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# The additive effects of quinine on antidepressant drugs in the forced swimming test in mice

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**Abstract** The aim of this study was to investigate if quinine plus antidepressant drugs (ADS) leads to an additive effect in the forced swimming test. Quinine (0.125, 0.5 mg/kg) and ADS (subactive doses) were given IP 45 and 30 min, respectively, before the test. When combined with QUIN, all drugs that act via inhibition of 5-HT uptake (imipramine, amitriptyline, citalopram, paroxetine, fluoxetine and fluvoxamine) significantly increased the swimming time of mice. Among trazodone, mianserin and iprindole (atypical ADS), only iprindole combined with quinine decreased the immobility (increased swimming) of the animals. The specific noradrenaline (NA) uptake inhibitors, desipramine and viloxazine, but not maprotiline, were also found to reduce the immobility time when pretreated with quinine. The mixed monoamine oxidase (MAO) inhibitor (pargyline) and MAO-A inhibitor (moclobemide) also shortened the period of immobility whereas the MAO-B inhibitor (nialamide) and the dopamine (DA) uptake inhibitor (bupropion) did not. Quinine's additive effects on several types of ADS is likely a result of blockade of potassium channels.

**Key words** Antidepressants · Quinine · Forced swimming test · Potassium channel blocker · Mice

## Introduction

Recent studies have shown that the clinical efficacy of lithium is related to its action on the 5-HT system (Heninger et al. 1983; Price et al. 1989). Nixon et al. (1994) found lithium (1 mEq/kg, subactive dose) significantly reduced the immobility time of mice in the forced swimming test (FST) when administered prior to subactive doses of a variety of antidepressants (ADS). The additive effect of lithium was strongest on ADS with serotoninergic properties. The mechanism involved in lithium's actions on the 5-HT system in the forced swimming test is unknown.

The FST is widely used to predict potential antidepressant action of compounds in humans. Immobility time is reduced by clinically relevant doses of tricyclic and atypical ADS, 5-HT uptake inhibitors and monoamine oxidase inhibitors (MAOIs) in mice and rats (Porsolt et al. 1977; Lucki et al. 1994). Furthermore, it was found that combined with clonidine, subactive doses of ADS (tricyclics, 5-HT uptake inhibitors and atypical ADS) produced significant anti-immobility effects in mice (Malinge et al. 1988; Bourin et al. 1991). Two 5-$HT_{1A}$ agonists, gepirone and buspirone, in combination with clonidine or lithium, also reduced immobility time (Hascoet et al. 1993). These results suggested that lithium, like clonidine, may potentiate the effects of subactive doses of ADS in the FST and these effects were greatest with drugs acting on the 5-HT system.

It has been found that the actions of lithium on 5-HT synthesis and in the 5-HT behavioural syndrome (Grahame-Smith and Green 1974) were similar to those of rubidium, caesium and quinine (Wang and Graham-Smith 1992). These studies provided evidence for reducing or blocking potassium channel conductance as a potential link in mediating the effects of lithium, as quinine is regarded as a calcium-activated potassium channel blocker (Atwater et al. 1979; Cherubini et al. 1984). In the present paper, the purpose was to determine the effect of subactive doses of quinine on subactive doses ADS in the FST in mice.

## Materials and Methods

### Animals

Naive male Swiss mice (Centre d'elevage Janvier, France), weighing 20–24 g, were housed at a constant room temperature

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(21 ± 1 °C) in standard conditions, with free access to food and water. Each experiment group consisted of ten randomly chosen mice. Mice were only used once.

The ethical rules of the French Ministry of agriculture for experiments with laboratory animals by law N ° 87.848 were followed.

### Drugs and treatment

The following drugs were used in the study: 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) and quinine (QUIN) (Sigma).

All drugs were dissolved in distilled water. QUIN and the ADS were injected, in a constant volume of 0.5 ml/20 g, IP 45 and 30 min, respectively, prior to the test. Vehicle control animals received distilled water only. Every experiment used nine groups of mice ($n = 10$), including a vehicle control, QUIN control, ADS controls and the ADS interactions with QUIN.

