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INFLUENCE OF CATECHOLAMINES ON SOME OF THE IMPORTANT CARBOHYDRATE AND LIPID INTERMEDIARY METABOLITES DURING THEIR PRESSOR RESPONSES

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Abstract—The concurrent changes in some of the important carbohydrate and lipid metabolites were studied at the time of the pressor responses of adrenaline, noradrenaline and depressor response of isoprenaline. Significant reductions in blood pyruvate and lactate occurred during the pressor responses of adrenaline and noradrenaline whereas the significant rise in these intermediary metabolites resulted during the depressor response of isoprenaline. The above changes in the intermediary metabolites could not be noticed when pressor or depressor responses of catecholamines were blocked by their respective blockers. The rise in blood glucose and free fatty acids was exhibited at or quickly after the pressor responses of adrenaline, noradrenaline, as well as depressor response of isoprenaline. Dibenzylene failed to block the catecholamine induced glycogenolysis and lipolysis whereas inderal could effectively block these reactions.

WHILE catecholamines evoke a pressor response and also promote glycogenolysis[1,2] and lipolysis[3–5] the question as to whether the metabolic effects are mediated with a virtually essential need for pressor action is still intriguing. It is suggested that both responses are independent and pressor response precedes the metabolic effect.[6] The fact that contractile effect of adrenaline on smooth muscle combines with decrease in content of energy rich phosphate compounds[7] indicates that the contractile mechanism of smooth muscle principally subsists on energy requirement. It has also been demonstrated that energy shortage induces failure to evoke contraction of smooth muscle.[8] In view of these facts it is imperative that the contractile mechanism during pressor action might deplete some of the metabolites to fulfil the energy requirement and apparently the glycogenolytic and lipolytic reactions induced by catecholamines could be of obligatory importance to compensate the metabolite store being initially expended for the pressor effect. The present investigation was therefore undertaken to obtain more direct evidence on concurrent changes in some of the important metabolic parameters of carbohydrates and lipids during the pressor responses of catecholamines. It was surmised that such data would elucidate the intrinsic relationship between the metabolic and pressor actions of catecholamines.

MATERIALS AND METHODS

Healthy dogs of either sex weighing 12–16 kg were divided in four groups employing 5 animals in each. The animals were fasted for 18 hr before they were used for hemodynamic and biochemical studies under chloralose (100 mg/kg, i.v.) anaesthesia.

Control response of adrenaline (Ad), noradrenaline (NAD) and isoprenaline (Iso) were obtained on animals of the first group. To the next three groups the adrenergic blockers, namely dibenzylene, inderal and dibenzylene together with inderal were given, respectively and catecholamine responses were taken $1\frac{1}{2}$ hr after pretreatment of the blockers.

The arterial blood pressure was recorded by the conventional method using a mercury manometer connected to carotid artery and trachea being cannulated in the preparation. Blood samples from all the groups were taken in indentical manner before catecholamine injection and at the peak responses of catecholamines (adrenaline, noradrenaline and isoprenaline) 1 μg/kg or at corresponding times with peak pressor response of catecholamines in cases pretreated with blockers (dibenzyline 5 mg/kg, inderal 2 mg/kg). The blood samples were also collected at 1 and 5 min after the responses.

Blood samples were analysed for pyruvate,[9] lactate,[10] glucose[11] and plasma free fatty acids.[12]

RESULTS

The significant reduction ($P < 0.05$) in blood pyruvate (Table 1) and lactate (Table 2) was observed at the peaks of the pressor responses of adrenaline and noradrenaline. The blood pyruvate remained reduced within 5 min of the post-pressor response. On the contrary, the depressor response induced by isoprenaline

TABLE 1. BLOOD PYRUVATE LEVEL 100 ml/mg PER MEAN ± S.D.

