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5-HT uptake blockade prevents the increasing effect of K_{ATP} channel blockers on electrically evoked [^{3}H]-5-HT release in rat and mouse neocortical slices

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Abstract

To explore if prolonged – as opposed to acute – 5-HT uptake blockade can lead to changes in the function of ATP-dependent potassium (K_{ATP}) channels, we investigated in rat and mouse neocortical slices the effects of K_{ATP} channel blockers on electrically evoked [^{3}H]-serotonin ([^{3}H]-5-HT) release after short- and long-term exposure to 5-HT uptake blockers. Glibenclamide (1 μM), a K_{ATP} channel blocker, enhanced the electrically evoked [^{3}H]-5-HT release by 66 and by 77%, respectively, in rat and in mouse neocortex slices. This effect was confirmed in the rat by tolbutamide (1 μM), another K_{ATP} channel antagonist. After short-term blockade (45 min) of 5-HT uptake, glibenclamide still increased the release of [^{3}H]-5-HT in the rat. Glibenclamide, however, failed to enhance [^{3}H]-5-HT release after long-term uptake blockade (210 min). In the mouse, however, both short- and long-term inhibition of 5-HT reuptake by citalopram (1 μM) prevented the facilitatory effect of glibenclamide. The Na^+/K^+-ATPase inhibitor ouabain (3.2 μM) abolished the glibenclamide-induced increase in [^{3}H]-5-HT release in both rat and mouse, suggesting that an operative Na^+/K^+-ATPase is a prerequisite for activation of K_{ATP} channels. The terminal 5-HT_{1B} autoreceptor-mediated feedback control was involved in the glibenclamide-induced increase in [^{3}H]-5-HT release only in mouse neocortical tissue, as evident from the use of the 5-HT_{1B} autoreceptor ligands metitepin (1 μM) and cyanopindolol (1 μM). These results suggest that in the rat long-term uptake blockade leads to an impaired activity of the Na^+/K^+-ATPase, which increases intracellular ATP and consequently closes K_{ATP} channels. In the mouse, however, short-term uptake blockade seems to already reduce the activity of the Na^+/K^+-ATPase and thereby the consumption of ATP. Blockade of 5-HT transporters thus may close K_{ATP} channels through increased intracellular ATP. The following slight depolarisation seems to facilitate 5-HT release. These results may contribute to a better understanding of the mechanisms involved in the clinical time latency of antidepressant efficacy of monoamine uptake blockers.
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1. Introductory statement

The pathology of depression involves dysfunction of monoamine neurotransmitter circuits in the central nervous system, particularly of serotonin (5-HT) and noradrenaline (NA) (for reviews, see Duman et al., 1997; Wong and Licinio, 2001; Nemeroff and Owens, 2002). Although most antidepressant drugs increase monoamine concentrations in the synaptic cleft within hours of initial treatment, the time latency to reach full clinical efficacy is several weeks (Nemeroff and Owens, 2002; Wong and Licinio, 2001, 2004). This delay may be the result of presynaptic and/or postsynaptic adaptative mechanisms secondary to reuptake inhibition, compatible with the assumption that changes in neurotransmission are only the initial trigger for slower adapting processes. Beside activation of intracellular second messenger cascades, regulation of gene expression (Vaidya and Duman, 2001) or desensitisation of autoreceptors (Drevets et al., 2000; Hasler et al., 2004; Shalom et al., 2004), modulation of potassium channels may be involved in the molecular and cellular mechanisms underlying the effects of antidepressant treatment. The closure of different subtypes of potassium channels resulted in an antidepressant-like effect in the forced swimming test (Galeotti et al., 1999; Kaster et al., in press), a well established animal model used to

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predict antidepressant efficacy of compounds in humans (Porsolt et al., 1978). The addition of the blocker of ATP-dependent K^+ (K_{ATP}) channels, glibenclamide, to subactive doses of selective serotonin reuptake inhibitors (SSRI) resulted in an improvement in the forced swimming test behaviour (Guo et al., 1995, 1996). In contrast to glibenclamide, K_{ATP} channel openers like cromakalim blocked the antidepressant-like effect of the SSRI paroxetine (Redrobe et al., 1996). Recently, Eckhardt et al. (2003) showed that the quasi-physiological [^{3}H]-noradrenaline ([^{3}H]-NA) release in rat neocortical slices is modulated through K_{ATP} channel blockade and that such a modulation was dependent on the duration of NA uptake blockade and on Na^+/K^+-ATPase activity. These observations suggest that K_{ATP} channels may influence neurotransmitter release, thereby playing a role in the mode of action of antidepressant drugs.

K_{ATP} channels are double tetramers formed of four inwardly rectifying K^+ channels (Kir) and four sulphonylurea receptors (SUR) subunits (for reviews, see Ashcroft and Gribble, 1998; Seino, 1999). K_{ATP} channels, characteristically closed by ATP, are present in numerous tissues including cardiac muscle, pancreatic β-cells and the central nervous system (Ashcroft and Gribble, 1998). The open probability of these channels directly depends on the intracellular ATP/ADP ratio. Therefore, K_{ATP} channels of the plasma membrane link the membrane potential to the metabolic state of the cell. K_{ATP} channel opening causes both hyperpolarisation of the resting membrane potential and shortening of the action potential duration, leading to a reduction of calcium influx and of subsequent neurotransmitter release. Although K_{ATP} channels are abundantly expressed in the brain, their physiological role in the CNS is poorly understood.