### Measurement of locomotor activity and immobility in mice

To determine appropriate subactive doses of QUIN, a range of doses of QUIN from 0.06 to 4 mg/kg were tested for their locomotor activity and immobility time. To rule out the possibility of a generalized increase in mobility induced by the combination of ADS with QUIN, two doses of each drugs combined with QUIN 0.5 mg/kg were administered to mice prior to placement in a photocell activity meter (OSYS) for 10 min. QUIN pretreatment took place 45 min and ADS 30 min prior to locomotor activity testing as described by Boissier and Simon (1965).

The forced swimming test used was basically the same as described in detail elsewhere (Porsolt et al. 1977). 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 non-parametric statistical methods due to a non-normal distribution. Data were analysed by the Kruskall-Wallis $H$ test for independent groups. Additional Newman-Keuls a posteriori tests were performed, when appropriate, to detect significant differences between groups (Keuls 1952; Armitage and Berry 1987). All analysis were conducted using the P.C.S.M. program (Deltasoft) for the IBM compatible microcomputer.

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

## Results

### Selection of the QUIN doses

Preliminary studies were undertaken to select an appropriate dose of QUIN. QUIN produced a significant reduction in locomotor activity of mice administered a dose of 64 mg/kg. However, in the FST, QUIN did not influence the immobility of mice even given a dose of 128 mg/kg (data not shown). These results indicated the QUIN had some sedative but no antidepressant effects at high dose. For the purposes of the present study, a lower range of QUIN was chosen to achieve a more specific effect and to prevent toxicity. In this range of 0.06–4 mg/kg, QUIN alone did not show any effect on immobility in the FST or locomotor activity of mice as compared to the control group (Fig. 1). When combined with QUIN 0.5 mg/kg, some ADS (AMI, TRA, MIA, IPR, MOC and PARG) produced a significant decrease in locomotor activity (sedative effects) (Table 1). More importantly, no ADS when combined with QUIN produced an increase in the locomotor activity of mice. These preliminary studies were undertaken to ensure that any increases in mobility observed in the FST were not due to a generalized locomotor effect produced by the drug combinations. Prior treatment with QUIN (0.125, 0.5 mg/kg), IMI and CIT were shown to significantly reduce the immobility time of mice in the FST. Therefore, the lower doses of 0.125 and 0.5 mg/kg were subsequently selected as subactive doses for the interaction studies in the FST. The subactive doses of ADS were chosen based on previous experiments in our laboratory (Bourin et al. 1991; Nixon et al. 1994).

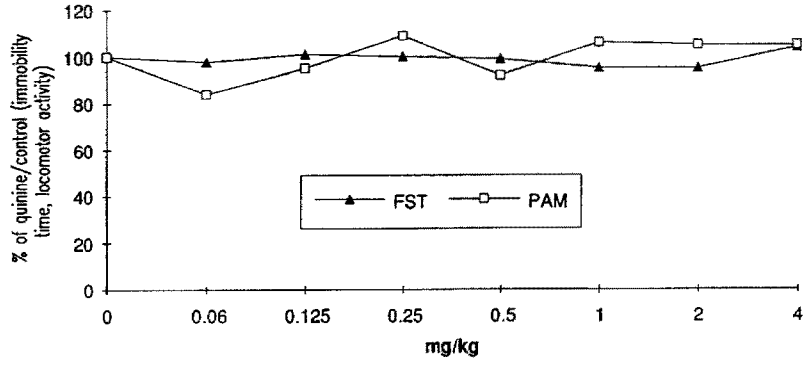


**Fig. 1** Effect of increasing doses of quinine on immobility time and locomotor activity of mice in the forced swimming test (*FST*) and the photocell activity meter (*PAM*), $n = 10$. *QUIN* was injected 45 min before the test. Mean immobility times and crossed-beams of controls in the FST and the PAM were 221 s and 128 crossed-beams, respectively

