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Ouabain – the insulin of the heart

Today, medical therapies for heart disease are based on a diverse range of drugs. Angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, β-adrenergic receptor antagonists, aldosterone receptor antagonists, as well as diuretics, and inotropic agents improve clinical symptoms and slow the progression of contractile dysfunction. Despite these therapeutic advances, heart failure is still associated with an annual mortality rate of 10% (1). The search for better treatments and optimisation of existing ones remain major challenges in cardiology.

Modulation of myocardial metabolism has become an accepted new approach to improve the performance of the dysfunctional myocardium (2). Alternatively, proven agents such as digitalis glycosides continue to be of interest. Digoxin is still used extensively worldwide, and it remains one of the most commonly prescribed drugs. The Digitalis Investigation Group trial has indicated that digoxin is quite effective in reducing cardiovascular hospitalisations (3). A proposal for a large digoxin study is being considered for funding in Europe (4). However, arrhythmia and a narrow therapeutic index limit its therapeutic application (5,6).

Although often used as research tool, the cardiac glycoside ouabain (referred to as g-Strophanthin in German) has become a niche product in treatment of heart diseases. Decades of practical use indicate benefits in prevention and treatment of acute heart attacks. Prophylactic and therapeutic use of ouabain is recommended in insufficiencies of the left ventricle. Several clinical studies with orally administered ouabain report exceptionally positive results for the treatment of cardiovascular diseases (7–9).

This clinical experience disappeared in time, yet there is mounting evidence that supports a re-evaluation of ouabain in the treatment of heart disease. In 1991, ouabain was identified as an endogenous hormone. This discovery has lead to an intense re-examination of the drug, its physiological functions and its mode of action (10–12).

Based on its chemical structure, ouabain is considered as a typical digitalis derivative. All digitalis derivatives bind to and inhibit the ubiquitous transmembrane protein Na+, K+-ATPase and increase the force of contraction of heart muscle. However, there are diverse biological responses to different derivatives both at the cellular and at the molecular level (13). There are marked differences between the effects of digoxin and ouabain. Only ouabain in small doses stimulates the sodium pump (14,15); digoxin does not show this effect (16). Moreover, digoxin was shown to induce changes in intracellular membrane traffic in neuronal cells, whereas ouabain does not possess this ability and even antagonised digoxin effect (17). A recent study confirmed the long-known clinical experience that ouabain has an inhibitory effect on cardiotoxicity induced by digitalis glycosides. Ouabain at a low dosage delayed the start of arrythmia induced by digoxin on guinea pig papillary muscle. In addition, ouabain at a low dosage but not at a high dosage delayed the development of digoxin-induced arrhythmia in anaesthetised guinea pigs (18). Thus, the long-known characteristic dose dependency of ouabain effects (19) has been confirmed.

Ouabain is different from digitalis glycosides

Clinical experience with ouabain

According to canonical explanations, ouabain and other digitalis derivatives should have similar therapeutic effects. However, clinical experience clearly indicates that ouabain is different from other digitalis derivatives. A most pronounced difference is the fast onset of action by ouabain. This effect was the basis for the chance discovery of ouabain in 1859 by the English botanist Kirk. He had discovered the fast onset of action of ouabain on the heart by using a toothbrush contaminated with Strophanthus seeds. The rapid onset of effect of oral ouabain was used in medical practice for a 'Strophanthin-quick-test': patients with suspected heart disease were given two tablets of 3 mg that they had to chew and distribute in the mouth. In the case of heart disease, a relief of complaints was observed within 5–10 min. This test was used routinely in German physicians' offices well into the 1970s.

Based on decades of extensive clinical experience with ouabain, the therapeutic profile of the drug and the disease profiles for which the use of ouabain is appropriate have been summarised in monographs and reviews (19–21). The main benefit is in prevention and treatment of acute heart attacks. Prophylactic and therapeutic use of ouabain is recommended in:

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congestive heart insufficiency without pronounced hypertrophy, coronary sclerosis, cardiogenic hypertension, asthma cardiale, exercise-induced cardiac insufficiency, angina pectoris and arrhythmias, including those that occur on treatment with digitalis. It is stated that ouabain 'has proven to be the most acceptable, most effective antidote for digitalis intoxication.'

Edens described 'the intravenous Strophanthin treatment as the safest treatment of organic-induced angina pectoris, including heart attack.' Digitalis causes a worsening of symptoms and is therefore contra-indicated. While under digitalis ECG abnormalities and arrhythmias can occur, these symptoms are either alleviated or completely abolished by ouabain (22,23). In addition, there are numerous clinical reports that ouabain lowers blood pressure in patients with heart diseases (24,25).

