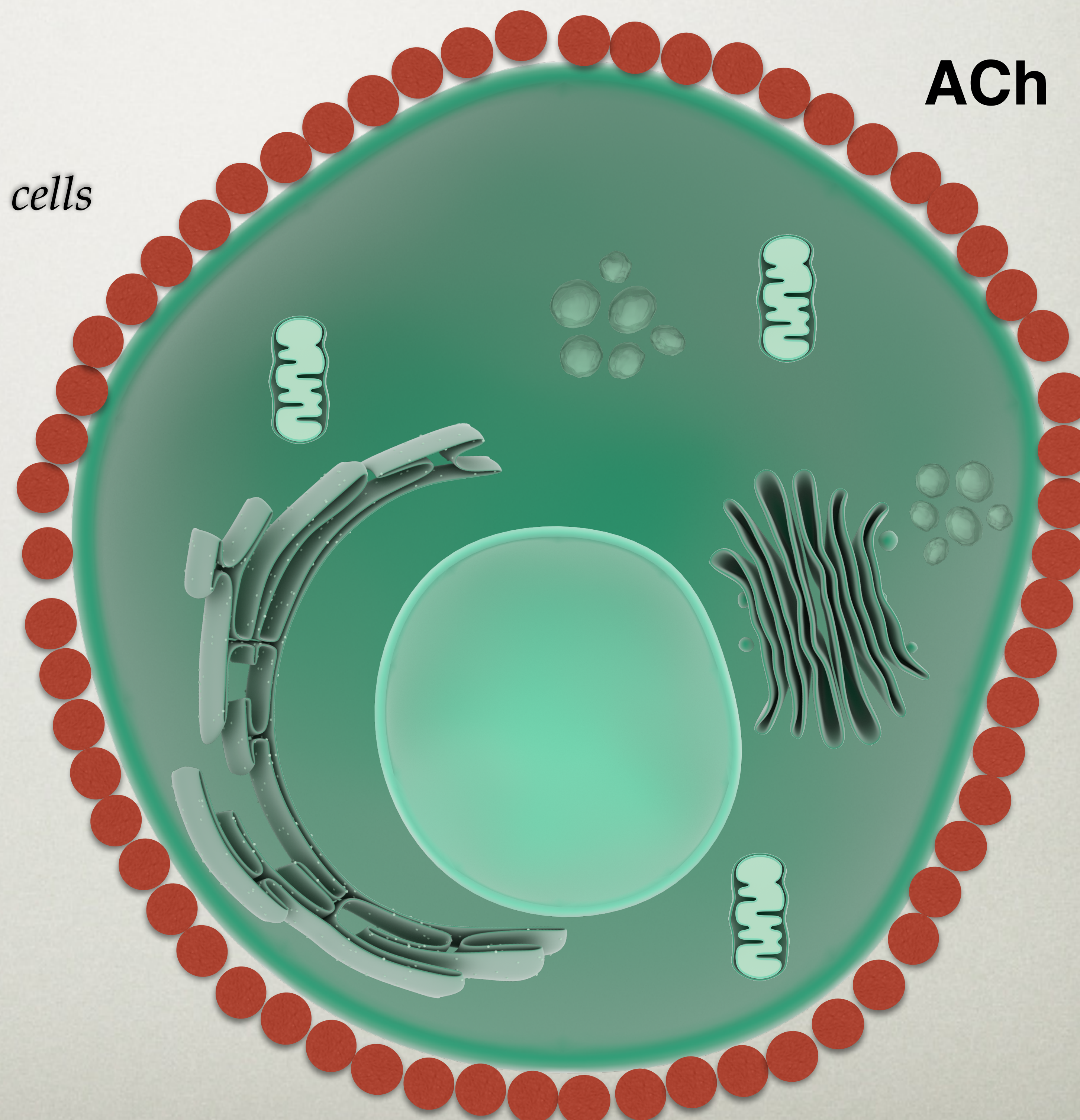
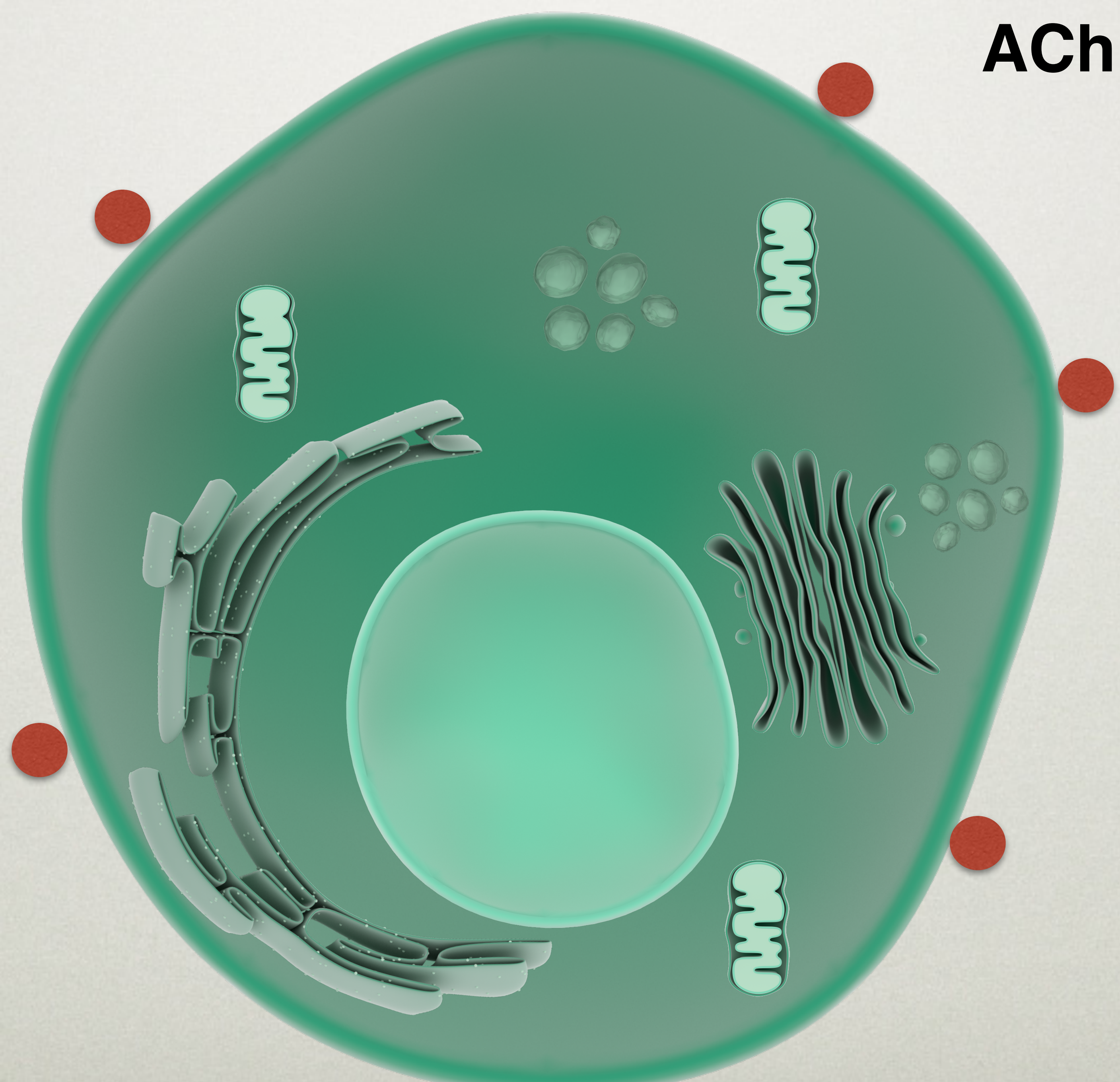
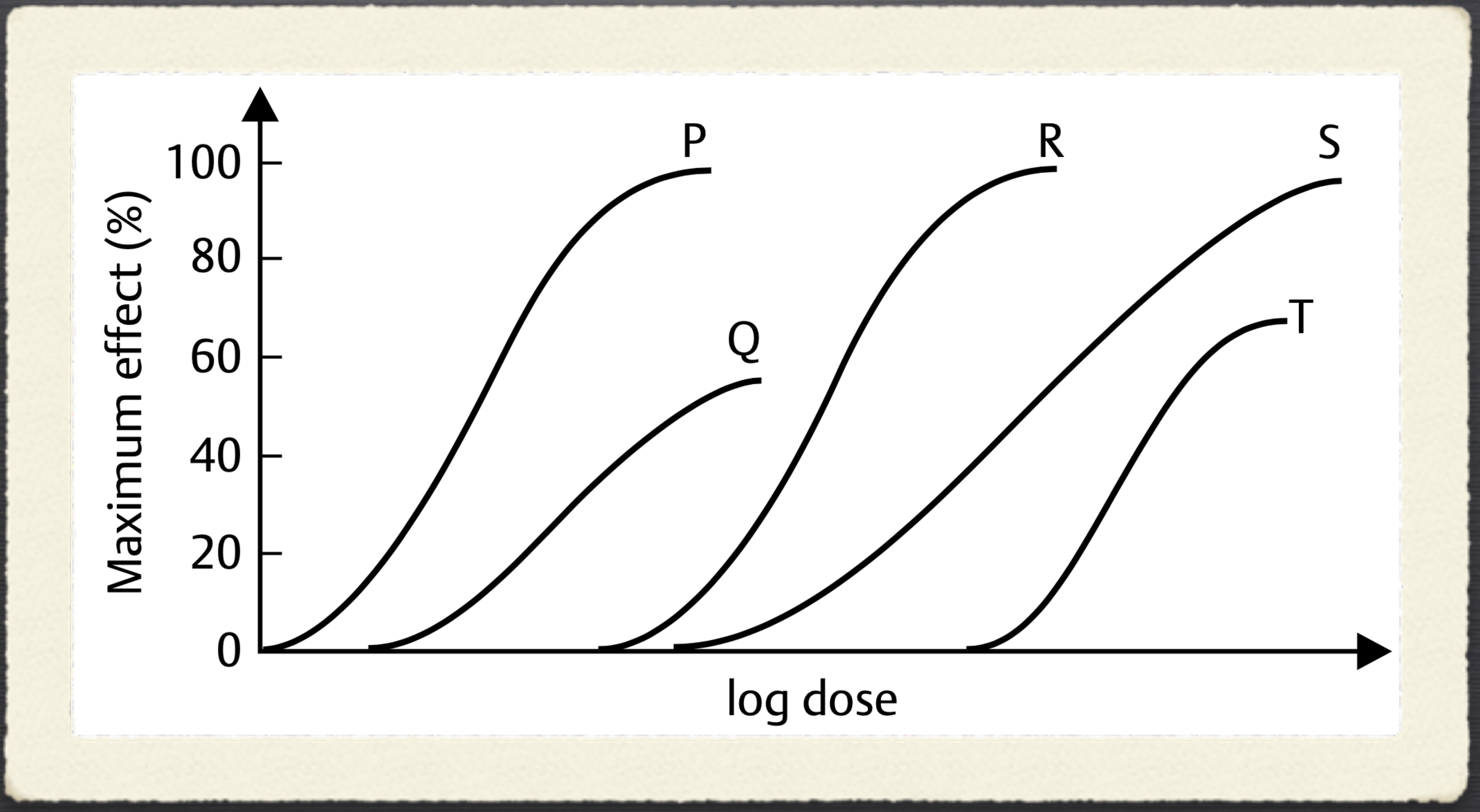