**Table 1** Effects of quinine (0.5 mg/kg, i.p. 45 min before the test) combined with antidepressants (i.p. 30 min before the test) on locomotor activity of mice in the photocell activity meter

| Quinine with ADS | Dose mg/kg | % change in locomotor activity (% of control) | Quinine with ADS | Dose mg/kg | % change in locomotor activity (% of control) |
|---|---|---|---|---|---|
| Imipramine | 4 | − 6 | Bupropion | 4 | −10 |
| | 8 | −34 | | 8 | 1 |
| Amitriptyline | 2 | − 7 | Trazodone | 0.5 | −29 |
| | 4 | −57** | | 4 | −40** |
| Desipramine | 2 | −10 | Mianserin | 2 | −45** |
| | 4 | − 9 | | 4 | −45** |
| Maprotiline | 4 | −18 | Iprindole | 32 | −59** |
| | 8 | −21 | | 64 | −82** |
| Viloxazine | 2 | − 6 | Moclobemide | 8 | −42** |
| | 4 | −13 | | 32 | −55** |
| Citalopram | 2 | 24 | RO16 6491 | 4 | −19 |
| | 4 | 1 | | 16 | −13 |
| Paroxetine | 1 | 7 | Nialamide | 4 | − 8 |
| | 2 | 16 | | 32 | −12 |
| Fluoxetine | 4 | −26 | Pargyline | 4 | −18 |
| | 8 | − 8 | | 32 | −28** |
| Fluvoxamine | 4 | 9 | | | |
| | 8 | 18 | | | |

*$P < 0.05$, **$P < 0.01$: using the Newman-Keuls test for non parametric data
Control and interaction groups consisted of ten mice. Mean crossed-beams of controls in the PAM was 130 crossed-beams

Interactions with QUIN and ADS at subactive doses

Various inhibitors of neuronal uptake of NA, 5-HT and DA were administered IP to mice pretreated with QUIN 0.125 and 0.5 mg/kg. The results are shown in Table 2. The data showed that IMI (4 mg/kg) in combination with both doses of QUIN decreased the immobility of mice. At a dose of 8 mg/kg IMI alone was effective in decreasing immobility. AMI at 4 mg/kg, combined with QUIN 0.5 mg/kg, produced a significant decrease (28% compared with the drug alone) in immobility time. The specific NA uptake inhibitors, DES and VIL, but not MAP, significantly reduced immobility when combined with QUIN. DES showed a potent interaction with both doses of QUIN. VIL with QUIN 0.125 mg/kg resulted in a small reduction (14%, $P > 0.05$) of immobility time. MAP 8 mg/kg with QUIN 0.5 mg/kg induced a 21% decrease in immobility, however due to a large standard deviation, the immobility time of the interaction compared with MAP alone was not significant. Four selective 5-HT uptake inhibitors were studied in combination with QUIN. All doses tested of these drugs were inactive when administered alone. When pretreated with QUIN, mice treated with CIT, PARO, FLUO and FLUV all showed increased mobility; however, FLUO was only significant with higher doses of QUIN. BUP, a specific DA uptake inhibitor, was unaffected by pretreatment with QUIN.

Three atypical ADS were also investigated in mice pretreated with QUIN (Table 3). Neither TRA nor MIA induced anti-immobility when used alone or in combination with QUIN, whereas IPR with QUIN led to a 14% reduction in immobility ($P < 0.01$). The additive effect between MAOIs and QUIN in the FST were also investigated (Table 4). All MAOIs alone were inactive. Coadministrated with QUIN, MOC (a reversible MAOI-A) as well as PARG, but not NIA (mixed MAOIs) showed a significant decrease in immobility. RO , a reversible MAOI-B, had no effect in the FST either alone or when combined with QUIN.

## Discussion

ADS of various classes were evaluated with regard to their effects when administered with QUIN in the FST. IMI and AMI are inhibitors of both 5-HT and NA uptake, whereas DES and VIL are selective NA reuptake inhibitors (Richelson and Pfenning 1984). CIT, PARO, FLUO and FLUV are selective 5-HT uptake inhibitors (Milne and Goa 1991; Caley and Weber 1993; Messiha 1993; Wilde et al. 1993). MOC is a selective MAO-A inhibitor (Haefely et al. 1993) and PARG is a mixed MAO inhibitor (Glover and Sandler 1986). All drugs described above that act on NA and/or 5-HT systems produced an anti-immobility effect (increased swimming time) in mice pretreated with QUIN. These anti-immobility effects were not dose dependent. Taken together, the present results suggest that NA and 5-HT systems are essentially linked in mediating antidepressant action on immobility in mice (Porsolt et al. 1977; Malinge et al. 1988; Bourin et al. 1991).

