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Additive Effects of Glyburide and Antidepressants in the Forced Swimming Test: Evidence for the Involvement of Potassium Channel Blockade

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GUO, W., K. TODD, M. BOURIN, M. HASCOET AND F. KOUADIO. *Additive effects of glyburide and antidepressants in the forced swimming test: Evidence for the involvement of potassium channel blockade.* PHARMACOL BIOCHEM BEHAV **54**(4) 725–730, 1996.—Evidence in the literature suggests that the modulatory effects of antidepressant drugs (ADS) on neuronal excitability, via the inhibition of K^+ channels, may be the final common pathway of pharmacological action. Therefore, we tested the hypothesis that combining the ATP-sensitive K^+ channel blocker glyburide with a variety of ADS would produce an additive effect and decrease the immobility time of mice in the forced swimming test (FST). Glyburide (GLY, IP, 30 and 50 mg/kg) and subactive doses of ADS were administered 45 and 30 min, respectively, prior to behavioral testing. Results showed that when combined with GLY, ADS whose main pharmacological effect is one of 5-HT uptake blockade (imipramine, amitriptyline, citalopram, paroxetine, fluoxetine, and fluvoxamine) were more effective in decreasing the amount of time mice were immobile, than when these drugs were administered alone. Some noradrenaline uptake inhibiting ADS (desipramine and viloxazine, but not maprotiline) were also significantly more effective in decreasing immobility time when combined with GLY than when administered alone. Pretreatment with GLY was found to have no effect on the dopamine uptake inhibitor bupropion, and out of the atypical ADS tested (trazodone, mianserine and iprindole), only coadministration with iprindole decreased the immobility time. Only the specific MAO-A inhibitor moclobemide was observed to have an antiimmobility effect when combined with GLY. Neither MAO-B specific (RO 16 6491) nor mixed MAO inhibitors (nialamide and pargyline) interacted with GLY to produce antiimmobility effects. These results corroborate and extend our previous report of the ADS enhancing effects of quinine in the same behavioral model, and suggest that the additive effects of quinine and GLY on ADS in FST are a result of K^+ channel blockade.

Antidepressants Glyburide Forced swimming test Potassium channel blocker Mice

RECENTLY, it was suggested that in the forced swimming test (FST), pretreatment with lithium had additive effects on antidepressants drugs (ADS), particularly those with action on the serotonin (5-HT) system (19). This additive effect was proposed to be a result of an inhibition of potassium channels. These data were subsequently extended by testing the effects of pretreatment with the potassium channel blocker quinine (7) on a variety of ADS in the FST (11). Results from this series of experiments revealed that quinine not only decreased the immobility time of mice administered 5-HT uptake inhibitors, but also those treated with noradrenaline (NA) uptake inhibitors. It was suggested that perhaps the effects of quinine were not specific to K^+ blockade, but also due to a metabolic interaction as quinine is a potent cytochrome P^{450} 2D6 inhibitor, the enzyme involved in the breakdown of many ADS (15,16).

To circumvent this metabolic confound, glyburide (GLY), an ATP-sensitive K^+ channel blocker that binds to both high- and low-affinity sites in pancreatic β and muscle cells and also crosses the blood–brain barrier to enter the central nervous system (CNS) (8,18,33) was used in the present study. Once

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in the CNS, blockade of ATP-sensitive K^+ channels may influence neurotransmitter release (1,3).

The present article was designed to try to establish if blockade of K^+ channels is important for the potentiation of subactive doses of ADS in the FST.

METHOD

Animals

Naive male Swiss mice (Centre d'elevage Janvier, France), weighing 20–24 g, were group housed under a 12 L:12 D cycle, at constant room temperature (21 ± 1°C), with free access to food and water. Mice were randomly assigned to one of the experimental groups. All experiments were conducted between 0900 and 1800 h.

All experiments were conducted within the guidelines of the French Ministry of agriculture for experiments with laboratory animals by law No. 87.848.