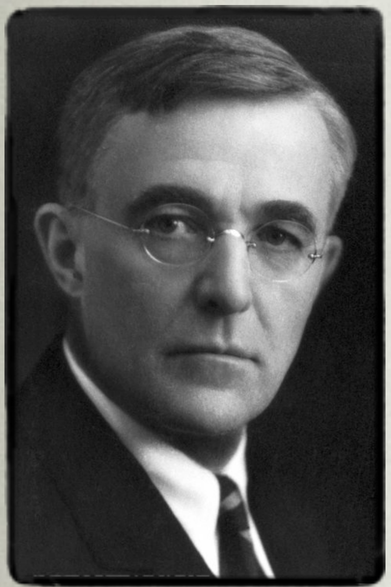
Superfície celular vs diâmetro molecular



Vamos Graficar?



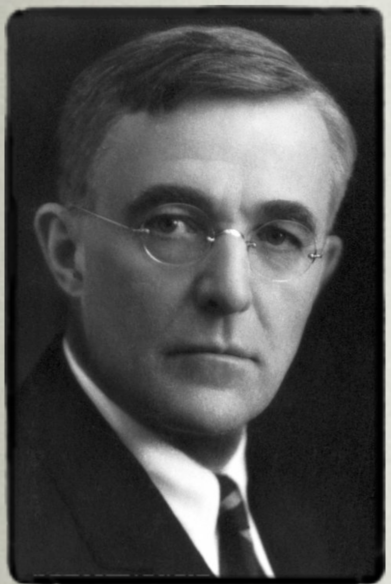
Isoterma de adsorção de Lagmuir



Irving Langmuir
(1881-1957)

Adsorção de gases às superfícies metálicas

Isoterma de adsorção de Lagmuir



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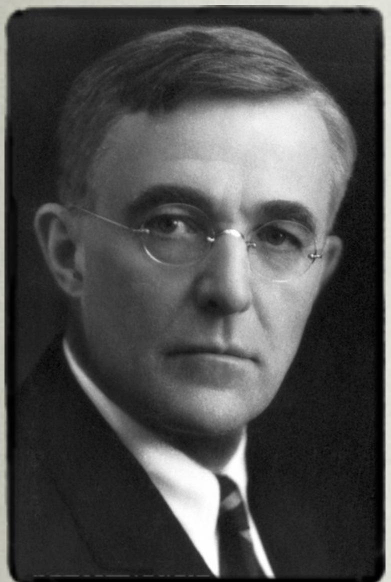

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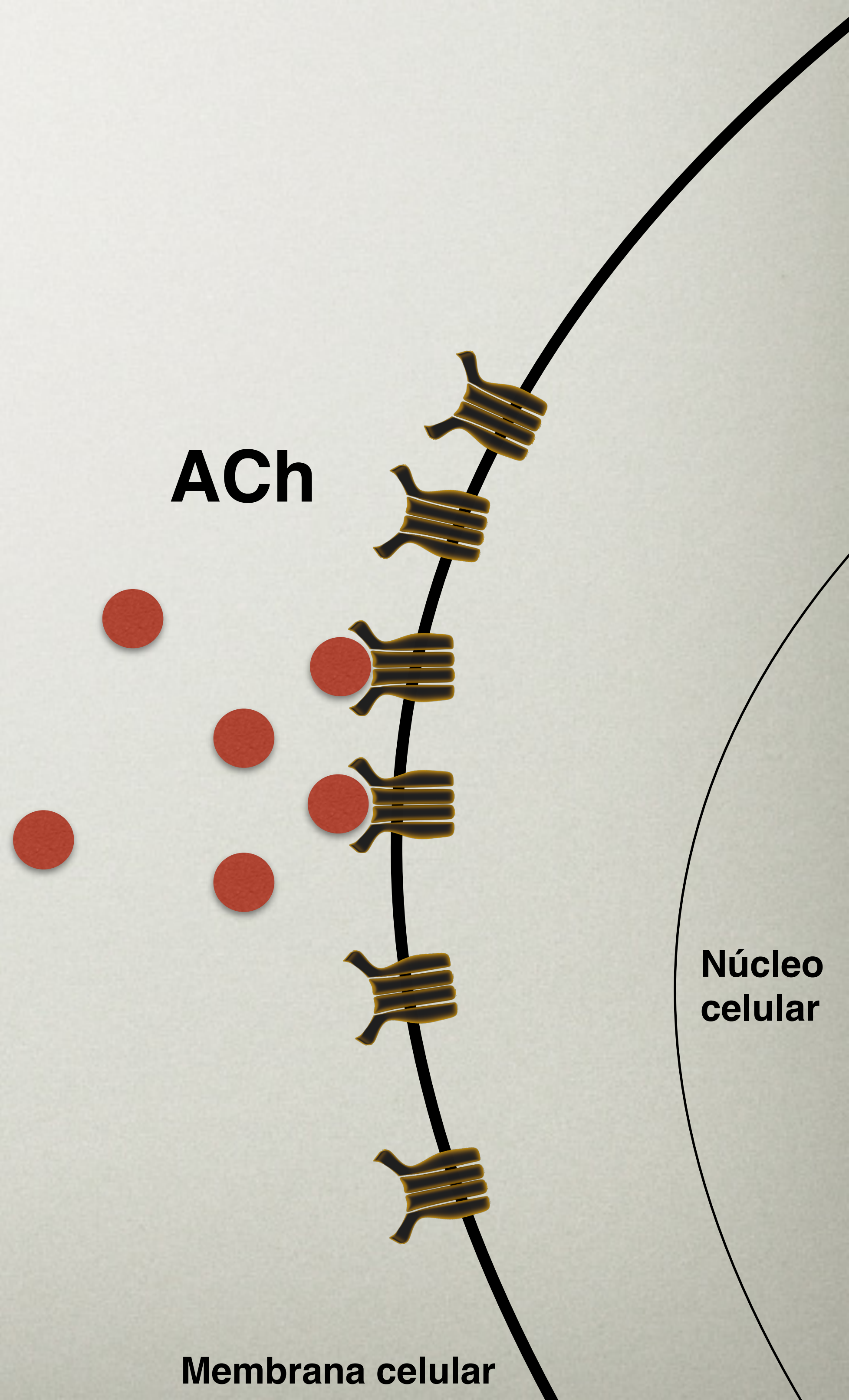

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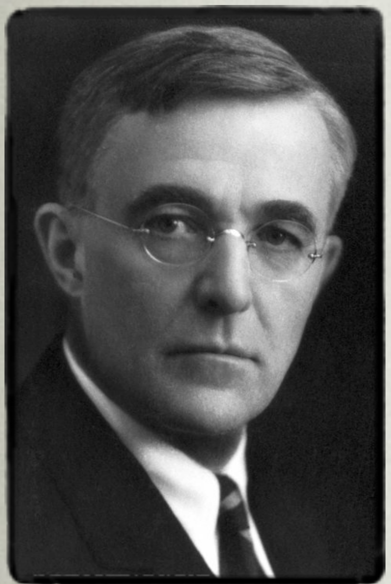