It has previously been demonstrated that potassium channel blockers prolong the presynaptic action potential, leading to an increase in $Ca^{2+}$ influse and enhanced neurotransmitter release (Katz and Miledi 1969; Benoit and Mambrini 1970; Kumamoto and Kuba 1985). Furthermore, it has been reported that $Ca^{2+}$-dependent

**Table 2** Effects of subactive doses of quinine (0.125 mg/kg or 0.5 mg/kg, IP 45 min before the test) combined with antidepressants inhibiting uptake (IP 30 min before the test) on immobility time of mice in the forced swimming test

| Drug | Dose (mg/kg) | % change in immobility time | | | | |
|---|---|---|---|---|---|---|
| | | Quinine alone (% of saline control) | | Drug alone (% of saline control) | Quinine + drug (% of drug alone) | |
| | | 0.125 | 0.5 | | 0.125 | 0.5 |
| *NA/5HT uptake inhibitors* | | | | | | |
| Imipramine | 4 | 0 | −2 | − 1 | −20**(b) | −14*(b) |
| | 8 | 0 | −2 | −19**(a) | − 9 | − 9 |
| Amitriptyline | 2 | −2 | −2 | −16**(a) | −11 | 4 |
| | 4 | −2 | −2 | −17*(a) | −14 | −28**(b) |
| *Specific NA uptake inhibitors* | | | | | | |
| Desipramine | 2 | −4 | 2 | −11*(a) | − 8*(b) | −26**(b) |
| | 4 | −4 | 2 | −12*(a) | −31**(b) | −29**(b) |
| Maprotiline | 4 | −3 | −2 | − 7 | − 5 | 0 |
| | 8 | −3 | −2 | −13 | 0 | −21 |
| Viloxazine | 2 | −1 | 2 | 7 | −13*(b) | −10 |
| | 4 | −1 | 2 | 0 | −14*(b) | − 3 |
| *Specific 5-HT uptake inhibitors* | | | | | | |
| Citalopram | 2 | 0 | −3 | − 4 | −16*(b) | −13*(b) |
| | 4 | 0 | −3 | 0 | −24*(b) | −17*(b) |
| Paroxetine | 1 | 5 | 0 | − 2 | − 1 | − 9 |
| | 2 | 5 | 0 | − 6 | −14**(b) | −23**(b) |
| Fluoxetine | 4 | −1 | −5 | − 4 | − 6 | − 3 |
| | 8 | −1 | −5 | − 4 | − 6 | −22*(b) |
| Fluvoxamine | 4 | 0 | −3 | 2 | −21*(b) | −19*(b) |
| | 8 | 0 | −3 | − 1 | −29*(b) | −16*(b) |
| *Specific DA uptake inhibitor* | | | | | | |
| Bupropion | 4 | −2 | 3 | 6 | − 3 | − 6 |
| | 8 | −2 | 3 | 0 | − 4 | − 4 |

Control and interaction groups consisted of ten mice. *Asterisks* indicate the significant degree of values using the Newman-Keuls test for non-parametric data: $P < 0.05$*, $P < 0.01$** versus (a) control group, or versus (b) ADS alone. Mean immobility times of saline controls were: 222 s (IMI), 231 s (AMI), 219 s (DES), 226s (MAP), 219 s (VIL), 224 s (CIT), 220 s (PARO), 225 s (FLUO), 223 s (FLUV), 214 s (BUP)