In the 1950s, a fierce scientific dispute erupted over the bioavailability of orally administered ouabain. In the 1970s, optimised enteric-coated formulations were introduced that have enteral absorption rates of up to 80% in cats (26). A drug based on such a formulation today is registered for insufficiency of the left ventricle in Germany, sold as prescription drug under the brand name Strodival®mr by Medapharma (Meda Pharma GmbH & Co. KG, Bad Homburg v.d.H., Germany). An investigation published in 2001 reports systemic bioavailability of 43–50% after oral administration in guinea pigs (27).

Ouabain modulates cardiac metabolism

Based on extensive clinical observations, it had been postulated that ouabain stimulates myocardial metabolism (19–21). Mechanistic studies have revealed that ouabain, in contrast to digitalis derivatives, indeed has pronounced effects on the cardiac metabolism. In dogs, ouabain increases lactic acid utilisation by the myocardium. Yet, digitoxin inhibits lactic acid utilisation by the myocardium (28). Ouabain as well as k-strophanthin reduce lactic acid concentration in the blood of patients with heart diseases (29,30).

The metabolic effect of ouabain is not limited to stimulation of lactic acid utilisation. Upon oral administration to male rats, ouabain increases the acetyl-coenzyme A/coenzyme A ratio in the myocardium (31). Contrary to digitoxin, ouabain stimulates fatty acid utilisation in the myocardium (32,33). Ouabain amplifies metabolic stimulation induced by acetylcholine and inhibits increased oxygen consumption induced by adrenaline (34). In the failing human myocardium, the positive haemodynamic effects of ouabain are not associated with additional energy consumption (35). In contrast, in healthy male subjects, digoxin reduces resting metabolic rate, respiratory quotient and fat oxidation (36). In an infarct model with the guinea pig heart, digoxin has no stimulating effects on cardiac metabolism (37). The digitalis derivative Lanatoside-C has no effect on substrate utilisation of the myocardium (38).

In addition to the effects on fatty acid metabolism, ouabain stimulates myocardial protein syntheses (39). Digitoxin inhibits myocardial protein synthesis (31).

von Ardenne demonstrated that in myocardial infarction induced by ligature in rat and rabbit hearts, the pH in myocardial tissue drops markedly. This acidification triggers a chain reaction that leads to cell death (40). Administration of ouabain in a myocardial infarct model in rats raises the pH of acidic cardiac tissue within a few minutes by up to 0.5 units. Digitoxin does not alter the pH. In addition, ouabain increases the rheological properties of blood by enhancing the plasticity of erythrocytes (41). Digitoxin does not influence the flexibility of erythrocytes.

The pH sensitivity of the myocardium is well documented. A drop in pH below 6.2 leads to irreversible damage. Therefore, in cardiac surgery, strict pH control is imperative (42). In the 'Strophanthin era', German surgeons routinely applied 0.3 mg ouabain pre-operatively and thereby observed significantly fewer complications (43).

The metabolic effects of ouabain are supported by *in vivo* studies. Ouabain significantly increases the endurance performance of rats. Hypertrophy of the heart is reduced by administration of ouabain (44). Orally administered ouabain improves physical endurance in guinea pigs (45) as well as in healthy volunteers (41). Digoxin, however, does not improve the performance of patients with coronary arterial disease. In a double-blind crossover study with k-strophanthidin and digoxin, only k-strophanthidin improved the performance of coronary patients (46).

Additional evidence confirms the mechanistic differences between ouabain and digitalis glycosides. Ouabain and digitalis derivatives develop their effects in different cellular spaces. Digitalis derivatives must penetrate into the cell interior to exert their effects, whereas ouabain develops its effect in the extracellular space (47). The pharmacokinetic behaviour of i.v.-administered ouabain and digitalis derivatives likewise suggests that their therapeutic effects are based on different receptors. The effect of i.v.-administered ouabain starts immediately after injection, reaches a maximum after 5 min, last 5–7 h and then rapidly declines (22). With i.v. -administered digoxin, effects slowly start 5–30 min

after injection, the maximum effect being reached only after 1–4 h (5).

Conclusion

Research on ouabain has suffered from the dogma that ouabain is a member of the digitalis glycosides. Recent research illustrates the uniqueness of ouabain and confirms the clinical experiences with ouabain, which have been known for decades. Ouabain modulates the metabolism of the heart; it stimulates substrate utilisation of the myocardium, removes lactate accumulated during heart diseases and reduces the amount of fatty acids in the blood. Ouabain is, as Aschenbrenner has formulated, the insulin of the heart. The uniqueness of ouabain ought to be recognised in future research as well as in clinical practice. Clinical studies with ouabain that correspond to current standards are warranted.

Disclosure

No conflict of interest.

H. Fürstenwerth
Unterölbach 3A, Leverkusen, Germany
Email: hauke@fuerstenwerth.com

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