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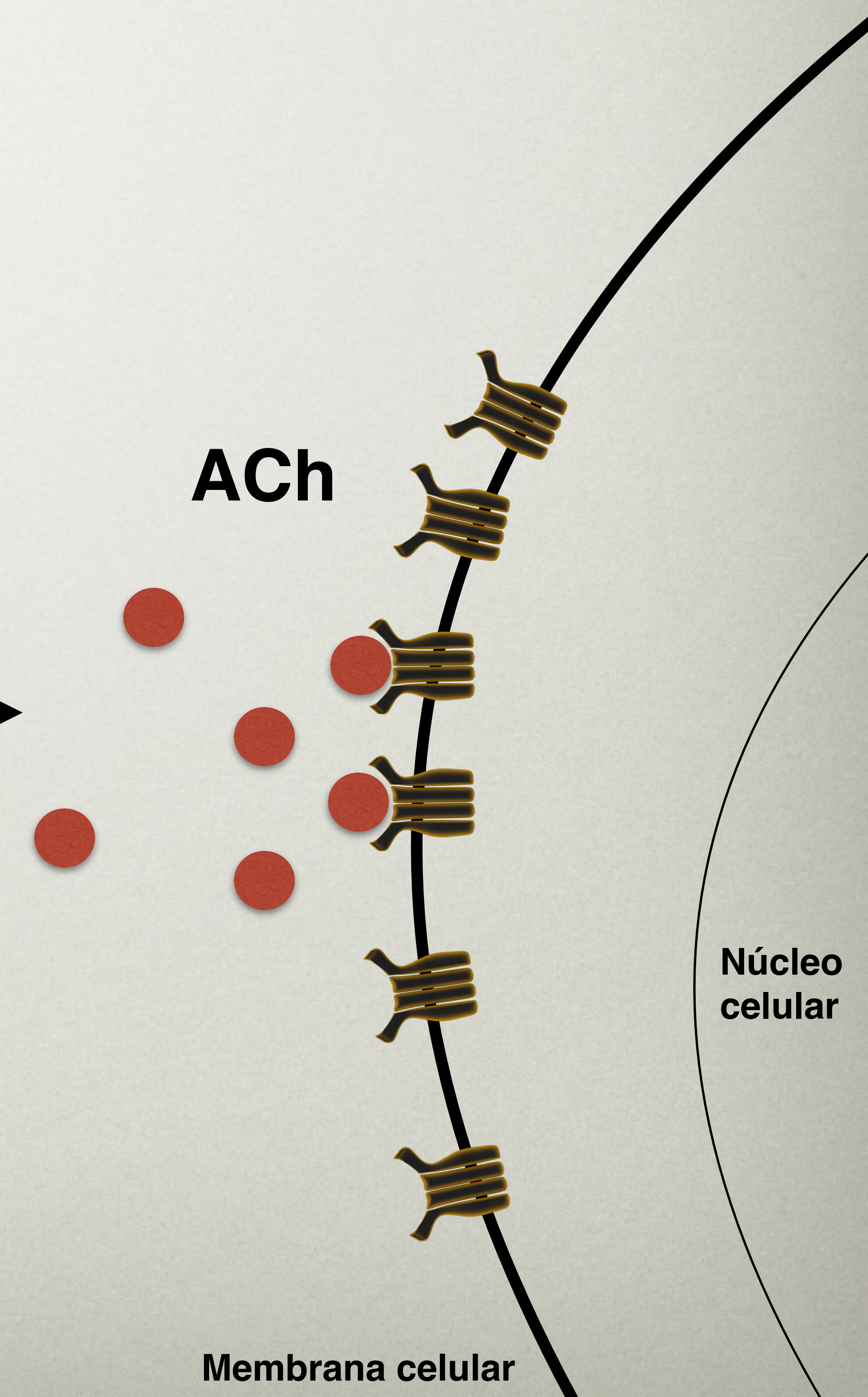
Quais fatores determinam a associação do fármaco com a "superfície" ?????????



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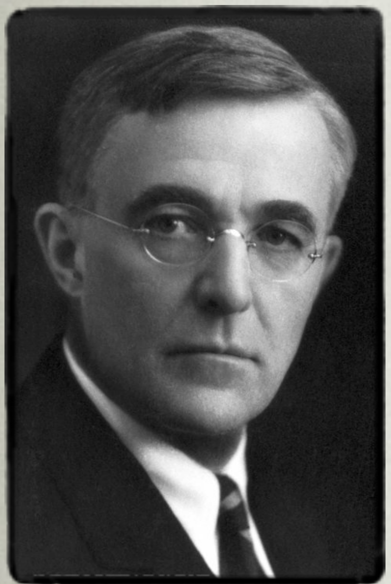

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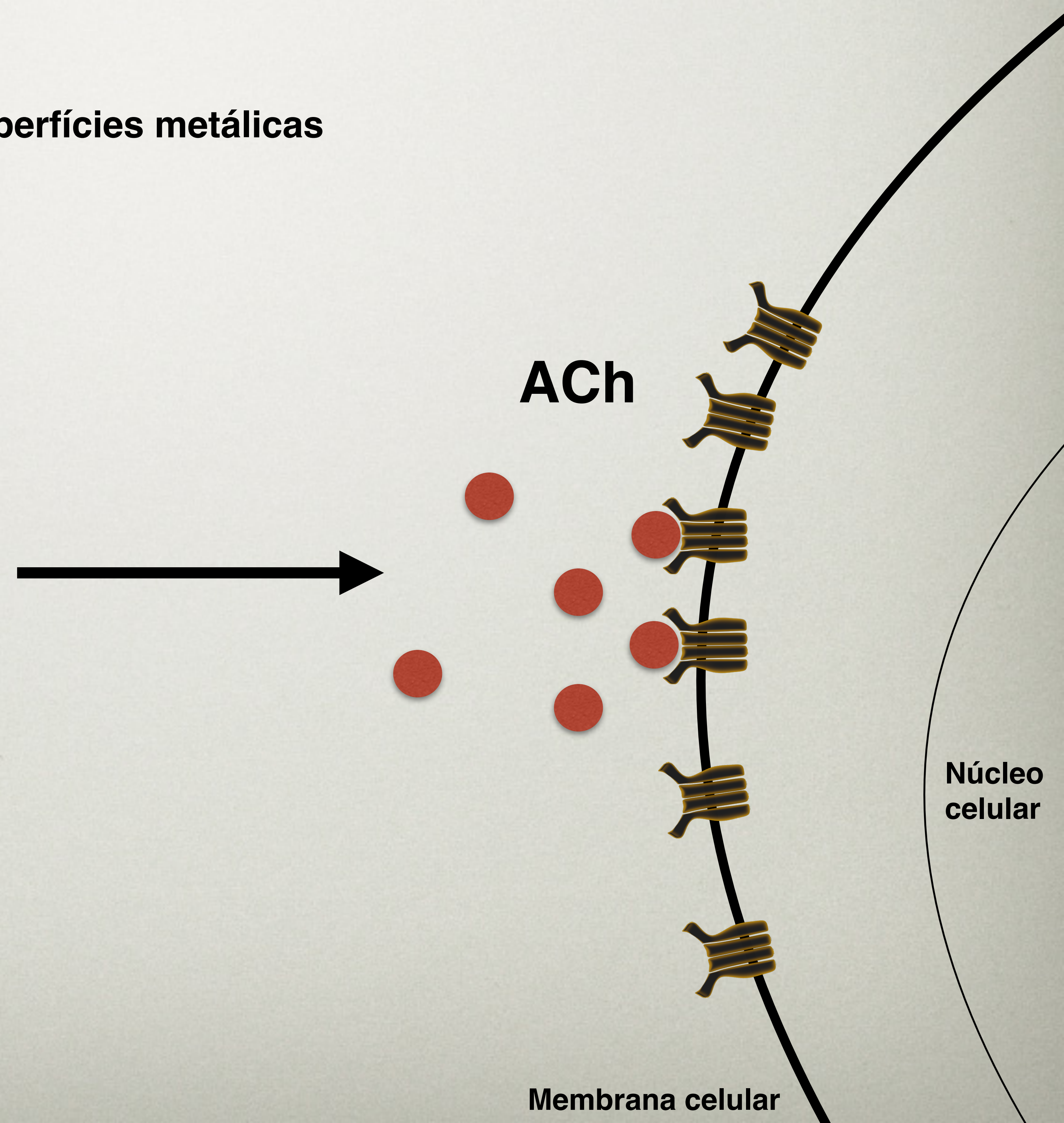
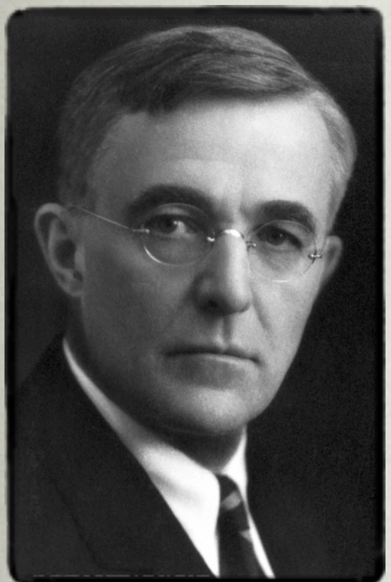