Drugs and Treatment

Amitriptyline HCL (AMI) and moclobemide (MOC) (Roche), imipramine HCl (IMI) and maprotiline HCl (MAP) (Ciba Geigy), desipramine HCl (DES) (Merck), viloxazine HCl (VIL) (Zeneca Pharma), trazodone HCl (TRA) (UPSA), mianserin HCl (MIA) (Organon), iprindole HCl (IPR) (Wyeth), citalopram HBr (CIT) (Lundbeck), paroxetine HCl (PARO) (Beecham), fluoxetine HCl (FLUO) (Lilly), fluvoxamine maleate (FLUV) (Duphar), nialamide (NIA) (Pfizer), pargyline (PARG), and RO 16 6491 (RO) (RBI), and bupropion (BUP) (Sigma) were dissolved in distilled water. GLY (Aldrich) was ultrasonically dispersed in distilled water with Tween 80 added to increase solubility. Subactive doses of ADS were based on previous reports in the literature (6,19).

For each study, two doses of GLY and two doses of ADS were injected IP, in a constant volume of 0.5 ml/20 g body weight, 45 and 30 min, respectively, prior to the test. Control animals received the vehicle only. Nine groups of mice (n = 20) were run per experiment of one ADS combined with GLY. Thus, a typical experiment for one ADS would consist of the following groups: vehicle, GLY controls, ADS controls, and the ADS interactions with GLY.

Measurement of Locomotor Activity and Immobility in Mice

The doses of GLY were chosen based on prior assessment of locomotor activity and immobility levels. Animals received one of a range of doses (20–100 mg/kg) and were placed in a photocell activity meter (OSYS). The locomotor activity of mice was tested for 10 min 45 min post GLY injection. To rule out the possibility of a generalized increase in mobility induced by the combination of ADS with GLY, doses of combination that significantly decreased immobility time in FST were studied in the photocell activity meter.

The forced swimming test used was the same as described in detail elsewhere (21). Briefly, mice were dropped individually into glass cylinders (height: 25 cm, diameter: 10 cm) containing 10 cm of water maintained at 23–25°C and left there for 6 min. A mouse was judged to be immobile when it floated in the water, in an upright position, and made only small movements to keep its head above water. The duration of immobility was recorded during the last 4 min of the 6-min test.

Statistics

Data were evaluated by nonparametric statistical methods due to a nonnormal distribution. Data were analyzed by the Kruskal–Wallis H-test for independent groups. Additional Steel a posteriori test was performed, when appropriate, to detect significant differences with the appropriate control group. All analysis were conducted using the P.C.S.M. program (Deltasoft) for the IBM compatible microcomputer.

The effects of ADS and GLY alone are expressed as percentage change of vehicle controls. For ADS interactions with GLY, the mean time of immobility of the treatment group is expressed as the percentage change from the appropriate control group.

RESULTS

Selection of the GLY Dose

Figure 1 shows the effects of various doses of GLY given to mice IP 45 min before testing. At a dose range of 20–100 mg/kg, GLY did not influence the immobility of mice in the FST compared with the control group. At the same dose range in the locomotor activity test, GLY 100 mg/kg produced a significant reduction in locomotor activity (43%, $p < 0.01$), indicative of a sedative effect. The lower doses of 30 and 50 mg/kg were, therefore, selected as subactive doses for the interaction studies.

Interactions of GLY With Subactive Doses of ADS

Table 1 reports the effects of the combined administration of GLY and 5-HT or NA uptake inhibiting ADS on immobility time. When combined with GLY, subactive doses of both IMI and AMI produced a reduction of more than 20% on immobility of mice. The specific NA uptake inhibitors DES and VIL when combined with GLY 50 mg/kg also significantly reduced immobility, whereas MAP with GLY 30 and 50 mg/kg failed to induce a significant decrease. All selective 5-HT uptake inhibitors studied had a potent interaction with GLY. CIT, FLUO, FLUV, and PARO pretreated with GLY, induced a stronger decrease in immobility at their subactive doses. BUP, a specific DA uptake inhibitor, did not affect immobility time when combined with either dose of GLY.

