from resistant depression (RD). As between 20–30% of depressed patients have RD, the presence of depression subtypes with distinct pathophysiology is suggested. The neurobiological approach to RD is aimed at identifying and characterizing these different subtypes of RD. Different underlying mechanisms which may play a role in RD include: the development of tolerance ("escape"), a "kindling" type of phenomenon, or no response to begin with. Different types of underlying pathophysiological mechanisms have been proposed for RD, including: higher incidence of HPA axis hyperactivity, lower availability of l-tryptophan to the brain, frontal or parietal perfusion defects, genetic factors, subtle abnormalities in the thyroid system, a combination of 5HT/HPA axis and brain lesion, or a combination of 5HT, NA and HPA abnormalities. In order to gain better knowledge of these different options, studies with RD patients, that provide a careful evaluation of the HPA axis and of serotonergic and noradrenergic responsivity, as well as evaluation of the thyroid system, are warranted. Tryptophan depletion and NE depletion have proven to be an effective tool in the study of depression and might be of particular interest in RD. Brain imaging, pre- and post-treatment, and a dichotomous comparison of changes in brain activity in patients who responded to treatment for RD might be of value. However, these have not yet been studied systematically. A combination of brain imaging with pharmacological challenge, or depletion with either 5HT or NE, might be of particular value, as these combine the "activation" of depression with a "snap shot" of brain activity. Patients with RD suffer greatly and need to be treated. Underlying various psychobiological abnormalities might assist us in tailoring a treatment specifically to the patient.

S60-4

PHARMACODYNAMICS AND PHARMACOKINETICS AS A POSSIBLE CAUSALITY IN RESISTANT DEPRESSION

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Treatment resistant depression (TRD) may involve various degrees of disequilibrium between pharmacodynamic and pharmacokinetic variables. The key neurotransmitters implicated in the actiology of depression are serotonin (5-HT), norepinephrine (NE) and dopamine (DA).

The ability of depletion strategies, which decrease 5-HT activity (administration of para-chlorophenylalanine (PCPA) or a low tryptophan diet), creates treatment resistance to the effect of antidepressants. This evidence strongly supports the importance of 5-HT for TRD.

There is limited evidence for a possible causal relationship between dysfunctional central NA and DA neurotransmission and TRD. However, it has been shown that: the addition of reserpine to tricyclic antidepressants (TCA) might augment the antidepressant effects in TRD; yohimbine, an alpha-2-blocker, may potentiate TCA therapy.

In the last years we have investigated the interactions between all three monoamine systems implicated in antidepressant action by studying the role of intracellular messengers which may represent a common target in the action of different antidepressants. In particular data on the effects of serotonin reuptake inhibitors (SSRI), SNRI and TCAs on the modifications of specific phosphoproteins and on the activity of protein kinases located at pre- and postsynaptic level will be presented.

Moreover, large individual differences in metabolism might represent a rationale for refractory depression.

In conclusion this presentation will deal with pharmacodynamic and pharmacokinetic factors with the aim to establish a possible casual relationship in TRD.

S60-5

GENERAL THERAPEUTIC STRATEGIES IN TRD: LIMITATIONS AND PROSPECTS

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Current strategies for treatment of resistant depression have been based on the results from a small number of controlled studies and to a larger extent on the possibly overoptimistic reporting of open case studies. The treatment of resistant depression needs to address the most common causes of non response, which are inappropriate dosage of antidepressants and poor compliance, before initiating more sophisticated approaches. Initially the antidepressant should be used in full or appropriate doses with adequate checks on individual metabolism or on compliance using drug plasma level monitoring where appropriate.

The results of investigations of the provocation of depression using pharmacological probes suggest that some depressions have a selective response to SSRIs while others are noradrenergic. These findings suggest a rational basis for (a) switching between different classes of an antidepressant in the case of nonresponse, or (b) augmenting an SSRI with a NARI or vice versa. A similar case can be made to suggest that double action antidpressants, eg venlafaxine, milnacipran, clomipramine or mirtazapine, might be tried in resistant depression although only venlafaxine has been studied in this population. Of the other augmentation strategies lithium is the best established and the use of T3 or of pindolol the least.

Some depressions appear to be truly refractory. Recurrent brief depression is the most common category with a prevalence as high as major depression. Recurrent brief depression does not appear to respond to SSRIs, RIMAs, or TCAs in placebo-controlled studies and more treatment studies are urgently needed.

S60-6

AUGMENTATION STRATEGIES IN TREATMENT RESISTANT DEPRESSION: PRECLINICAL AND CLINICAL ASPECTS

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Several augmentation strategies have been devised over the last two decades. This presentation will focus on two of them: lithium and pindolol additions in treatment-resistant depression.

Lithium, even when administered at low doses, increases rapidly the function of (5-HT) neurons. Using single cell recording, we have shown that a short-term (2 or 3 days) lithium treatment enhances the efficacy of the stimulation of the ascending 5-HT pathway in suppressing the firing activity of dorsal hippocampus pyramidal neurons and that this phenomenon was attributable to a presynaptic effect of lithium. However, there is some evidence from other groups that a sub-set of 5-HT_{1A} receptors might be sensitized by short-term lithium.

The efficacy of lithium addition in treatment-resistant depression has been thoroughly documented. The most striking feature is perhaps that lithium has been found to potentiate all types of antidepressant treatments tested thus far (including sleep deprivation). The onset of action varies greatly: some patients improved within 24–72 hrs, while a fair number will show a significant improvement only after two weeks.

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