Associação=

Isoterma de adsorção de Lagmuir



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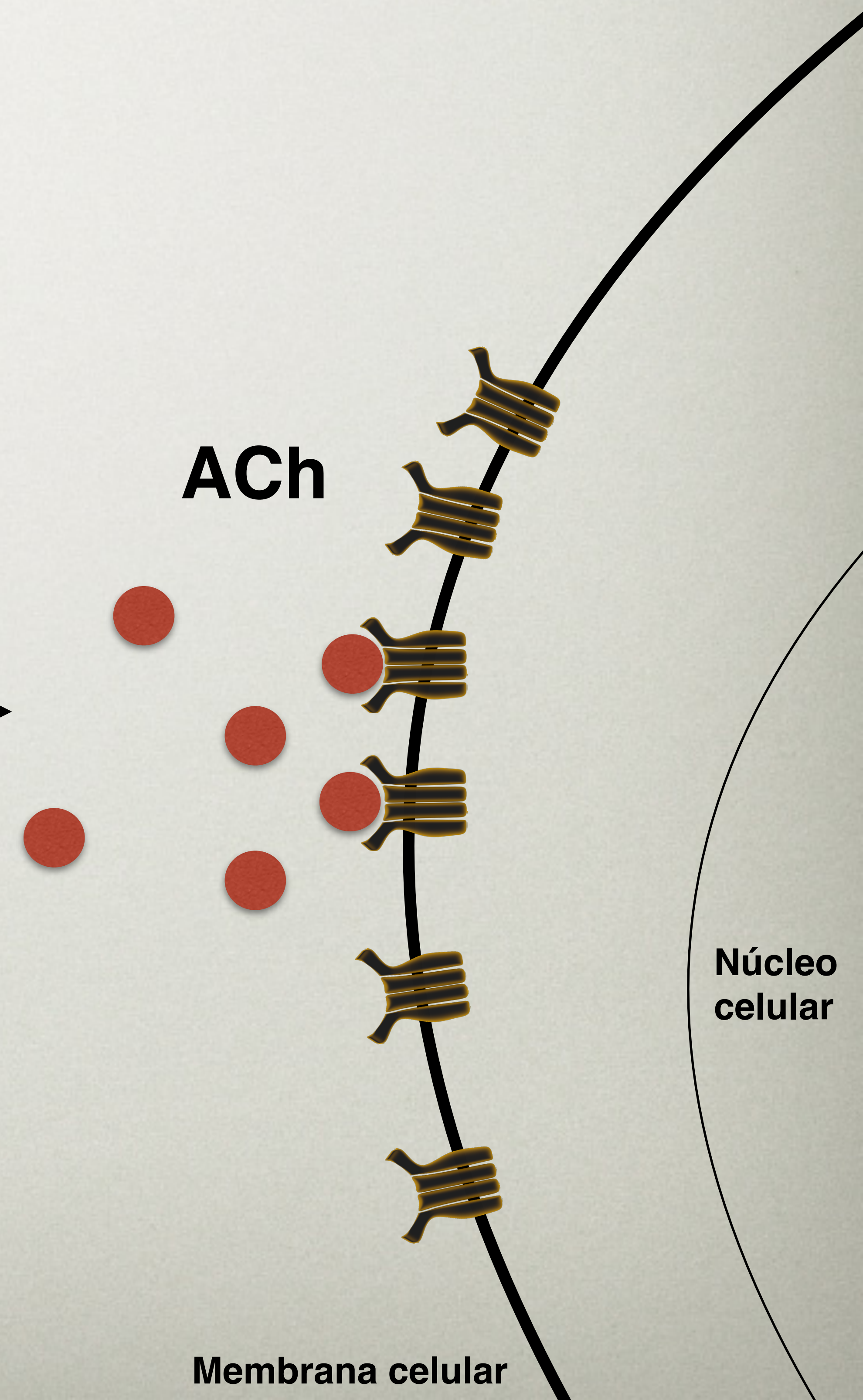
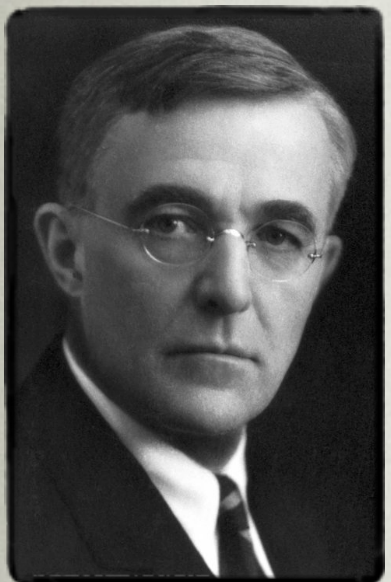


Associação= K_1.[A].[R]

Isoterma de adsorção de Lagmuir



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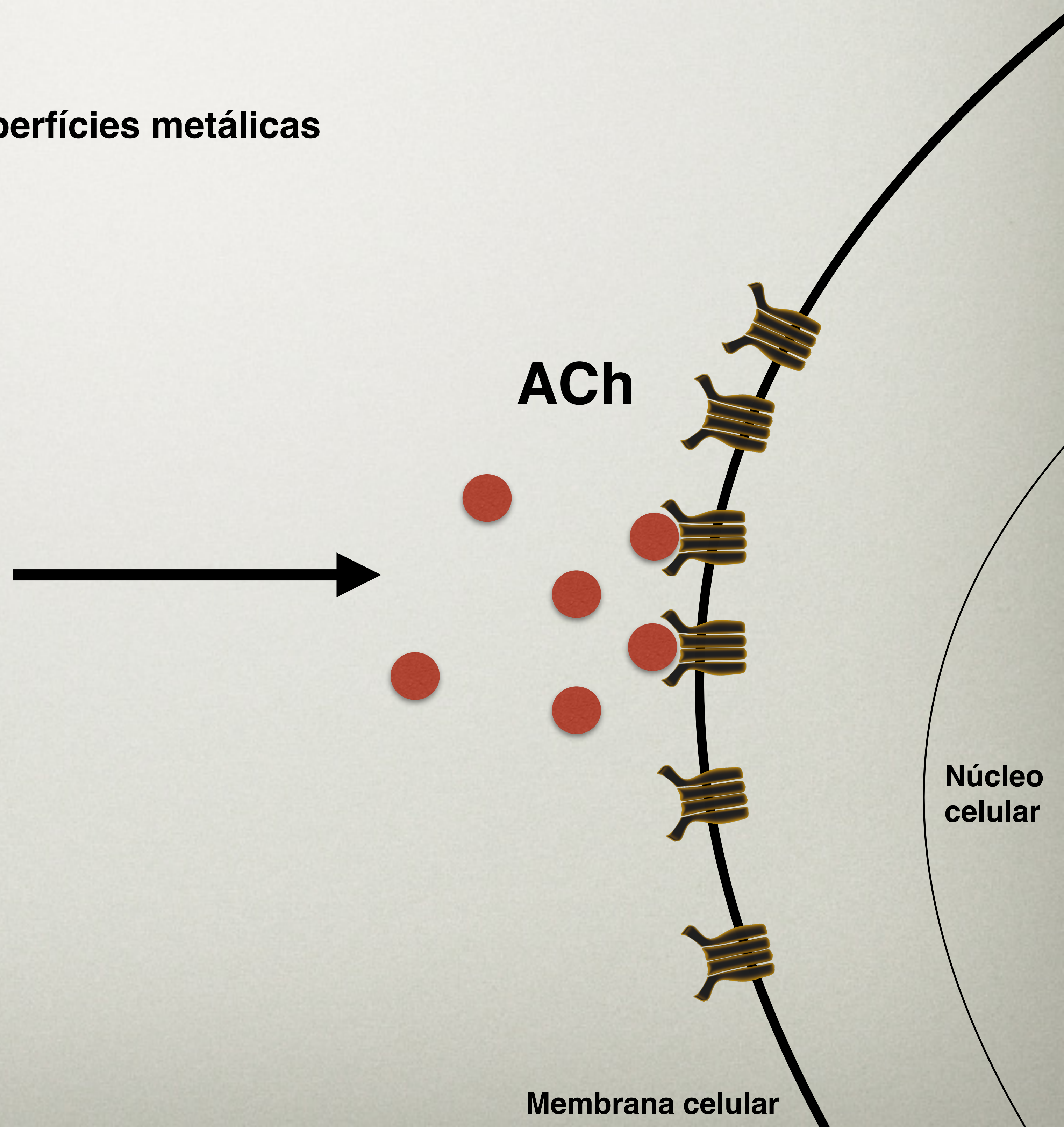
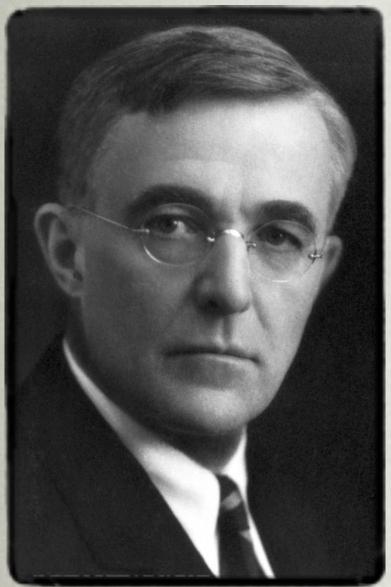


Associação= K_1.[A].[R]