Table 2 shows the effects of atypical ADS when combined with GLY in FST. At a dose of 64 mg/kg, IPR alone was effective in decreasing immobility. With this dose, IPR plus GLY 50 mg/kg, produced an even greater decrease (22% of drug alone, $p < 0.05$). Neither TRA nor MIA influenced the immobility time when administered alone or combined with GLY. Four monoamine oxidase inhibitors (MAOI) were also investigated in this report (Table 3). All MAOI alone were inactive. MOC 32 mg/kg (MAOI-A) combined with GLY 30 and 50 mg/kg induced a significant reduction in immobility time (respectively 18%, $p < 0.05$ and 31% $p < 0.01$). Nialamide 32 mg/kg combined with GLY 30 mg/kg weakly decreased the immobility time (9%, $p < 0.05$). No other MAOI exhibited additive effects on mobility of mice pretreated with GLY.

When combined with glyburide (30 or 50 mg/kg) some ADS produced a significant decrease in locomotor activity (Table 5). More importantly, no ADS when combined with GLY produced an increase in the spontaneous locomotor activity of mice.

DISCUSSION

The FST is widely used to predict the antidepressant action of drugs in humans. The immobility time of mice in the FST is reduced by the majority of ADS, including TCA, atypical antidepressants, MAOI and 5-HT uptake inhibitors (6,21). In

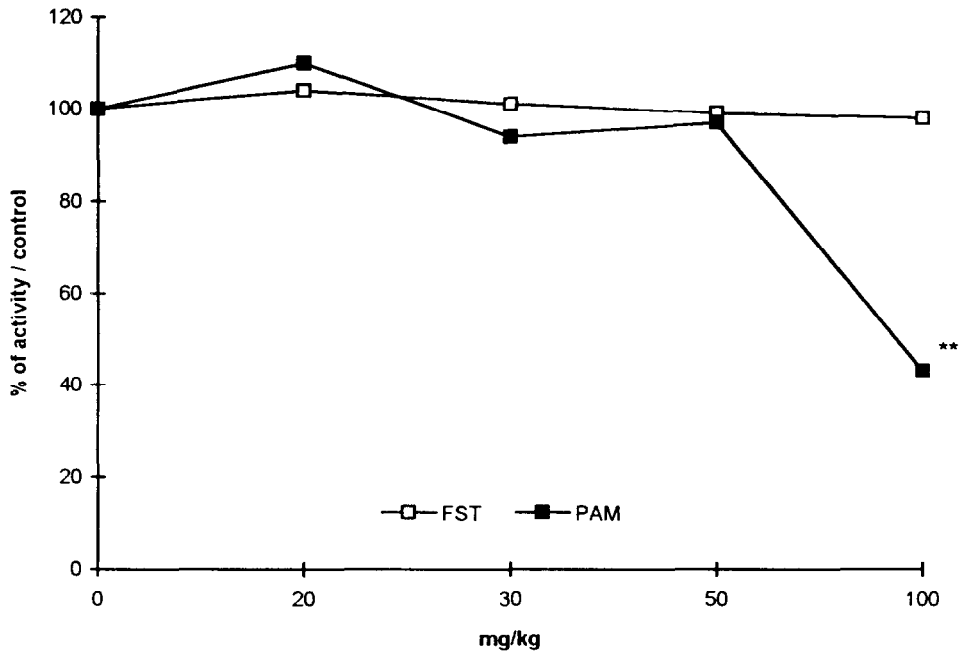

FIG. 1. Effect of increasing doses (IP) of glyburide on immobility time and locomotor activity of mice in the forced swimming test (FST) and the photocell activity meter (PAM) ($n = 10$, $^{**}p < 0.01$). GLY was injected 45 min before the test. Mean immobility times and crossed beams of controls in the FST and the PAM were 225 s and 121 crossed beams, respectively.

the present article, pretreatment of mice with inactive doses of GLY, followed by the administration of subactive doses of 5-HT uptake inhibitors (CIT, PARO, FLUO, FLUV), NA uptake inhibitors (IMI, AMI, DES, VIL), a MAOI-A (MOC) or an atypical ADS (IPR), but not a DA uptake inhibitor (BUP), also significantly reduced immobility in FST. These results indicate that GLY interacts with ADS involved in NA and 5-HT systems in such a way as to reduce the immobility time of mice in the FST.