Drugs	Before catecholamines (5)	After catecholamine injections		
		Peak response (5)	1 min after response (5)	5 min after response (5)
Ad control	1·215 ± 0·13	1·03 ± 0·07*	0·714 ± 0·08*	0·768 ± 0·13*
Ad after dibenzylene	0·82 ± 0·12	0·79 ± 0·33	0·835 ± 0·26	0·895 ± 0·27
Ad after inderal	0·37 ± 0·04	0·205 ± 0·03*	0·273 ± 0·03*	0·3 ± 0·03*
Ad after dibenzylene + inderal	0·84 ± 0·23	0·7 ± 0·28	0·93 ± 0·3	0·94 ± 0·31
NAD control	1·025 ± 0·11	0·84 ± 0·08*	0·945 ± 0·09	1·0 ± 0·1
NAD after dibenzylene	0·765 ± 0·13	0·765 ± 0·25	0·935 ± 0·24	0·934 ± 0·13
NAD after inderal	0·4 ± 0·04	0·32 ± 0·03*	0·278 ± 0·05	0·6 ± 0·06
NAD after dibenzylene + inderal	1·16 ± 0·3	1·25 ± 0·4	0·98 ± 0·5	0·4 ± 0·04
Iso control	0·82 ± 0·19	1·23 ± 0·01*	1·12 ± 0·08	1·15 ± 0·17
Iso after dibenzylene	0·715 ± 0·1	0·95 ± 0·01*	0·925 ± 0·1*	0·725 ± 0·2
Iso after inderal	0·52 ± 0·08	0·31 ± 0·08*	0·51 ± 0·07	0·45 ± 0·05
Iso after dibenzylene + inderal	0·38 ± 0·2	0·78 ± 0·32*	0·78 ± 0·35	0·49 ± 0·08

Numbers in parentheses represent the number of observations.
* Significantly different from controls before catecholamine injection $P < 0.05$.
Ad = adrenaline. NAD = noradrenaline. Iso = isoprenaline.

TABLE 2. BLOOD LACTATE LEVEL 100 ml/mg MEAN ±S.D.

Drugs	Before catecholamines (5)	After catecholamine injections: At peak response (5)	1 min after response (5)	5 min after response (5)
Ad control	20·06 ± 2·68	7·86 ± 2·46*	17·3 ± 3·46*	17·3 ± 3·46*
Ad after dibenzylene	9·03 ± 2·97	7·58 ± 2·78	7·924 ± 3·17	13·82 ± 0·52*
Ad after inderal	7·566 ± 2·41	5·158 ± 1·9	8·164 ± 1·72	8·144 ± 1·24
Ad after dibenzylene + inderal	3·728 ± 2·68	1·784 ± 0·28*	1·972 ± 0·26*	6·06 ± 0·55*
NAD control	17·12 ± 1·79	13·6 ± 2·01*	16·26 ± 1·95	15·8 ± 2·25
NAD after dibenzylene	11·256 ± 2·42	9·98 ± 1·43	10·416 ± 2·71	9·86 ± 2·16
NAD after inderal	4·56 ± 0·93	3·04 ± 0·24*	6·65 ± 1·77*	12·91 ± 1·12*
NAD after dibenzylene + inderal	5·526 ± 0·88	3·424 ± 0·74*	8·064 ± 1·76*	14·016 ± 0·76*
Iso control	11·24 ± 2·3	14·28 ± 2·96	15·39 ± 2·56	15·02 ± 1·39
Iso after dibenzylene	10·94 ± 1·95	13·142 ± 4·02	11·94 ± 2·74	11·096 ± 2·71
Iso after inderal	13·67 ± 0·67	7·468 ± 2·06*	7·816 ± 2·2*	6·708 ± 1·8*
Iso after dibenzylene + inderal	4·016 ± 0·76	2·424 ± 0·05*	4·038 ± 0·72	3·364 ± 0·31

Numbers in parentheses represent the number of observations.
* Significantly different from controls values before catecholamines injection $P < 0·05$.
Ad = adrenaline. NAD = noradrenaline. Iso = isoprenaline.

TABLE 3. BLOOD GLUCOSE LEVEL 100 ml/mg MEAN ±S.D.

Drugs	Before catecholamines (5)	After catecholamine injections: At peak response (5)	1 min after response (5)	5 min after response (5)
Ad control	90·96 ± 7·24	116·0 ± 10·9*	133·92 ± 10·3*	143·92 ± 10·8*
Ad after dibenzylene	79·784 ± 4·52	101·6 ± 16·7*	112·78 ± 17·8*	120·72 ± 9·55*
Ad after inderal	88·8 ± 0·56	86·4 ± 1·55	76·36 ± 4·23*	74·44 ± 2·32*
Ad after digenzylene + inderal	95·84 ± 9·026	94·4 ± 6·52	120·56 ± 3·46*	112·42 ± 5·86*
NAD control	96·24 ± 6·5	102·92 ± 11·0	107·6 ± 9·28*	122·72 ± 11·51*
NAD after dibenzylene	115·32 ± 11·9	92·2 ± 17·1*	107·2 ± 17·1	86·86 ± 5·55*
NAD after inderal	76·772 ± 3·72	90·44 ± 3·08*	75·32 ± 0·28	77·38 ± 9·83
NAD after dibenzylene + inderal	103·32 ± 7·716	73·77 ± 7·934*	72·52 ± 8·8	95·9 ± 11·95
Iso control	99·6 ± 15·8	108·00 ± 15·5	132·88 ± 10·2*	125·38 ± 10·19*
Iso after dibenzylene	95·38 ± 10·21	93·9 ± 10·27	93·90 ± 10·2	116·72 ± 21·0
Iso after inderal	94·7 ± 0·86	84·06 ± 5·68	67·8 ± 4·16*	106·64 ± 2·78
Iso after dibenzylene + inderal	95·1 ± 12·11	101·26 ± 6·07	98·3 ± 10·23	105·4 ± 7·77