Dissociação=

Isoterma de adsorção de Lagmuir



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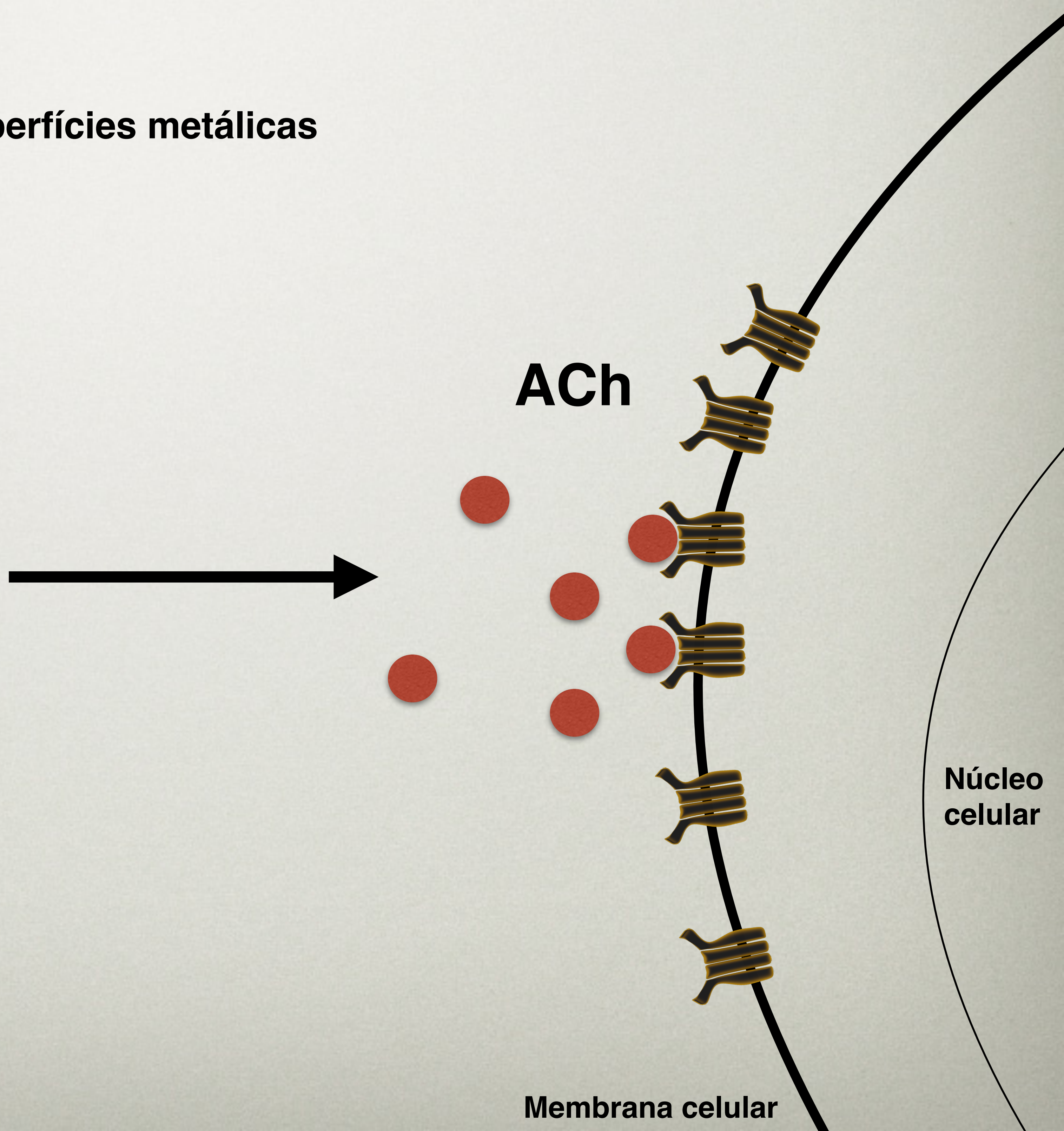
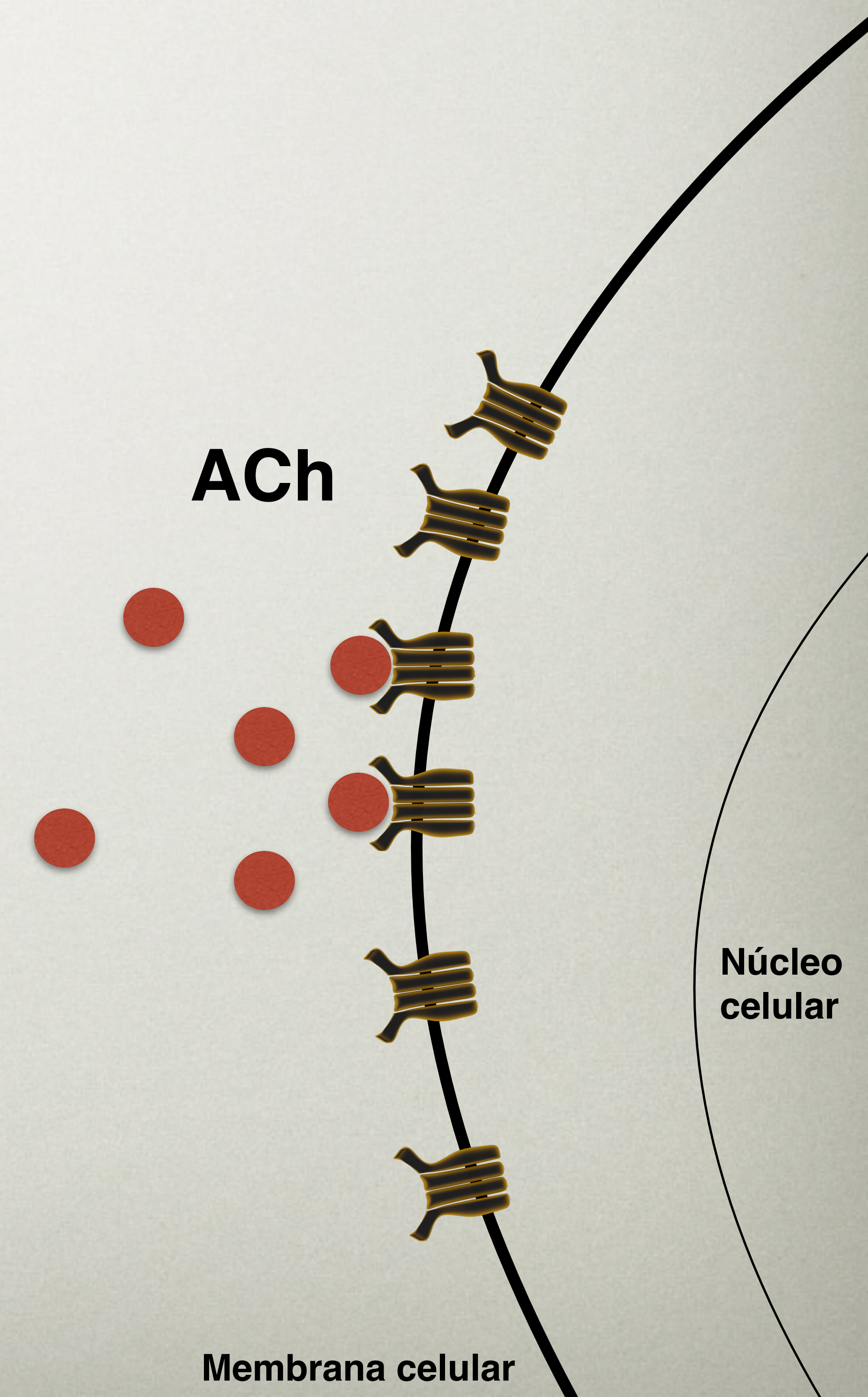