ATP-sensitive K^+ channels (K_{ATP}) exist extensively in the nervous system, and play a role in neurosecretion at nerve terminals (1,4). It is well accepted that blocking K_{ATP} channels induces a depolarization that activates voltage-dependent Ca^{2+} channels, enhancing Ca^{2+} influx, thus increasing the intracellular Ca^{2+} concentration (13,34). The increased intracellular Ca^{2+} concentration may, in turn, trigger Ca^{2+}-dependent 5-HT and NA release from 5-HT (9) and adrenergic nerve terminals (32). GLY has a potent blocking effect on K_{ATP} channel activity in brain tissue and induces neurotransmitter release (28). All ADS that have additive effects with GLY in the FST have been reported to enhance synaptic 5-HT and NA levels by inhibiting their uptake or metabolism (12,23). It is possible that the synergism of GLY and ADS may lead to an increase of neurotransmitter at the synapse due to inhibition of either uptake or enzymatic breakdown coupled with an increased duration of depolarization and thus produce an antidepressant effect (decreased immobility time) at subactive doses. Further, the three fused ring structure of the tricyclic ADS is known to be ideally suited for the blockade of neural K^+ channels (20,31), and this may contribute to their clinical efficacy. The fact that the tricyclic atypical ADS IPR reduced immobility when combined with GLY, whereas the tetracyclic ADS MAP did not, may be explained in part by the nature of their chemical structures. BUP is a specific inhibitor of DA uptake (23) and had no effect alone or when combined with GLY in the present study. This result suggests that increasing synaptic DA levels (through prolonged depolarization via K^+ channel blockade) is not important for an antidepressant like effect in the FST.

Our series of studies (11,19) on subactive doses of ADS with lithium, quinine, and GLY in the FST were initiated to determine which mechanism was involved in the antiimmobility effect induced by clinically relevant doses of ADS. The comparative effects of pretreatment with either lithium, quinine, or GLY are displayed in Table 4. These data show that quinine and GLY have different efficacy profiles than lithium, particularly with respect to NA uptake inhibitors.

K_{ATP}-sensitive and Ca^{2+} activated potassium channels are present both pre- and postsynaptically (10,17). The effects of GLY and quinine are attributed to the blockade of potassium permeability, which results in a prolongation of nerve action potential and enhanced Ca^{2+} influx that trigger neurotransmitter release (5,24). Morever, it has recently been reported that the modulatory effects of ADS on neuronal excitability via the inhibition of Ca^{2+}-activated K^+ channels may be the final common pathway of pharmacologically different ADS (27). The present study employing GLY, supports the previous work of Guo et al. (11) who reported that pretreatment of quinine with the same ADS showed a similar attenuation of immobility time. Taken together, these results strongly suggest that potassium channels mediated the additive effects of both GLY and quinine on ADS in the FST.

Many studies have shown that lithium causes a dramatic enhancement of 5-HT function (22,30). A previous study from our laboratory showed that given acutely, lithium potentiated the antiimmobility effects in the FST induced by subactive

TABLE 1

EFFECTS OF SUBACTIVE DOSES OF GLYBURIDE (30 mg/kg OR 50 mg/kg, IP 45 MIN BEFORE THE TEST) COMBINED WITH ANTIDEPRESSANTS INHIBITING NEUROTRANSMITTER UPTAKE (IP 30 MIN BEFORE THE TEST) ON IMMOBILITY TIME OF MICE IN THE FORCED SWIMMING TEST

