# EFFECT OF TRASICOR (OXPRENOLOL) ON METABOLISM OF HIGH-ENERGY PHOSPHORUS COMPOUNDS IN THE MYOCARDIUM OF RATS DURING EARLY ONTOGENY

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Trasicor (oxprenolol) was given as a single intraperitoneal injection to albino rats aged 7, 14, and 30 days and 3-5 months in doses of predetermined sensitivity and stability for each age group. Injection of the preparation in low doses increased the ATP concentration in the animals aged 7 and 14 days but did not affect its level in the rats of the other age groups. In high doses Trasicor lowered the ATP concentration (not significantly in adults) and raised the inorganic phosphorus level. Judging from the degree of lowering of ATP, adult animals and those aged 7 days were most resistant to the preparation.

KEY WORDS: myocardium; ontogeny; ATP – content; β-adrenergic blocking agents (Trasicor).

The preparation Trasicor (oxprenolol), which is 1-isopropyl-amine-3-(o-allyloxyphenoxy)-2-propanol hydrochloride [8], with a β-adrenergic blocking action, has recently been used with success in clinical cardiology. The ability of Trasicor to abolish and prevent arrhythmias of varied genesis [12], its hypotensive action [10], its low toxicity, and its negligible side effects during prolonged administration [13] have attracted the attention of clinicians to this preparation.

However, the special features of the response of the child to administration of this drug have not yet been adequately studied. In experimentally induced arrhythmias, and also in diseases of the heart accompanied by considerable disturbances of the cardiac rhythm, the energy supply of the myocardium is known to be deficient [6].

The object of this investigation was to study the effect of Trasicor on the metabolism of high-energy phosphates in the heart muscle in the early stages of postnatal ontogeny.

## EXPERIMENTAL METHOD

Experiments were carried out on 198 noninbred albino rats aged 7, 14, and 30 days (of both sexes) and 3-5 months (adult males). An aqueous solution of Trasicor was injected once intraperitoneally after preliminary determination of the sensitivity (I) and resistance (II) doses for each age group by the scheme described in [5]: I) 110, 42, 43, and 22 mg/kg, respectively, and II) 400, 212, 217 and 69 mg/kg, respectively. The animals were decapitated after electrocardiographic changes had developed under the influence of the preparation in the sensitivity or resistance dose. The heart was quickly removed and frozen in liquid nitrogen, the tissue was homogenized, and the content of ATP, ADP, and AMP was determined by electrophoresis on paper followed by spectrophotometry [14] and that of inorganic phosphorus (IP) by a calorimetric method [4]. The results were subjected to statistical analysis in the usual way [2].

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TABLE 1. Effect of a Single Injection of Trasicor in Sensitivity and Resistance Doses on the Concentrations of Adenine Nucleotides (in $\mu$moles/g) and of IP (in $\mu$g%)

| Index studied | Age of rats (days) | | | |
|---|---|---|---|---|
| | 7 | 14 | 30 | adult |
| ATP: | | | | |
| Control | 0,57±0,014 | 0,66±0,041 | 0,77±0,047 | 1,69±0,04 |
| Sensitivity dose | 0,69±0,015* | 0,84±0,023* | 0,83±0,025 | 1,75±0,037 |
| Resistance dose | 0,48±0,013* | 0,54±0,016* | 0,42±0,022* | 1,51±0,08 |
| ADP: | | | | |
| Control | 0,68±0,041 | 0,63±0,037 | 0,73±0,044 | 1,38±0,05 |
| Sensitivity dose | 0,79±0,014* | 0,84±0,023 | 0,76±0,021 | 1,98±0,057* |
| Resistance dose | 0,53±0,022* | 0,50±0,023* | 0,92±0,016* | 1,10±0,27* |
| AMP: | | | | |
| Control | 0,53±0,04 | 0,59±0,037 | 0,42±0,034 | 0,39±0,02 |
| Sensitivity dose | 0,49±0,02* | 0,53±0,027 | 0,49±0,018 | 0,25±0,018* |
| Resistance dose | 0,39±0,015* | 0,38±0,019* | 0,26±0,014* | 0,44±0,021 |
| ATP + ADP + AMP: | | | | |
| Control | 1,78±0,012 | 1,85±0,093 | 1,92±0,092 | 3,31±0,13 |
| Sensitivity dose | 1,99±0,02* | 2,21±0,031* | 2,89±0,02 | 2,99±0,091 |
| Resistance dose | 1,42±0,013* | 1,43±0,039* | 1,58±0,016* | 3,08±0,045 |
| ATP/ADP: | | | | |
| Control | 0,86±0,07 | 1,05±0,042 | 1,06±0,068 | 1,21±0,02 |
| Sensitivity dose | 0,86±0,08 | 1,01±0,044 | 1,10±0,05 | 1,76±0,011* |
| Resistance dose | 0,88±0,025 | 1,06±0,049 | 0,43±0,026* | 1,35±0,044* |
| IP: | | | | |
| Control | 24,6±0,93 | 28,2±1,06 | 44,5±1,0* | 44,8±1,9 |
| Sensitivity dose | 23,5±1,1 | 27,2±2,3 | 47,6±0,6* | 34,4±0,37* |
| Resistance dose | 29,2±0,7* | 49,5±2,6* | 69,5±1,05* | 50,7±0,86* |