Numbers in parentheses represent the number of observations.
* Significantly different from controls values before catecholamine injection $P < 0·05$.
Ad = adrenaline. NAD = noradrenaline. Iso = isoprenaline.

was accompanied by significant elevation in blood pyruvate and a mild increase in lactate levels. Apart from these differential responses in pyruvate and lactate concentrations during pressor or depressor responses plasma free fatty acids (Table 4) rose significantly ($P < 0.05$) at the time of pressor responses of adrenaline and noradrenaline as well as the depressor response of isoprenaline. A significant increase in blood glucose level was observed at pressor response to Ad or immediately after pressor and depressor responses to NAD and Iso respectively (Table 3).

TABLE 4. PLASMA FREE FATTY ACIDS μ equiv/l. MEAN $\pm$S.D.

Drugs	Before catecholamines (5)	After catecholamine injections: At peak response (5)	1 min after response (5)	5 min after response (5)
Ad control	324·8 ± 42·03	540·0 ± 74·82*	860·5 ± 87·1*	852·5 ± 88·26*
Ad after dibenzylene	320·0 ± 28·12	380·0 ± 31·3*	500·0 ± 32·2*	500·0 ± 35·78*
Ad after inderal	450·0 ± 35·3	400·0 ± 22·37*	375·0 ± 32·2*	447·0 ± 31·3
Ad after dibenzylene + inderal	325·0 ± 31·3	330·0 ± 31·3	355·0 ± 32·55	450·0 ± 35·7
NAD control	470·0 ± 53·5	760·0 ± 88·26*	968·0 ± 84·6*	961·0 ± 88·6*
NAD after dibenzylene	350·0 ± 27·6	500·0 ± 29·07*	580·0 ± 35·7*	560·0 ± 35·7*
NAD after inderal	455·0 ± 50·2	425·0 ± 22·3	475·0 ± 35·7	490·0 ± 22·37*
NAD after dibenzylene + inderal	320·0 ± 29·9	320·0 ± 29·07	450·0 ± 35·78*	460·0 ± 35·78*
Iso control	350·0 ± 35·35	450·0 ± 36·22*	400·0 ± 22·4*	380·0 ± 35·35
Iso after dibenzylene	425·0 ± 33·22	450·0 ± 36·22	400·0 ± 22·3	375·0 ± 35·3*
Iso after inderal	380·0 ± 30·6	358·0 ± 36·2	410·0 ± 22·3	380·0 ± 22·37
Iso after dibenzylene + inderal	450·0 ± 37·2	355·0 ± 36·2*	400·0 ± 22·4*	370·0 ± 35·3*

Numbers in parentheses represent the number of observations.
* Significantly different from controls values before catecholamine injection $P < 0.05$.
Ad = adrenaline. NAD = noradrenaline. Iso = isoprenaline.

Pretreating the animals with α-blocker dibenzylene caused a reversal of the adrenaline response from a pressor to depressor response and significantly blocked pressor action of noradrenaline. It also concomitantly prevented the lowering of pyruvate and lactate associated with pressor activities of Ad and NAD. Dibenzylene neither interfered with the depressor response of isoprenaline nor did it affect the increase of pyruvate or lactate caused by isoprenaline. Also dibenzylene could not block the rise in glucose and FFA effected by any one of adrenaline, noradrenaline and isoprenaline.

Whereas the β-blocker, inderal, failed to interfere with pressor actions of adrenaline and noradrenaline, it also did not inhibit appreciably the reduction in pyruvate and lactate concentrations accompanying the pressor phenomenon. On the other hand, inderal not only blocked depressor response of isoprenaline but also prevented pyruvate and lactate accumulation.

