Metabolic Effects of Pargyline in the Dog* (34081)

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A decrease in blood sugar has been demonstrated after the repeated administration of monoamine-oxidase inhibitors (MAOI) (1, 2). A lower activity of the sympathetic system, which participates in the regulation of blood glucose levels, was postulated as the major factor leading to this effect (2, 3). On the other hand, one dose or one exposure to MAOI exerts a sympathetic effect observed in circulatory parameters and in isolated preparations. It was of interest, therefore, to determine whether and to what extent the sympathetic effect of one dose of MAOI is reflected in metabolic parameters. Changes in plasma glucose, lactate, glycerol, and free fatty acids (FFA), and of oxygen consumption, were measured in normal and reserpine-pretreated dogs during and after one dose of pargyline.

Methods. Experimental procedure. Experiments were performed on 10 mongrel dogs (11.7 ± 0.5 kg) fasted for 18 hr before the experiment. Each animal was anesthetized with Na pentobarbital iv, intubated with a cuffed endotracheal tube, and mechanically ventilated with 100% O_2 in order to maintain normal acid-base equilibrium and O_2 saturation in arterial blood throughout the experiment. Polyethylene catheters were inserted in both femoral arteries and one femoral vein. After the administration of the anesthetic agent the animals were ventilated for at least 30 min before the first samples were taken for control measurements.

Pargyline administration. Each of the 5 dogs was anesthetized with Na pentobarbital, 35 mg/kg. After the control period, pargyline (50 mg/kg) was administered iv over a period of 15 min. The experiment was continued for 105 min after the end of pargyline administration.

Reserpine pretreatment and pargyline administration. Five dogs were treated with reserpine (0.25 mg/kg twice daily) for 3 days prior to the experiment. The dose of Na pentobarbital required was less than in the previous group (approximately 5 mg/kg). After the control period, pargyline (50 mg/kg) was administered iv for 15 min and the experiment was continued, as in the first series, for 105 min after the end of pargyline administration.

Measurements. Mean blood pressure and pulse rate were continuously recorded by means of a Statham pressure transducer. Midesophogeal temperature was maintained constant within 1° during the procedure. $\dot{V}_{O_2}$ was measured continuously by the closed-circuit method (4). Samples of arterial blood were collected anaerobically in heparinzed cooled syringes and immediately analyzed for pH and pCO_2 by the Astrup triple-pH method. Aliquots of the blood were centrifuged in a refrigerated centrifuge and the plasma was prepared for determination of free fatty acids (FFA), glucose, glycerol, and lactic acid. FFA was determined by the method of Dalton and Kowalski (5) and glucose by the method of Saifer and Gerstenfeld (6). Glycerol concentration was measured by an enzymatic procedure in which glycerolkinase in the presence of ATP transforms glycerol to glycerol-P and ADP. The amount of glycerol is then determined from the decrease in NADH in the presence of phosphoenolpyruvate using pyruvate kinase and lactate dehydrogenase. Lactic acid concentration was

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determined enzymatically from the formation of NADH using lactate dehydrogenase. The determinations were made in duplicate and the control measurements are the average of two samples. After each collection of blood a small amount of saline was infused to flush the arterial catheter. No heparin was used during the procedure except in the saline filling the catheters before their insertion at the beginning of the experiment. Reserpine (Serpasil) was obtained from the Ciba Pharmaceutical Co., Summit, New Jersey, and pargyline HCl (Eutonyl) from the Abbott Laboratories, Chicago, Illinois. The results were statistically analyzed by Student's *t* test.