**Table 3** Effects of subactive doses of quinine (0.125 mg/kg or 0.5 mg/kg, IP 45 min before the test) combined with atypical antidepressants (IP 30 min before the test) on immobility time of mice in the forced swimming test

| Drug | Dose (mg/kg) | % change in immobility time | | | | |
|---|---|---|---|---|---|---|
| | | Quinine alone (% of saline control) | | Drug alone (% of saline control) | Quinine + drug (% of drug alone) | |
| | | 0.125 | 0.5 | | 0.125 | 0.5 |
| *Atypical antidepressants* | | | | | | |
| Trazodone | 0.5 | −4 | 3 | 1 | −14 | − 9 |
| | 4 | −4 | 3 | − 2 | − 9 | − 5 |
| Mianserin | 2 | 1 | 0 | − 5 | − 3 | −13 |
| | 4 | 1 | 0 | − 3 | − 8 | − 7 |
| Iprindole | 32 | 1 | 0 | − 3 | −15*(b) | −14**(b) |
| | 64 | 1 | 0 | −13*(a) | −14**(b) | −11*(b) |

Control and interaction groups consisted of ten mice. *Asterisks* indicate the significant degree of values using the Newman-Keuls test for non-parametric data: $P < 0.05$*, $P < 0.01$** versus (a) control group, or versus (b) ADS alone. Mean immobility times of saline controls were: 214 s (TRA), 228 s (MIA), 228 s (IPR)

5-HT synthesis and release were potentiated through stimulating the 5-HT presynaptic autoreceptors by decreasing potassium conductance (Hamon et al. 1979; Gohert 1980; Sawada and Nagatsu 1986). Similarly, prejunctional alpha$_2$-adrenoceptor mediated NA release was enhanced by decreasing the permeability of potassium ions (Morita and North 1981; Zimanyi et al. 1988). In our study, QUIN, a $Ca^{2+}$-dependent potassium channel blocker, when administered concomitantly with ADS acting on NA and 5-HT systems,

**Table 4** Effects of subactive doses of quinine (0.125 mg/kg or 0.5 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

| Drug | Dose (mg/kg) | % change in immobility time | | | | |
|---|---|---|---|---|---|---|
| | | Quinine alone (% of saline control) | | Drug alone (% of saline control) | Quinine + drug (% of drug alone) | |
| | | 0.125 | 0.5 | | 0.125 | 0.5 |
| MAOI-A | | | | | | |
| Moclobemide | 8 | 0 | −2 | −4 | −16**(b) | −17**(b) |
| | 32 | 0 | −2 | −1 | −10 | −12 |
| MAOI-B | | | | | | |
| RO 16 6491 | 4 | 2 | −1 | 0 | 0 | 0 |
| | 16 | 2 | −1 | 0 | − 4 | −11 |
| MIXED | | | | | | |
| Nialamide | 4 | 2 | −1 | −8 | 5 | 10 |
| | 32 | 2 | −1 | 4 | − 3 | − 6 |
| Pargyline | 4 | −2 | 0 | −1 | − 4 | −23**(b) |
| | 32 | −2 | 0 | −4 | − 7 | −14*(b) |

Control and interaction groups consisted of ten mice. *Asterisks* indicate the significant degree of values using the Newman-Keuls test for non-parametric data: $P < 0.05$*, $P < 0.01$** versus (a) control group, or versus (b) ADS alone. Mean immobility times of saline controls were: 231 s (MOC), 224 s (RO), 224 s (NIA), 228 s (PARG)

produced anti-immobility in this behavioral paradigm. These results indicate that enhancing NA and 5-HT transmitter release via potassium channel blockade may be involved in the increased anti-immobility effects of ADS.

Prior evidence exists to suggest that tricyclic antidepressants could inhibit $Ca^{2+}$- dependent potassium channels in neurones (Ogata et al. 1989; Wooltorton and Mathie 1993) and that they exhibit additivity with tetraethyl ammonium and QUIN (Kamatchi and Ticku 1991). In the present investigation, low doses of tricyclic antidepressants (IMI, AMI, DES), which have no effect on their own, were found to produce strong anti-immobility effects when combined with a pretreatment of low doses of QUIN. This result suggests that a synergism of potassium channel blockade exists, with concomitant treatment with tricyclic ADS and QUIN resulting in more transmitter synthesis and release, and inducing an anti-immobility effect.