The simultaneous administration of dibenzylene and inderal prior to catecholamines effectively blocked the rise of blood glucose and plasma FFA by all the three catecholamines. A slight rise in blood pressor was observed when Ad or NAD were injected after dibenzylene conjointly with inderal, which corresponded somewhat with a reduction in the magnitude of reduction in the pyruvate level during Ad and NAD induced pressor response. However, pretreatment with dibenzylene and inderal together could not appreciably suppress the depletion of lactate associated with Ad and NAD induced pressor responses.

It must be noted that neither the α-blocker or the β-blocker alone could significantly reduce blood pyruvate and lactate (the values indicated before catecholamine injections in Tables 1 and 2). The β-blocker, inderal had much profound effect in inducing the fall in blood pyruvate and lactate as compared to dibenzylene, the α-blocker. Both the blockers did not appreciably reduce the blood glucose and plasma FFA levels (Tables 3 and 4). Similar observations have been made with dibenzylene and inderal on changes in blood pyruvate, lactate, glucose and FFA by the earlier workers.[13,14]

DISCUSSION

The findings show significant decreases in blood pyruvate and lactate levels together with pressor responses to Ad and NAD. In contrast the depressor response to Iso is associated with significant elevations in blood pyruvate and lactate levels. Incidently it is documented that considerable energy is utilized for smooth muscle contraction[7,15] and adrenaline augments the utilization of pyruvate and lactate.[16] In accordance with these facts, we assume that the reductions in pyruvate and lactate concentrations accompanying pressor activities, may be due to their increased requirement for replenishment of energy that was expended for contractile mechanism of the vascular muscles. It may, however, be considered that catecholamines elicit several actions on the carbohydrate metabolism. For example, liver glycolysis is induced by α-receptor activation, whereas muscle glycogenolysis and liver glycogenesis are by β-receptor activation.[17] Adrenaline would act on all these receptors by virtue of having α and β activities. However, acceleration of liver glycolysis, together with muscle glycogenolysis by adrenaline, should cause resultant increase in pyruvate and lactate levels even though glycogenesis is also stimulated by adrenaline. Noradrenaline would also activate glycolysis by α-receptor stimulation in liver and favour the production of pyruvate and lactate. Actually, it has been noticed that these intermediary metabolites are depleted significantly at pressor activities which substantiates the possibility of pyruvate and lactate being utilized as a requirement at this time. It may further be suggested that formation of pyruvate and lactate by Ad and NAD do not compensate the utilization of these metabolites in case both occur concomitantly at pressor response or there is time resolution between these two events. On the other hand, a significant rise simultaneously with depressor response to isoprenaline, manifests sparing of pyruvate which may perhaps result in impairment in utilization of pyruvate at relaxing phase of the smooth muscle. Some increase in lactate level could be seen at this time which was not significant. Isoprenaline induces muscle glycogenolysis by β-receptor activation[17] which would result in lactacidemia since muscle glycogenolysis leads to lactic acid production instead of hyperglycemia.[18] Isoprenaline also induces

corresponding stimulation of liver glycogenesis which is likely to favour the conversion of lactate into pyruvate. In view of this it is difficult to correlate the increase in pyruvate level with the depressor response to isoprenaline.

The characteristic decline in pyruvate and lactate associated with pressor activities of Ad and NAD is abolished by α-blocker dibenzylene. Since blocker is expected to inhibit glycolysis and cause further decline of these metabolites the evidence indicating actual counteracting fall in pyruvate and lactate with blocking pressor response is suggestive of a correction of utilization of the intermediary metabolites with the pressor activity. However, it may be noted that dibenzylene with the dose used, induces pressor reversal of adrenaline to depressor response but pyruvate and lactate do not seem to increase above the control values as it has been noted in case of isoprenaline induced depressor response. On this basis accumulation of pyruvate and lactate by isoprenaline cannot be claimed to have resulted by its depressor action.

The plasma fatty acids have markedly elevated at both pressor as well as depressor responses of catecholamines, presumably due to abilities of all the catecholamines to stimulate the mobilization of free fatty acids from adipose tissue.[19,20] It is interesting to find the rapid release of free fatty acids by catecholamines to evoke striking increase in FFA level together with the pressor phenomenon. The hyperglycemic effect is only seen to associate with pressor action of Ad. In case of NAD and Iso such effect is progressive after their pressor or depressor activities. Whether the lipolytic and glycogenolytic effects of catecholamines have terminal consequences on pressor activities is not yet clear. Perhaps these processes could be conceived of obligatory importance in contributing to the stores of intermediary metabolites, initially utilized for the pressor activity. The catecholamine induced glycogenolysis and lipolysis are effectively inhibited by β-blocker which is in confirmation with the earlier reports.[21,22]

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