Results. Effect of pargyline. Mean blood pressure increased gradually from a control value of 140 mm Hg to 153 mm Hg after pargyline administration ($p<.05$). Heart rate increased from 189 (beats/min) to a maximum of 213 ($p<.001$) 15 min after the end of pargyline infusion and slowly returned to near control values by the end of the experiment. pHa and $PaCO_2$ did not change significantly throughout the experiment. Blood glucose increased consistently but not significantly from a control value of 118.5 mg/100 ml to a maximum of 137.5 mg/100 ml 45 min after pargyline. Blood lactate de-

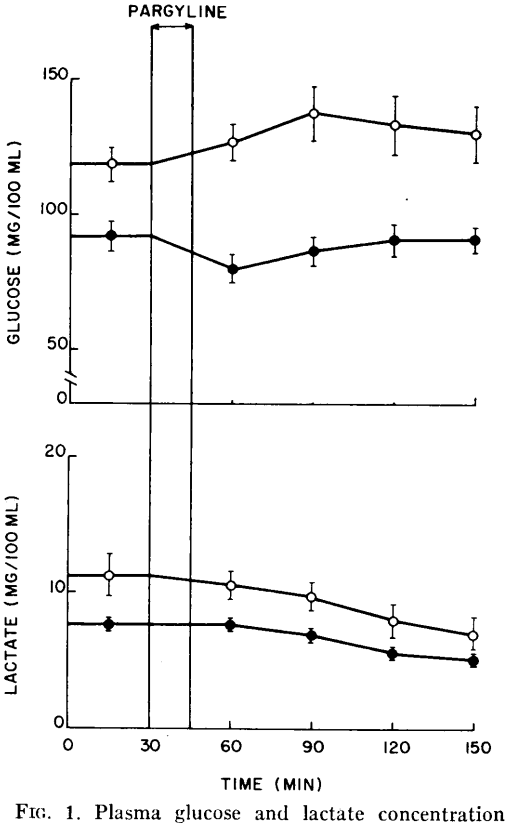

FIG. 1. Plasma glucose and lactate concentration after the infusion of pargyline (50 mg/kg) in normal (open dots) and reserpinized (closed dots) dogs. Points represent the mean values from five experiments; vertical lines represent SEM.

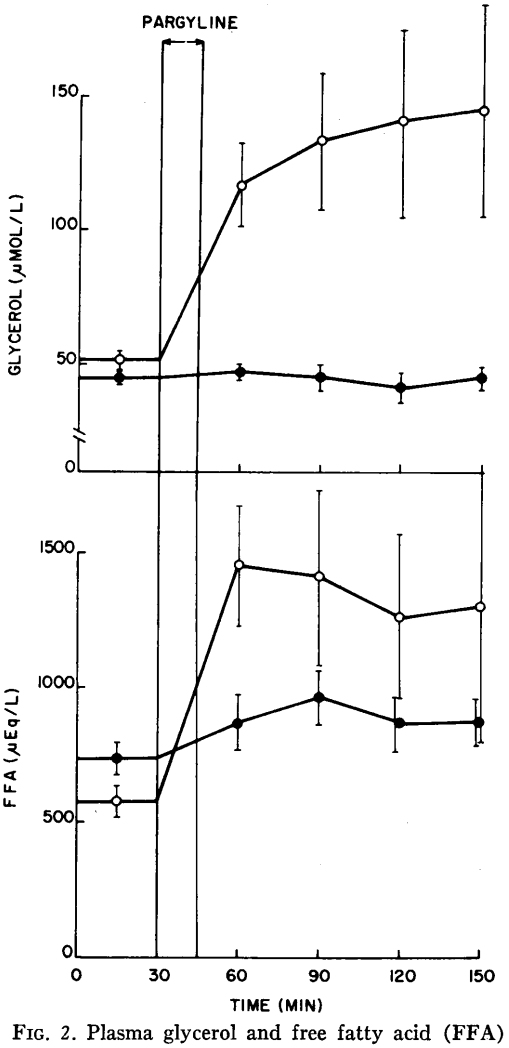

FIG. 2. Plasma glycerol and free fatty acid (FFA) concentration after the infusion of pargyline (50 mg/kg) in normal (open dots) and reserpinized (closed dots) dogs. Points represent the mean values from five experiments; vertical lines represent SEM.