		% Change in Immobility Time				
		Glyburide Alone (% of Saline Control)			Glyburide + Drug (% of Drug Alone)	
Drug	Dose (mg/kg)	30	50	Drug Alone (% of Saline Control)	30	50
NA/5-HT Uptake inhibitors						
Imipramine	4	−4	2	0	−14(b)†	−22(b)†
	6	−4	2	−1	−21(b)*	−27(b)†
Amitriptyline	2	−2	−4	2	−8	−19(b)†
	4	2	4	6	22(b)*	22(b)*
Specific NA uptake inhibitors						
Desipramine	2	−3	1	−4	−11	−6
	4	−3	1	−5	−16	−17(b)†
Maprotiline	4	−4	−2	5	−6	−10
	8	−4	−2	−4	−3	0
Viloxazine	2	−4	1	1	−11(b)†	−21(b)†
	4	−4	1	−8	−2	−17
Specific 5-HT uptake inhibitors						
Citalopram	2	−3	0	2	−22(b)†	−23(b)†
	4	−3	0	−10	−5	−17
Paroxetine	1	−2	−3	−6	−19(b)†	−19(b)†
	2	−2	−3	−9	−24(b)*	−37(b)†
Fluoxetine	4	2	0	6	−16(b)†	−19(b)†
	8	2	0	−2	−18(b)†	−19(b)*
Fluvoxamine	4	−1	−4	−4	−11	−9
	8	−1	−4	−10	−11	−25(b)†
Specific DA uptake inhibitor						
Bupropion	4	0	0	−4	−6	−3
	8	0	0	−4	−2	−2

Symbols indicate the significant degree of values using the Steel test for nonparametric data. *$p < 0.05$, †$p < 0.01$ vs. (a) control group, or vs. (b) drug alone($n = 20$). Mean immobility times of saline controls were: 226s (IMI), 221s (AMI), 224s (DES), 218s (MAP), 227s (VIL), 219s (CIT), 225s (PARO), 215s (FLUO), 227s (FLUV), and 223s (BUP).

doses of ADS with 5-HT properties (19). This result is supported by some direct electrophysiological and biochemical data that showed that short-term treatment of lithium increases depolarization-evoked release of endogenous 5-HT in the hippocampus, and this may be related to the rapid antidepressant action of the drug (5,26). Additionally, both chronic and acute lithium treatment has been reported to inhibit the enzyme inositol-1-phosphatase and cause accumu-

TABLE 2

EFFECTS OF SUBACTIVE DOSES OF GLYBURIDE (30 mg/kg OR 50 mg/kg, IP 45 MIN BEFORE THE TEST) COMBINED WITH ATYPICAL ANTIDEPRESSANTS (IP 30 MIN BEFORE THE TEST) ON IMMOBILITY TIME IN THE FORCED SWIMMING TEST

		% Change in Immobility Time				
		Glyburide Alone (% of Saline Control)			Glyburide + Drug (% of Drug Alone)	
Drug	Dose (g/kg)	30	50	Drug Alone (% of Saline Control)	30	50
Atypical antidepressants						
Trazodone	0.5	−4	−5	−2	−7	6
	4	−4	−5	−3	1	−6
Mianserin	2	1	−3	−1	−15	−4
	4	1	−3	−6	−1	−2
Iprindole	32	0	−3	2	−23(b)†	−11(b)*
	64	0	−3	−15(a)*	2	−22(b)*

Symbols indicate the significant degree of values using the Steel test for nonparametric data. *$p < 0.05$, †$p < 0.01$ vs. (a) control group, or vs. (b) drug alone ($n = 20$). Mean immobility times of saline controls were: 228s (TRA), 223s (MIA), and 224s (IPR).

TABLE 3

EFFECTS OF SUBACTIVE DOSES OF GLYBURIDE (30 mg/kg OR 50 mg/kg, IP 45 MIN BEFORE THE TEST) COMBINED WITH MONOAMINE OXIDASE INHIBITORS (MAOI)(IP 30 MIN BEFORE THE TEST) ON IMMOBILITY TIME OF MICE IN THE FORCED SWIMMING TEST

		% Change in Immobility Time				
		Glyburide Alone (% of Saline Control)		Drug Alone (% of Saline Control)	Glyburide + Drug (% of Drug Alone)	
Drug	Dose (mg/kg)	30	50		30	50
MAOI-A						
Moclobemide	8	1	−4	−1	−7	−8
	32	1	−4	−1	−18(b)*	−31(b)†
MAOI-B						
RO 16 6491	4	−3	−2	0	−11	−8
	16	−3	−2	−4	−12	−8
MIXED						
Nialamide	4	−2	−4	−1	−11	−5
	32	−2	−4	−6	−9(b)*	−4
Pargyline	4	0	−2	1	−2	−8
	32	0	−2	−1	−8	−6