MAP, a specific NA uptake inhibitor (Richelson and Pfenning 1984), produced 21% reduction of immobility, yet failed to reach significance. One possible explanation for this result is that its tetracyclic structure was sterically prohibited from affecting potassium channels. Recent studies have shown that VIL, another specific NA uptake inhibitor, also inhibits both monoamine oxidase A and B isozymes, resulting in increased catecholamine and serotonin levels in vivo and in vitro (Martinez et al. 1986). VIL, the MAO A inhibitor MOC and the non-specific MAO inhibitor PARG, all at sub-active doses, produced anti-immobility effects when mice were pretreated with QUIN. Subactive doses of 5-HT uptake inhibitors showed similar effects. These results are consistent with previous reports showing that the 5-HT releaser fenfluramine reduced immobility in rats (Porsolt et al. 1979). Thus, the additive effects of QUIN with subactive doses ADS may be explained by elevation of brain NA and 5-HT concentrations due to potentiation of neuronal activation by potassium channel blockade.

The most potent pharmacologic action of the atypical ADS, MIA and TRA is their blockade of the $5\text{-HT}_{2A/2C}$ receptor (Sanders-Bush and Conn 1989; Marek et al. 1992). It has been reported that 5-HT uptake inhibitors and $5\text{-HT}_{1A}$ receptor agonists reduce immobility in FST, but that other 5-HT subreceptor agonists and 5-HT receptor antagonists did not (Lucki et al. 1994). Our results concur with this finding, in that no dose combination of QUIN with MIA or TRA reduced immobility. In contrast, the atypical ADS IPR, which possesses a tricyclic structure, differed from other atypical ADS and produced an anti-immobility effect with QUIN. The ability of QUIN to potentiate the activity of IPR provides support for the theory that blocking potassium channels and increasing synaptic transmitter concentration may be a mechanism of action for QUIN's effect on ADS in the FST.

BUP works primarily through dopamine related mechanisms by inhibiting DA uptake (Ferris et al. 1983; Richelson and Pfenning 1984). Our finding that QUIN did not influence the anti-immobility time produced by BUP suggests that the DA system is not directly involved in potentiation of ADS at subactive doses by pretreatment with QUIN.

In summary, this experiment was designed to investigate the effects of pretreatment with QUIN on ADS in the FST and compare the results to those found with pretreatment with lithium (Nixon et al. 1994). It was previously reported, that pretreatment with lithium enhanced the anti-immobility effects of ADS which act on the 5-HT system in mice. Previous studies have shown that chronic or acute treatment with lithium increases 5-HT synthesis and release (Berggren 1986;

Friedman and Wang 1988; Sharp et al. 1991), potentiates hyperactivity produced by MAOI plus L-tryptophan (Grahame-Smith and Green 1974) and decreases 5-HT mediated head-twitches and 5-HT1a induced hypothermia in mice (Wang and Grahame-Smith 1992). These data indicate that lithium's effect seems to be an enhancement of 5-HT function. Recently, the major effector mechanism of lithium was demonstrated to be inhibition of cAMP formation and inositol-1-phosphatase activity; however, these effects of lithium were not confirmed to be 5-HT specific (Price et al. 1990). Our data showed that pretreatment with QUIN resulted in an enhancement of not only serotonergic ADS, but also those acting specifically on NA systems, atypical and MAOI ADS. The common factor seems to be increasing synaptic availability of neurotransmitter, likely as a result of QUIN blockade of $Ca^{2+}$-dependent potassium channels. This blockade induces prolonged neuronal activity, leading to increased presynaptic release and thus, synaptic availability of neurotransmitter. Another possible contributor to QUIN's effects, results from metabolism. Specifically, QUIN is a known inhibitor of the liver enzyme cytochrome $P_{450}$ II D 6 (Kobayashi et al. 1989). It is this enzyme that is responsible for the deactivation, through hydroxylation, of many antidepressant compounds. Further studies are required and underway to assess the relative contributions of both potassium channel blockade, and metabolic inhibitor as mechanism of action in QUIN's potentiating effects of ADS.