Associação= $K_1.[A].[R]$

Dissociação= $K_2.[AR]$

Equilíbrio químico dinâmico

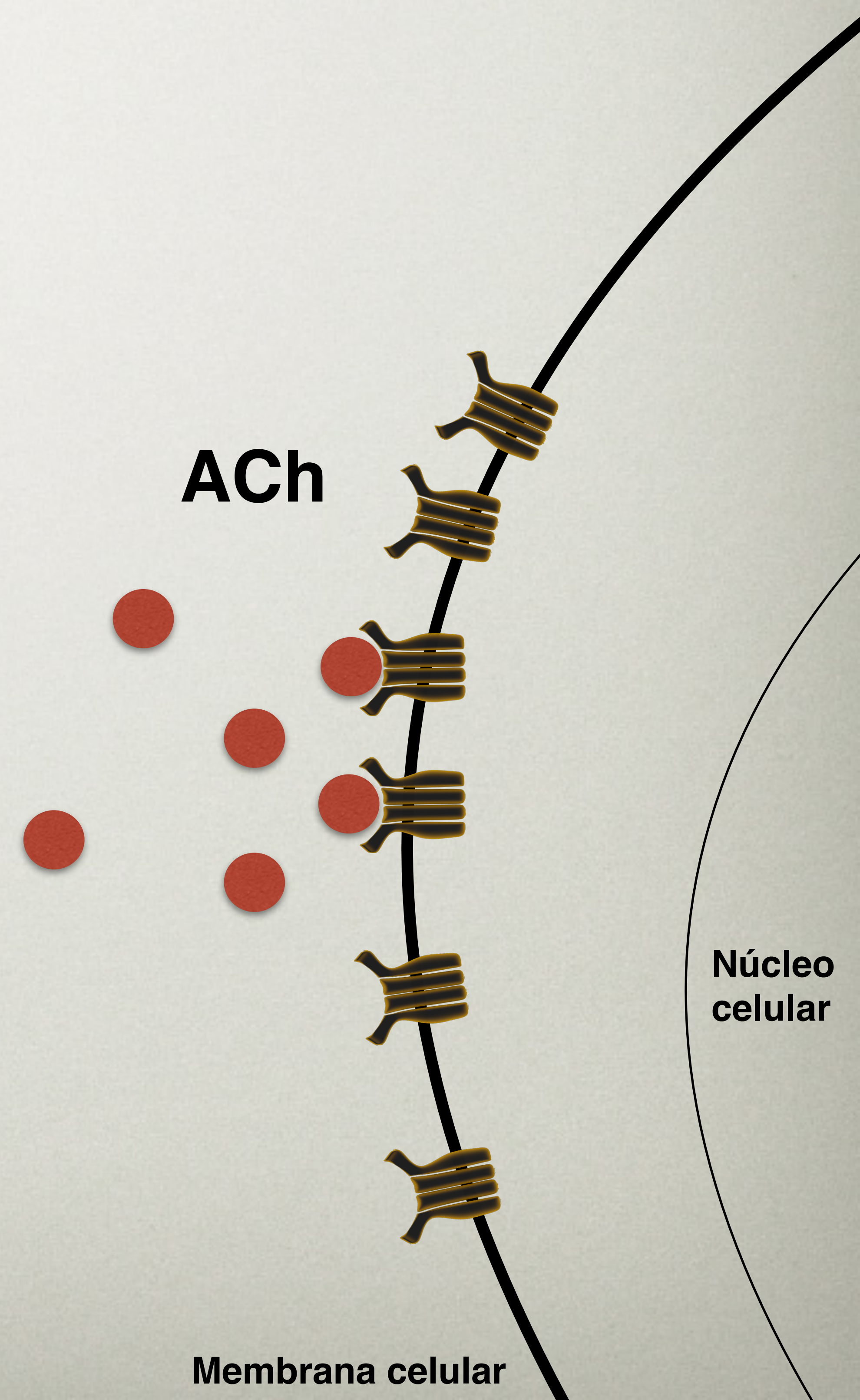
$$K_1.[A].[R] \rightleftharpoons K_2.[AR]$$