Notes. P calculated relative to control. Results for which $P < 0.05$ marked by asterisk.

## EXPERIMENTAL RESULTS AND DISCUSSION

Control tests of the content of adenine nucleotides and IP during early postnatal ontogeny in the rat myocardium agreed with data obtained earlier [3].

Injection of Trasicor in the sensitivity dose caused a significant increase (Table 1) in the content of ATP, ADP, and total adenine nucleotides, accompanied by a decrease in the AMP level in the heart muscle of 7-day rats. The ATP/ADP ratio and the IP content were not significantly altered. A similar response was observed in the 14-day animals. These results are connected with the $\beta$-blocking action of the preparation and were most marked in animals aged 2 weeks, i.e., at a time of increasing strength of sympathetic influences, with control cardiac activity at this stage of ontogeny [1, 9]. The absence of changes in the ATP/ADP ratio at a time of increase in the ATP content evidently points to a decrease in the utilization of energy to meet the functional needs of the myocardium, which, in turn, is directly dependent on a decrease in the metabolic activity of the catecholamines and unconnected with an increase in ATP synthesis. In the 30-day rats, injection of the compound caused no significant changes in the parameters studied, evidently because of differences in the character of nervous regulation and metabolism of the heart at this stage of ontogeny. At this age the adrenergic apparatus of the myocardium is known to be fully developed, whereas the mechanisms of central inhibition, which are cholinergic in nature [1] and to some extent balance the increased tone of the sympathetic system, are only just coming into operation. The sympathomimetic effect of Trasicor [17] possibly weakens its metabolic action at this stage of function of the heart.

In rats aged 3-5 months, injection of this $\beta$-adrenergic blocking agent was followed by a decrease in the concentrations of ADP, AMP, and IP and an increase in the ATP/ADP ratio in the absence of any change in the level of ATP and of total adenine nucleotides, in agreement with data published previously [11]. Changes affecting the adenine nucleotides in the same direction were found in acute experiments with anaprilin [7].

Injection of Trasicor in the sensitivity dose (Table 1) lowered the ATP concentration at all age groups (not significantly in the adult animals), the ADP concentration (except in 30-day rats, in which this parameter was increased), and the AMP concentration (unchanged in the adults). The content of total adenine nucleotides was lowered in the 7- and 14-day rats and unchanged in the myocardium of the animals of the other age groups. The ATP/ADP ratio in animals aged 7 and 14 days remained at the level of the control values, it was reduced in the 30-day animals, and increased in the adults. At all age groups there was a significant increase in the IP concentration. Trasicor in the resistance dose thus lowered the ATP level at all stages of ontogeny investigated. This phenomenon is evidently linked with the ability of the compound (like other $\beta$-blocking agents with a similar mechanism of action – alprenolol, pronetalol, ICI 50.172 [15]) in large doses to induce considerable uncoupling of excitation and contraction. Potentiation of the sympathomimetic effect of Trasicor in this dose likewise cannot be ruled out. It will be noted that, judging from

the degree of lowering of the ATP level, adult and 7-day rats were more resistant to this dose of the preparation. Activation of glycolysis can take place without the participation of $\beta$-adrenergic receptors in this process [11]. The greater resistance of the 7-day rats was probably due to the high content of carbohydrates and the rapid course of glycolysis (glycogenolysis) – the characteristic source for the replenishment and supply of energy in the myocardium in the early stages of ontogeny [16].

The reaction of high-energy phosphates of the myocardium to Transicor (oxprenolol) thus shows special features in the early stages of ontogeny. The low sensitivity and high resistance of 7-day rats compared with animals of older age groups must be taken into consideration.

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