Effects of Caffeine on the Contractility and Membrane Potentials of Rat Atrium[1]

Although it has been known for almost a century that caffeine activates the contractile activity of muscle, the mechanism of this response has yet to be defined[2-4]. It has been recently proposed that caffeine initiates a process in muscle that leads to contraction, without intervention or alterations of transmembrane potential changes or underlying permeability changes[5]. In the work reported here, the effects of caffeine on the transmembrane potentials and mechanical activity were simultaneously recorded to determine if there were any transmembrane potential changes when the contractile event was changed.

The transmembrane potentials and mechanical activity of 5 isolated atria taken from rats were recorded according to the methods reported previously[6]. The isolated atria were maintained in Krebs-Ringer-bicarbonate, pH 7.4, 30 °C, and electrically-stimulated at a rate of 200/min. The individual experiments were divided into 4 phases: (1) a 60 min equilibration period, (2) a 30 min control period during which at least 150 records are taken and serve as the control, (3) a 30 min period during which the tissue is exposed to the drug and records are taken at 3 min intervals, and (4) a wash-out period during which the drug has been removed from the tissue chamber and the reversibility of the drug induced response was followed and records taken. Period (3) was further divided into 3 time sequences: (a) 5–10 min, (b) 15–25 min, and (c) 25–30 min. The records taken during these time sequences were then statistically manipulated to arrive at the data obtained in the Table.

The effects of $5 \cdot 10^{-4} M$ caffeine, which was found to be the threshold concentration for the experimental conditions employed, on the measured characteristics are found in the Table. While there were no significant changes in the resting and action potential magnitudes, there were statistically significant changes in the other measured electrical characteristics. The depolarization rate had increased during the 30 min exposure period. It is of interest that there was not a proportional increase in the conduction time, since these 2 events are theoretically independent. It is also obvious that there was a configurational change in the action potential configuration, since an increase in the repolarization rate would usually result in a decrease in the action potential area.

Caffeine induced a transient positive increase in the developed tension during the initial 5–10 min after addition of the drug. The developed tension was still significantly elevated after a 30 min exposure to caffeine. There were no significant changes in the latent period, developed tension-peak time or duration during the positive inotropic response. Subsequent removal of the drug from the tissue bath resulted in a complete restoration of the measured characteristics to the control levels.

Previous work on muscle, both skeletal and cardiac, has been primarily concerned with correlating changes in resting or action potential magnitudes with the magnitude of contraction. Although this interpretation may be valid with drugs like acetylcholine or norepinephrine as they influence electrical and mechanical characteristics of cardiac muscle, this was not the case found with increased Ca^{++} ions (unpublished data). Whereas acetylcholine increased repolarization rate and decreased contractile magnitude, and norepinephrine decreased repolarization rate and increased contractile magnitude in electrically driven atria, Ca^{++} increased the repolarization rate and also increased the contractile magnitude.

The data found in the work reported here would seem to indicate that the action potential-depolarization rate can be correlated with the increased contractile response. The increased depolarization rate would allow more Na^+ to enter the cell which in turn would facilitate the release of Ca^{++} for contractile activation. Even though the contractile magnitude subsequently decreases with a continuing increased depolarization rate, this would be justified by an increased Na^+ efflux to restore the normal Na^+ equilibrium within the cell. This would in effect decrease the available Ca^{++} for contractile activation and result in a decreased contractile magnitude.

Effects of caffeine on the isolated rat atrium

Parameter	5–15 min[a]	15–25 min	25–30 min
Resting potential	− 0.5[b]	− 0.9	− 1.8
Action potential magnitude	− 0.3	− 2.3	− 0.9
Action potential duration	− 15.5	− 2.8	− 2.4
Action potential area	− 17	−	+ 3.9
Action potential[c] rise time	+ 22.0	+ 22.1	+ 29.7
Repolarization rate	+ 15	+ 4.0	+ 4.1
Conduction rate	0	0	+ 4.1
Latent period	+ 0.4	+ 3.2	+ 0.9
Developed tension magnitude	+ 20.2	+ 8.0	+ 3.6
Developed tension duration	− 1.3	+ 0.6	− 1.6
Developed tension rise time (to peak)	+ 0.7	+ 3.7	+ 1.4

[a] Time after addition of caffeine. [b] Over all (% changes): the test readings were compared with means of the control period to calculate % changes. [c] Depolarization rate.

Zusammenfassung. Der Einfluss von Coffein auf Kontraktion und Membranpotential des Atriums der Ratte ergibt: Verkürzung der Dauer des Aktionspotentials und Beschleunigung der Geschwindigkeit von Repolarisation und Depolarisation. Ein möglicher Zusammenhang dieser Änderungen mit der erhöhten Kontraktilität wird diskutiert.

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[2] J. W. Pickering, J. Physiol., Lond. *14*, 383 (1893).
[3] R. H. Cheney, J. Pharmac. exp. Ther. *54*, 42 (1935).
[4] R. H. Cheney, J. Pharmac. exp. Ther. *54*, 213 (1935).
[5] J. Axelsson and S. Thesleff, Acta physiol. scand. *44*, 55 (1958).
[6] P. B. Hollander and J. L. Webb, Circulation Res. *3*, 604 (1955).

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