Equilíbrio químico dinâmico

$$K_1.[A].[R] \rightleftharpoons K_2.[AR]$$

$$K_1.[A].[R] = K_2.[AR]$$

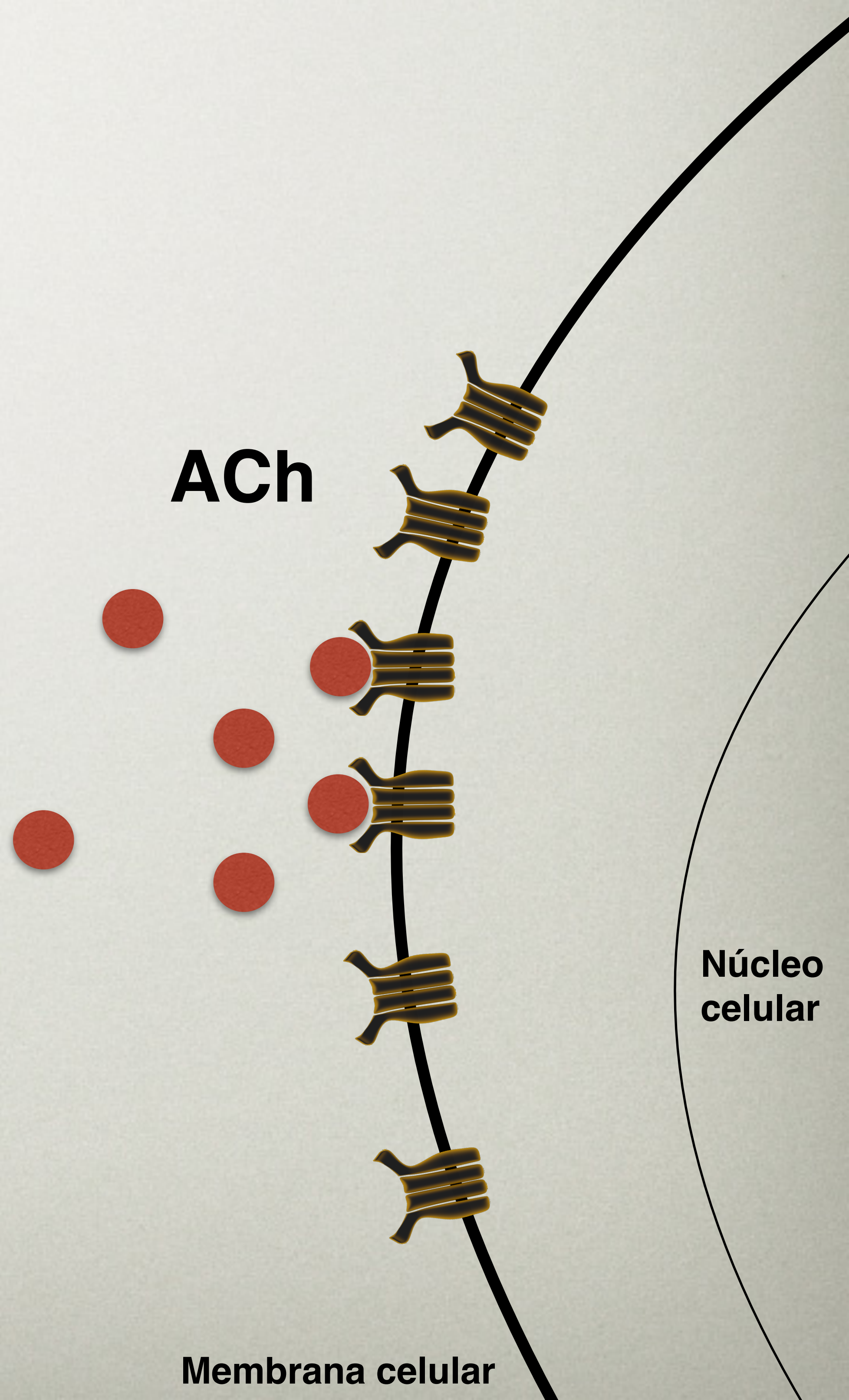


Equilíbrio químico dinâmico

$$K_1.[A].[R] \rightleftharpoons K_2.[AR]$$

$$K_1.[A]\,\boxed{[R]} = K_2.[AR]$$

$$\downarrow$$



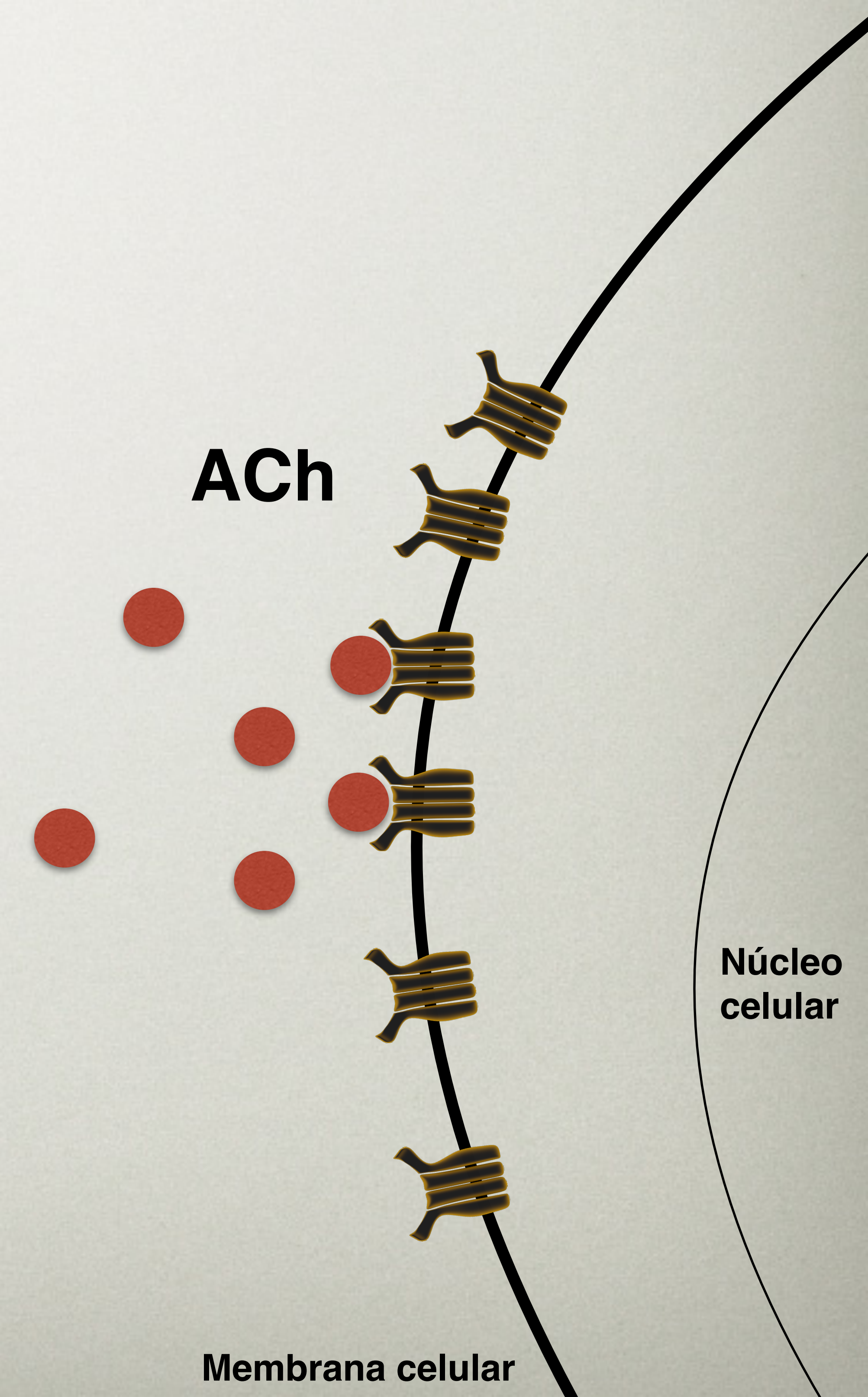
Equilíbrio químico dinâmico

$$K_1.[A].[R] \rightleftharpoons K_2.[AR]$$

$$K_1.[A].\boxed{[R]} = K_2.[AR]$$

↓

$$K_1.[A].(1 - [AR]) = K_2.[AR]$$



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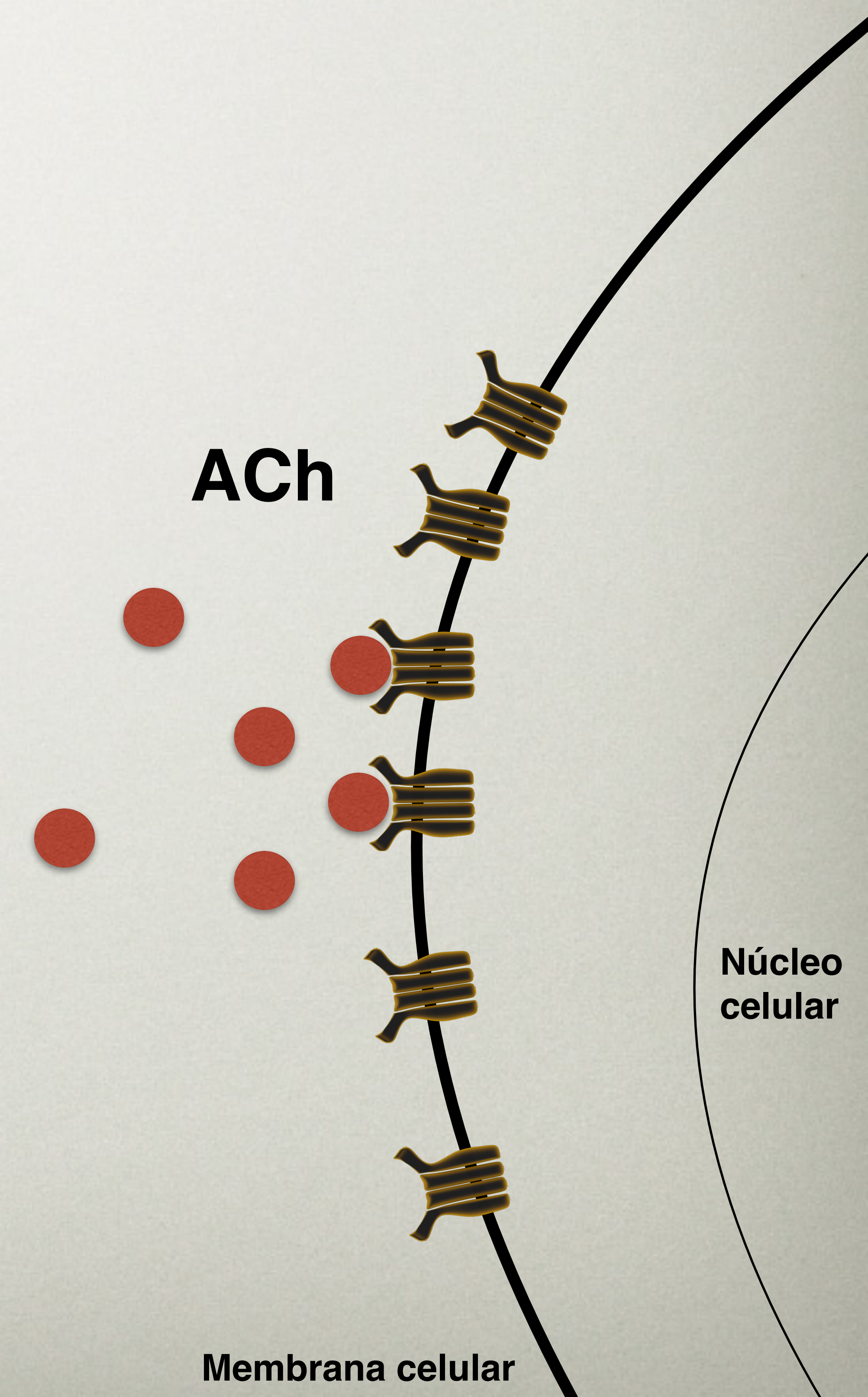


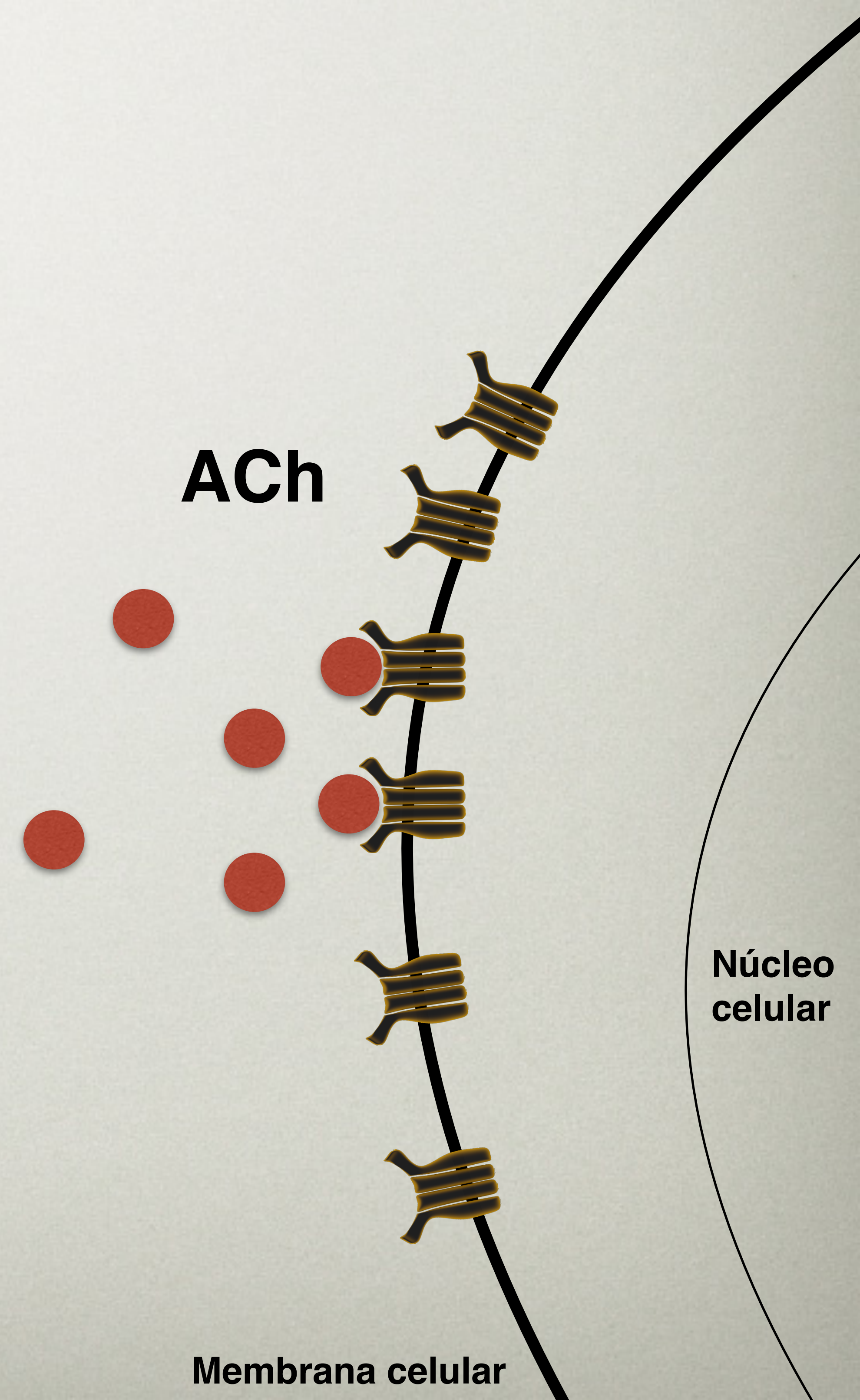
Equilíbrio químico dinâmico

$$K_1.[A].[R] \rightleftharpoons K_2.[AR]$$

$$K_1.[A].[R] = K_2.[AR]$$

$$K_1.[A].(1-[AR]) = K_2.[AR]$$

$$[A].(1-[AR]) = \frac{K_2}{K_1}.[AR]$$



Equilíbrio químico dinâmico

$$K_1.[A].[R] \rightleftharpoons K_2.[AR]$$

$$K_1.[A].[R] = K_2.[AR]$$

$$[A].(1-[AR]) = K_A.[AR]$$

$$K_1.[A].(1-[AR]) = K_2.[AR]$$

$$[A].(1-[AR]) = \frac{K_2.[AR]}{K_1}$$

Equilíbrio químico dinâmico

$$K_1.[A].[R] \rightleftharpoons K_2.[AR]$$

$$K_1.[A].\boxed{[R]} = K_2.[AR]$$

$$\downarrow$$

$$K_1.[A].(1-[AR]) = K_2.[AR]$$

$$[A].(1-[AR]) = \frac{K_2.[AR]}{K_1}$$

$$[A].(1-[AR]) = K_A.[AR]$$

K_A = Constante de dissociação em equilíbrio

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

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$$[A].(1-[AR]) = K_A.[AR]$$

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Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