creased steadily during the experiment from a control value of 11.2 mg/100 ml to 7 mg/100 ml at the end of the experiment (Fig. 1). Plasma FFA increased significantly from a control value of 578 μEq/liter (by 152%, $p<.01$) 15 min after the end of pargyline administration and remained elevated throughout the experiment. Plasma glycerol exhibited a continuous and significant rise after pargyline administration from a control value of 51.4 to a maximum of 144.7 μmol/liter by the end of the experimental period (by 181%, $p<.01$) (Fig. 2). $\dot{V}_{O_2}$ also increased significantly after pargyline administration, from a control value of 7.1 to a maximum of 8.25 ml/kg/min 15 min after the end of infusion and remained at this level throughout the experimental period (an increase of 17–19%, $p<.01$) (Fig. 3).

Effect of pargyline after reserpine pretreatment. In this series of experiments, mean blood pressure and heart rate did not change significantly during and after pargyline administration, from a starting control value of 96 mm Hg and 81 beats/min respectively. pHa and $PaCO_2$ remained within the control range throughout the study. Blood glucose tended to decrease, from a control value of 92 mg/100 ml to 80 mg/100 ml 15 min after the end of pargyline administration, and 30 min later was back to control and remained so throughout the study. Lactate, as in the previous group, decreased steadily but not significantly, from a control value of 7.6 mg/100 ml to 5.2 mg/100 ml by the end of the experiment (Fig. 1). Plasma FFA tended to increase from a control value of 736 to a maximum of 966 μEq/liter 45 min after the end of pargyline administration, decreasing to 880 μEq/liter by the end of the experiment; these changes were not significant. Plasma glycerol and $\dot{V}_{O_2}$ in reserpinized dogs did not change after pargyline administration (Figs. 2 and 3).

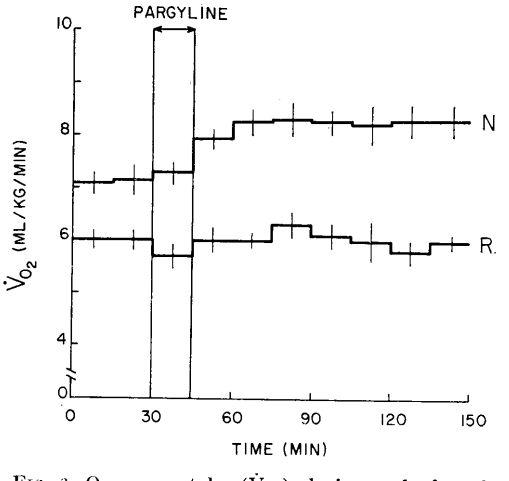

FIG. 3. Oxygen uptake ($\dot{V}_{O_2}$) during and after the infusion of pargyline (50 mg/kg) in normal (N) and reserpinized (R) dogs. Vertical lines represent SEM.

Discussion. The prompt, marked, and sustained increase in plasma glycerol, FFA, and oxygen consumption observed in normal dogs after one dose of pargyline is indicative of a substantial sympathetic effect. At the same time an increase in heart rate and mean blood pressure was also noted. In control animals infused with saline none of the variables measured changed significantly during the experimental period. In reserpine-pretreated dogs, none of the above changes occurred after the same dose of pargyline, as would be expected since pargyline does not have any sympathomimetic or amphetamine-like activity *per se* (7) but has an indirect effect, mediated by endogenous catecholamines through a mechanism closely related to the inhibition of MAO. This agrees well with the results obtained on isolated nictitating membrane of the cat (8) where pretreatment with reserpine significantly reduced the response to pargyline. The observation of marked increases in plasma glycerol and FFA along with only moderate increases in blood glucose also supports the assumption that the action of pargyline is mediated by norepinephrine, made available in higher concentration at receptor sites through the inhibition of MAO. The importance of sympathetic innervation, as well as MAO activity has been demonstrated in adipose tissue (9, 10).