The current study was undertaken to investigate whether the duration of uptake blockade by the SSRIs citalopram (Cit; Hyttel, 1994) and fluvoxamine (Flu; Owens et al., 1997) interacts with the effects of K_{ATP} channels on 5-HT release in rat and mouse neocortical slices, analogously to conditions seen with NA release upon blockade of NA transporters in rat neocortical slices (Eckhardt et al., 2003). In order to provide some insights into the possible mechanisms underlying the effect of glibenclamide we investigated whether blockade of Na^+/K^+-ATPase, known to be involved in regulation of neuronal excitability, alters the influence of K_{ATP} channels on [^{3}H]-5-HT release. Furthermore, we evaluated whether activation or blockade of terminal 5-HT autoreceptors may influence the effect of K_{ATP} channel closure.

2. Experimental procedures

2.1. Materials

[1,2-^{3}H(N)]-5-HT (specific activity 30 Ci/mmol) was purchased from Perkin-Elmer, USA. The following drugs were kindly provided by or purchased from the sources indicated: citalopram hydrobromide and glibenclamide (RBI-Biotrend, Germany); cyanopindolol fumarate (Sandoz, Switzerland); fluvoxamine maleate (Duphar, The Netherlands); ouabain (Sigma, Gemany); metitepin maleate (Hoffmann-La Roche, Switzerland); tolbutamide (ICN-Biomedicals, USA); ouabain (Sigma, Gemany). citalopram hydrobromide, fluvoxamine maleate, metitepin maleate and ouabain were dissolved in distilled water, glibenclamide was dissolved in ethanol and further diluted with buffer; cyanopindolol fumarate was dissolved in DMSO and further diluted with buffer; tolbutamide was directly dissolved in the vessel which contained superfusion buffer. Possible effects of all vehicles were controlled in each assay.

2.2. Tissue source

Wistar rats weighing 200–300 g and strain B6 CBA mice weighing 25–30 g of both sexes were maintained according to institutional policies and guidelines. All efforts were made to minimize both the suffering and the number of animals. All animal experiments were carried out in accordance with the National Institutes of Health guide for the care and use of laboratory animals. The animals were decapitated under anaesthesia with CO_2 and the brains were rapidly removed and rinsed three times with ice-cold buffer. The buffer used for tissue collection, incubation and superfusion (see below) contained (mM): NaCl 121, KCl 1.8, $CaCl_2$ 1.3, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, glucose 10 and ascorbic acid 0.06. Before use, the medium was saturated with 95% O_2, 5% CO_2 and the pH adjusted to 7.4.

2.3. Superfusion experiments

Neocortical tissues of both species were dissected and sliced perpendicularly to the surface (350 μm thick slices, McIllwain Tissue Chopper, Bachofer, Germany). The slices of each species were incubated for 60 min in medium prewarmed to 37 °C containing 0.1 μM [^{3}H]-5-HT. After incubation the slices were transferred to superfusion chambers (volume 100 μl) and then superfused with buffer (37 °C) at a rate of 0.4 ml/min. A preperiod of superfusion (165 min) served to remove excess radioactivity and cell detritus. The superfusion fluid was only collected after this preperfusion, continuously as 5 min fractions in vials containing 3 ml Ultima Gold liquid scintillation cocktail (Packard Bioscience, The Netherlands). During superfusion slices were stimulated electrically (270 rectangular pulses, 40 mA, 3 Hz). At the end of experiments, the slices were removed from the chambers and dissolved in 0.5 ml Soluene-350® (Packard Instruments). The solubilised slices were mixed with 10 ml, the superfusate fractions with 3 ml, of liquid scintillation cocktail (Ultima Gold®) and tritium content was determined by liquid scintillation spectrometry (Tri-Carb liquid scintillation analyzers 2100 TR, Packard Instruments). The duration of preperfusion and superfusion, time of drug application and stimulation (S_1, S_2) are displayed in Fig. 1 (for abbreviations see legends to Figs. 2 and 3 and Tables 1–4). 5-HT uptake blockers were either absent or added 15 min (''short-term'' uptake blockade) or 180 min (''long-term'' uptake blockade) prior to S_1 and remained present throughout the experiment.

The outflow of tritium was calculated as a fraction of the tritium content of the corresponding slice at the onset of the respective collection period (fractional rate, 5 min^{-1}). The [^{3}H]-overflow elicited by electrical stimulation was calculated as the difference ''total tritium outflow from the onset of the respective stimulation to 20 min afterwards'' minus ''estimated basal outflow''; basal outflow was assumed to decline linearly from the collection period before to the collection period 20 min after the onset of stimulation. The stimulation-evoked [^{3}H]-overflow was then expressed as a percentage of the tritium content of the slice at the beginning of the respective stimulation. For further evaluation, ratios or differences were calculated of the overflow evoked by S_2 and the overflow evoked by S_1. Moreover, effects of drugs were calculated for each single slice as percentage of control, using the corresponding mean control S_2/S_1 ratio or $S_2 - S_1$ difference as the reference. To quantify possible drug or vehicle effects on basal tritium outflow ratios of the fractional [^{3}H]-efflux during the 5-min collection period just before S_2 and S_1 were calculated (b_2/b_1 ratio). None of them affected basal ratios at the concentrations used in all experiments performed (data not shown).

2.4. Statistics

Results (S_1 values, S_2/S_1 ratios and $S_2 - S_1$ differences of the [^{3}H]-overflow-representing quasi-physiological 5-HT release according to Göthert (1982) and Feuerstein et al. (1987a, 1996) are given as arithmetic means of n individual data with 95% confidence intervals (CI_{95}) to indicate probability (Altman, 1991). When appropriate, the S_2/S_1 ratios and the $S_2 - S_1$ differences were normalised (S_2/S_{1norm}, $S_2 - S_{1norm}$ values), i.e. each single ratio was divided by

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