## References


Armitage P, Berry G (1987) Statistical methods in medical research 2nd edn.: Blackwell, Oxford, pp 203–205

Atwater I, Dawson CM, Ribalet B, Rojas E (1979) Potassium permeability activated by intracellular calcium ion concentration in the pancreatic beta cell. J Physiol 288:575–588

Benoit PR, Mambrini J (1970) Modification of transmitter release by ions which prolong the presynaptic action potential. J Physiol 210:681–695

Berggren U (1986) Effects of chronic lithium treatment on brain monoamine metabolism and amphetamine-induced locomotor stimulation in rats. J Neural Transm 64:239–250

Boissier JR, Simon P (1965) Action de la caféine sur la motilité de la souris. Arch Int Pharmacodyn 158:212–221

Bourin M, Colombel MC, Malinge M, Bradwejn J (1991) Clonidine as a sensitizing agent in the forced swimming test for revealing antidepressant activity. J Psychiatr Neurosci 16:199–203

Caley CF, Weber SS (1993) Paroxetine: a selective serotonin reuptake inhibiting antidepressant. Ann Pharmacother 27: 1212–1222

Cherubini E, North RA, Surprenant A (1984) Quinine blocks a calcium-activated potassium conductance in mammalian enteric neurons. Br J Pharmacol 83:3–5

Ferris RM, Cooper BR, Maxwell RA (1983) Studies of bupropion's mechanism of antidepressant activity. J Clin Psychiatry 44:74–78

Friedman E, Wang HY (1988) Effect of chronic lithium treatment on 5-hydroxtryptamine autoreceptors and release of 5-[$^3$H] hydroxtryptamine from rat brain cortical, hippocampal, and hypothalamic slices. J Neurochem 50:195–201

Glover V, Sandler M (1986) Clinical chemistry of monoamine oxidase. Cell Biochem Func 4:89–97

Gohert M (1980) Serotonin-receptor-mediated modulation of $Ca^{2+}$-dependent 5-hydroxytryptamine release from neurones of the rat brain cortex. Naunyn-Schmiedeberg's Arch Pharmacol 314: 223–230

Grahame-Smith DG, Green AR (1974) The role of brain 5-hydroxytryptamine in the hyperactivity produced in rats by lithium and monoamine oxidase inhibition. Br J Pharmacol 52:19–26

Haefely W, Burkard WP, Cesura A, Colzi R, Kettler R, Lorez HP, Martin JR, Moreau JL, Richards JG, Schaffner R, Scherchlicht R, Sepinwall J, Prada MD (1993) Pharmacology of moclobemide. Clin Neuropharmacol 16[Suppl 2]:S8–18

Hamon M, Bourgoin S, Artaud F, Glowinski J (1979) The role of intraneuronal 5-HT and of tryptophan hydroxylase activation in the control of 5-HT synthesis in rat brain slices incubated in $K^+$ enriched medium. J Neurochem 33:1031–1042

Hascoet M, Bourin M, Khimake S (1993) Additive effect of lithium and clonidine with 5HT1a agonists in the forced swimming test. Prog Neuro-psychopharmacol Biol Psychiatry 18:381–396

Heninger GR, Charney DS, Sternberg DE (1983) Lithium carbonate augmentation of antidepressant treatment: an effective prescription for treatment-refractory depression. Arch Gen Psychiatry 40:1335–1342

Kamatchi GL, Ticku MK (1991) Tricyclic antidepressants inhibit $Ca^{2+}$-activated $K^+$-efflux in cultured spinal cord neurons. Brain Res 545:59–65

Katz B, Miledi R (1969) Tetrodotoxin-resistant electric activity in presynaptic terminals. J Physiol 203:459–487

Keuls M (1952) The use of studentized range in connection with an analysis of variance. Euphytica 1:112–122

Kobayashi S, Murray S, Watson D, Sesardic S, Davies DS, Boobis AR (1989) The specificity of inhibition of debrisoquine 4-hydroxylase activity by quinidine and quinine in the rat is the inverse of that in man. Biochem Pharmacol 38:2795–2799

Kumamoto E, Kuba K (1985) Effects of $K^+$-channel blockers on transmitter release in bullfrog sympathetic ganglia. J Pharmacol Exp Ther 235:241–247