Other investigators have reported sympathetic effects caused by one dose or exposure (*in vitro*) to MAOI. Increased heart rate, contractile force, and blood pressure were observed in dogs after MAO inhibition, as well as increased action of dopamine, tryptamine, and tyramine, but not of norepinephrine, on

heart contractile force and arterial pressure (11). Similar data have been presented by Spencer *et al.* (12) and Eble and Rudzik (13). Positive inotropic and chronotropic effects on spontaneously beating, isolated atria (14), papillary muscle (15, 16), and nictitating membrane (8, 17, 18) after MAO inhibition have also been reported. On the other hand, inhibition of MAO did not have a sympathetic effect in reserpinized preparations (8, 16, 18). These findings are in agreement with the present results and support the conclusion that the sympathetic effect of MAOI is mediated by catecholamines although the mechanism is not completely understood.

The sympathetic response which occurs at the onset of MAO inhibition by pargyline may be of interest for two reasons. (1) It is not known to what extent this sympathetic effect reflected in increases of plasma glycerol, FFA, oxygen consumption, heart rate, and blood pressure might be harmful to patients receiving similar compounds where a decrease in sympathetic tone is desirable. (2) Repeated administration of MAOI is accompanied by decrease of sympathetic tone, reflected in a reduction of blood pressure and decreased level of some metabolic parameters (1–3, 19–22).

In an attempt to explain the "biphasic" action of MAOI; *i.e.*, sympathetic effect at the onset of MAO inhibition and decrease of sympathetic tone after repeated administration, the following working hypothesis is suggested. There are two explanations postulated for the decrease of sympathetic tone occurring after repeated administration of MAOI: (1) a decreased rate of catecholamine synthesis and turnover, both induced by a negative feedback mechanism (23, 24); (2) an accumulation of octopamine as a "false transmitter" (25–27). Both mechanisms take into account the fact that the concentration of intracellular amines (mostly bound) is increased as a result of less amine being exposed to metabolism by MAO (28). It is known that catecholamines may be displaced from binding sites by other amines (29). The displaced amine; *e.g.*, norepinephrine, is then in a position to act on effector cells and thereby mediates the sympathetic effect of the displacing amine. This may be the situation which occurs immediately after the administration of MAOI. As a consequence of the inhibition of MAO, the concentration of endogenous tyramine (along with other amines) increases (25, 27, 28, 30, 31) which, among other factors (25) leads to the build-up and accumulation of octopamine. However, before octopamine is formed in amounts sufficient to function as a "false transmitter," tyramine, due to its increased concentration at the cellular level, may act as an indirectly acting sympathomimetic amine, especially since, at the same time, the amount of bound catecholamines is also increased. It is conceivable that both these processes, increasing amounts of bound catecholamine and increasing concentration of tyramine at the cellular level, occur at the onset of MAO inhibition and prior to (actually, they are prerequisites for) a decrease in the activity of the sympathetic system, due either to a slowdown of catecholamine synthesis and turnover (23, 24) or to accumulation of octopamine (25, 27) or both.

More experimental work is required in order to test the validity of the explanation proposed above. The question still remains as to what extent the sympathetic effect of MAOI occurring at the onset of MAO inhibition warrants caution in the use and dosage of these drugs in patients more liable to damage by an increase of sympathetic tone *per se* and its metabolic consequences.

Summary. Pargyline (50 mg/kg) was administered to dogs with and without reserpine pretreatment in order to determine to what extent the sympathetic action observed at the onset of MAO inhibition is reflected in metabolic parameters. In normal dogs, both blood pressure and heart rate increased gradually during and after pargyline infusion, $\dot{V}_{O_2}$ and plasma FFA and glycerol increased significantly after pargyline infusion and remained elevated throughout the experiment. None of these changes were observed in reserpine-pretreated dogs after pargyline administration. The importance of this sympathetic response, mainly reflected in elevation

of $\dot{V}O_2$, glycerol, and FFA, in the therapeutic use of MAOI remains to be assessed.

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