$$[A] - [A][AR]$$

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

$$[A] - [A][AR] =$$

Equilíbrio químico dinâmico

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Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

$$[A] - [A][AR] = K_A.[AR]$$

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

$$[A] - [A][AR] = K_A.[AR]$$

$$[A] = K_A.[AR] + [A][AR]$$

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

$$[A] - [A][AR] = K_A.[AR]$$

$$[A] = K_A.[AR] + [A][AR]$$

$$[A] =$$

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

$$[A] - [A][AR] = K_A.[AR]$$

$$[A] = K_A.[AR] + [A][AR]$$

$$[A] = [AR]$$

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

$$[A] - [A][AR] = K_A.[AR]$$

$$[A] = K_A.[AR] + [A][AR]$$

$$[A] = [AR]($$

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

$$[A] - [A][AR] = K_A.[AR]$$

$$[A] = K_A.[AR] + [A][AR]$$

$$[A] = [AR]\,(K_A$$

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

$$[A] - [A][AR] = K_A.[AR]$$

$$[A] = K_A.[AR] + [A][AR]$$

$$[A] = [AR]\,(K_A +$$

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

$$[A] - [A][AR] = K_A.[AR]$$

$$[A] = K_A.[AR] + [A][AR]$$

$$[A] = [AR](K_A + [A]$$

Equilíbrio químico dinâmico

$$[A].(1-[AR]) = K_A.[AR]$$

$$[A] - [A][AR] = K_A.[AR]$$

$$[A] = K_A.[AR] + [A][AR]$$

$$[A] = [AR]\left(K_A + [A]\right)$$

Concentração de agonista vs ocupação de receptores

$$[A] = [AR]\left(K_A + [A]\right)$$

Concentração de agonista vs ocupação de receptores

$$[A] = [AR]\left(K_A + [A]\right)$$

Concentração de agonista vs ocupação de receptores

$$[A] = [AR](K_A + [A])$$

$$[AR] = \frac{[A]}{(K_A + [A])}$$

Equação de *Hill-Langmuir*

Concentração de agonista vs ocupação de receptores

$$[A] = [AR]\left(K_A + [A]\right)$$

$$[AR] = \frac{[A]}{\left(K_A + [A]\right)}$$

Equação de *Hill-Langmuir*

Quando, $[A] = K_A$ → 50% de ocupação

Ocupação vs Resposta

$$[AR] = \frac{[A]}{(K_A + [A])}$$

Ocupação vs Resposta

$$[AR] = \frac{[A]}{(K_A + [A])}$$

$$y = [AR]$$

Ocupação vs Resposta

$$[AR] = \frac{[A]}{(K_A + [A])}$$

$y = [AR]$ $\quad$ $y =$ **Resposta**

Ocupação vs Resposta

$$[AR] = \frac{[A]}{(K_A + [A])}$$

$$y = [AR] \qquad y = \textbf{Resposta}$$

$$\frac{y}{100} =$$

Ocupação vs Resposta

$$[AR] = \frac{[A]}{(K_A + [A])}$$

$$y = [AR] \qquad y = \textbf{Resposta}$$

$$\frac{y}{100} = \frac{[A]}{(K_A + [A])}$$

Ocupação vs Resposta

$$[AR] = \frac{[A]}{(K_A + [A])}$$

$y = [AR]$ $\quad$ $y =$ **Resposta**

$$\frac{y}{100} = \frac{[A]}{(K_A + [A])}$$ Rearranjo $$\frac{y}{100-y} = \frac{[A]}{K_A}$$

Ocupação vs Resposta

$$\frac{y}{100-y} = \frac{[A]}{K_A}$$

Ocupação vs Resposta

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↓ **Aplicando Logaritmo nos dois lados da equação**

Ocupação vs Resposta

$$\frac{y}{100-y} = \frac{[A]}{K_A}$$

↓ **Aplicando Logaritmo nos dois lados da equação**

$$\log\left(\frac{y}{100-y}\right) = \log[A] - \log K_A$$

Ocupação vs Resposta

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↓ **Aplicando Logaritmo nos dois lados da equação**

Lembre-se… log (x/y)= log x - log y

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Equação de reta $\mathbf{y = ax + b}$

Ocupação vs Resposta

$$\frac{y}{100-y} = \frac{[A]}{K_A}$$

Aplicando Logaritmo nos dois lados da equação

Lembre-se… log (x/y)= log x - log y

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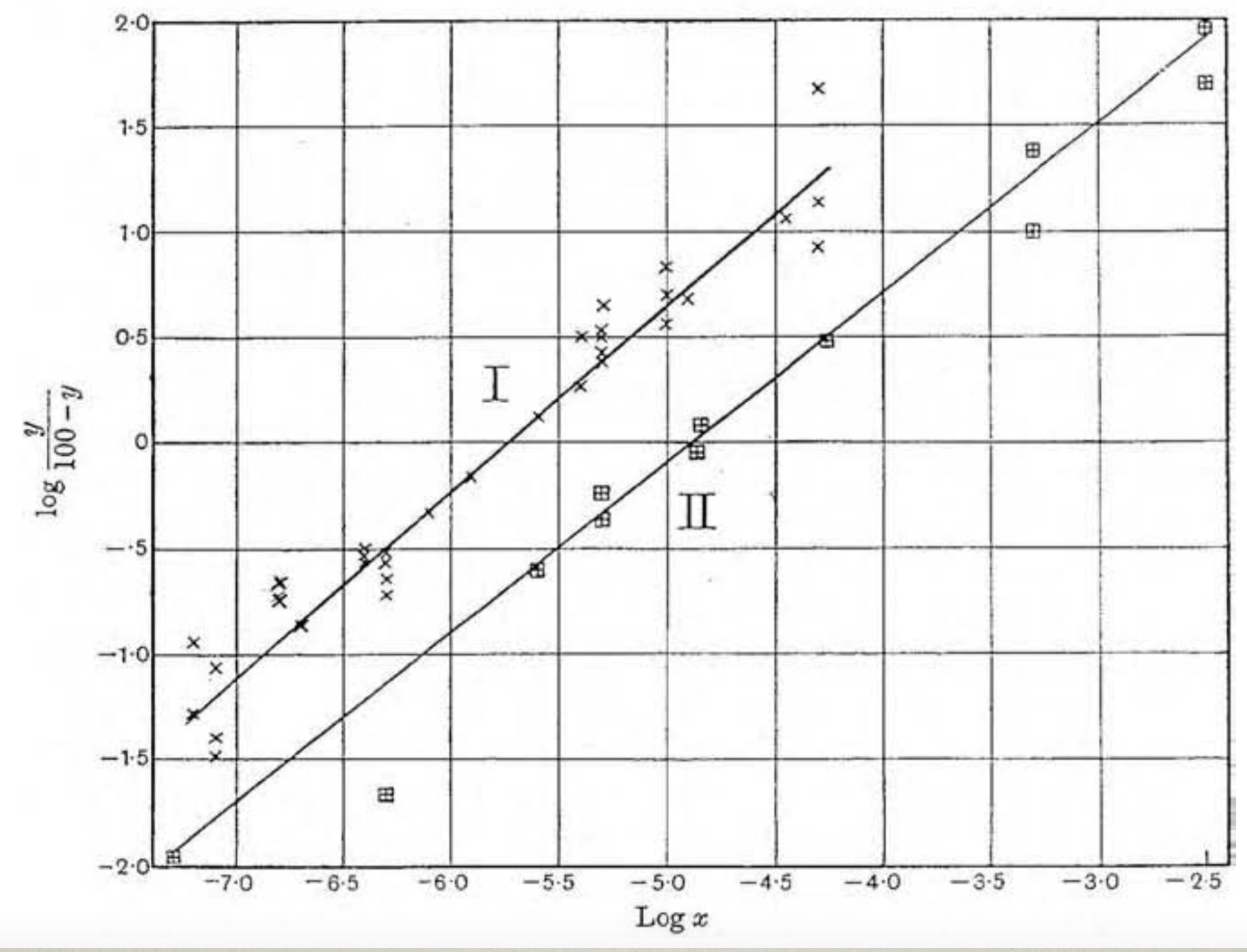
Equação de reta

$$y = ax + b$$

Coeficiente angular = slope

Resultados do Clark



Clark, A. J., *J. Physiol.*, 61, 530–547, 1926.

Vamos Graficar?