Lucki I, Singh A, Kreiss DS (1994) Antidepressant-like behavioral effects of serotonin receptor agonists. Neurosci Biobehav Rev 18:85–95

Malinge M, Bourin M, Colombel MC, Larousse C (1988) Additive effects of clonidine and antidepressants drugs in the mouse forced-swimming test. Psychopharmacology 96:104–109

Marek GJ, McDougle CJ, Price LH, Seiden LS (1992) A comparison of trazodone and fluoxetine: implications for a serotonergic mechanism of antidepressant action. Psychopharmacology 109:2–11

Martinez BC, Dominiak P, Kees F, Grobecker H (1986) Inhibition of monoamine oxidase by viloxazine in rats. Arzneimittelforschung 36:800–803

Milne RJ, Goa KL (1991) Citalopram: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. Drugs 41:450–477

Messiha FS (1993) Fluoxetine: a spectrum of clinical applications and postulates of underlying mechanisms. Neurosci Biobehav Rev 17:385–396

Morita K, North RA (1981) Clonidine activates membrane potassium conductance in myenteric neurons. Br J Pharmacol 74: 419–428

Nixon MK, Hascoet M, Bourin M, Colombel MC (1994) Additive effects of lithium and antidepressants in the forced swimming test: further evidence for involvement of the serotoninergic system. Psychopharmacology 115:59–64

Ogata N, Yoshii M, Narahashi T (1989) Psychotropic drugs block voltage-gated ion channel in neuroblastoma cells. Brain Res 476:140–144

Porsolt RD, Bertin A, Jalfre M (1977) Behavioural despair in mice: a primary screening test for antidepressants. Arch Int Pharmacodyn 229:327–336

Porsolt RD, Bertin A, Blavet N, Deniel N, Jalfre M (1979) Immobility induced by forced swimming in rats: effects of agents which modify central catecholamine and serotonin activity. Eur J Pharmacol 57:201–210

Price LH, Charney DS, Delgado PL, Heninger GR (1989) Lithium treatment and serotonergic function: neuroendocrine and behavioral responses to intravenous L-tryptophan in affective disorder patients. Arch Gen Psychiatry 46:13–19

Price LH, Charney DS, Delgado PL, Heninger GR (1990) Lithium and serotonin function: implications for the serotonin hypothesis of depression. Psychopharmacology 100:3–12

Richelson E, Pfenning M (1984) Blockade by antidepressants and related compounds of biogenic amine uptake into rat brain synaptosomes: most antidepressants selectively block norepinephrine uptake. Eur J Pharmacol 104:277–286

Sanders-Bush E, Breeding M, Knoth K, Tsutsumi M (1989) Sertraline-induced desensitization of the serotonin 5-HT-2 receptor transmembrane signalling system. Psychopharmacology 99: 64–69

Sawada M, Nagatsu T (1986) Stimulation of the serotonin autoreceptor prevents the calcium-calmodulin-dependent increase of serotonin biosynthesis in rat raphe slices. J Neurochem 46: 963–967

Sharp T, Bramwell SR, Lambert P, Grahame-Smith DG (1991) Effect of shart- and - long term administration of lithium on the release of endogenous 5-HT in the hippocampus of the rat in vivo and vitro. Neuropharmacology 30:977–984

Wang H, Grahame-Smith DG (1992) The effects of rubidium, caesium and quinine on 5-HT mediated behaviour in rat and mouse-3. Quinine. Neuropharmacology 31:425–431

Wilde MI, Plosker GL, Benfield P (1993) Fluvoxamine: an updated review of its pharmacology, and therapeutic use in depressive illness. Drugs 46[5]:895–924

Wooltorton JRA, Mathie A (1993) Block of potassium currents in rat isolated sympathetic neurones by tricyclic antidepressants and structurally related compounds. Br J Pharmacol 110: 1126–1132

Zimanyi I, Folly G, Vizi ES (1988) Inhibition of $K^+$ permeability diminishes alpha$_2$-adrenoceptor mediated effects on norepinephrine release. J Neurosci Res 20:102–108