Symbols indicate the significant degree of values using the Steel test for nonparametric data. *$p < 0.05$, †$p < 0.01$ vs. (a) control group, or vs. (b) drug alone ($n = 20$). Mean immobility of saline controls were: 227s (MOC), 228s (RO), 230s (NIA), and 225s (PARG).

lation of inositol 1,4,5-trisphosphate (IP_3) (14) in mouse brain (29). Furthermore, it has been investigated that IP_3 induces Ca^{2+} release from brain microsomes (25), which in turn, activates physiological responses. Therefore, the additive effects of lithium with subactive doses of ADS in the FST may be explained by enhanced neuronal 5-HT release through accumulating IP_3 in specific neuronal cells and increasing the intracellular Ca^{2+} concentration.

In conclusion, the present results suggest that by pretreating mice with potassium channel blockers such as GLY, subactive doses of ADS possessing both NA and 5-HT action, be-

TABLE 4

COMPARED WITH INTERACTION OF LITHIUM (19), QUININE (11), AND GLYBURIDE ON ADS-INDUCED IMMOBILITY OF MICE IN FORCED SWIMMING TEST

	Interaction With ADS		
ADS	Lithium	Quinine	Glyburide
NA/5-HT Uptake inhibitors			
Imipramine	*	*	*
Amitriptyline	—	*	*
NA uptake			
Desipramine	—	*	*
Maprotiline	—	—	—
Viloxazine	—	*	*
5-HT uptake inhibitors			
Citalopram	*	*	*
Paroxetine	*	*	*
Fluoxetine	*	*	*
Fluvoxamine	*	*	*
DA uptake inhibitor			
Bupropion	—	—	—
Atypical antidepressants			
Trazodone	*	—	—
Mianserin	*	—	—
Iprindole	*	*	*
MAOI			
Moclobemide	*	*	*
RO 16 6491	—	—	—
Nialamide	—	—	*
Pargyline	—	*	—

*Significantly additive interaction; $p < 0.05$.

TABLE 5

EFFECTS OF GLYBURIDE (30 AND 50 mg/kg, IP 45 MIN BEFORE THE TEST) COMBINED WITH ANTIDEPRESSANTS (IP 30 MIN BEFORE THE TEST) ON LOCOMOTOR ACTIVITY OF MICE IN THE PHOTOCELL ACTIVITY METER ($n = 10$)

		% Change in Locomotor Activity		
			Glyburide + Drugs (% of Drugs Alone)	
Drugs ADS	Dose mg/kg	Drugs Alone (% of Control)	30	50
Imipramine	4	−20	−25	−26
	6	−35(a)*	6	−17
Amitriptyline	2	−26	—	−34(b)*
	4	−35	−20	−23
Desipramine	4	−31(a)*	—	−6
Viloxazine	2	−17	−19(b)*	−38(b)†
Citalopram	2	3	−20(b)*	−8
Paroxetine	1	12	−47(b)*	−30
	2	22	−44(b)*	−40(b)*
Fluoxetine	4	−19	−18	−20(b)*
	8	−3	−28	−35(b)*
Fluvoxamine	8	6	—	−8
Iprindole	32	−54(a)*	−11	−19(b)*
	64	−78(a)†	—	−8
Moclobemide	32	−54(a)†	−9	−18
Nialamide	32	−8	−24(b)†	—

*$p < 0.05$, †$p < 0.01$, vs. (a) saline control or (b) drug alone.

come effective at producing antiimmobility effects in the FST typically seen with clinically relevant doses of the same drugs. The mechanism responsible for this increase in efficacy is likely a net increase in the amount of synaptic neurotransmitter following prolonged depolarization due to Ca^{2+} influx. The effects of GLY and quinine on potentiating antiimmobility of ADS at subactive doses in FST differ from that of lithium, possibly due to increasing intracellular Ca^{2+}, which influences neuronal transmitters release by directly blocking K^+ channels and affecting second messenger systems (IP_3), respectively.

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