elimination half-life and elevation in steady state plasma concentrations-and dose adjustment may therefore be necessary in elderly patients.

The pharmacokinetic profile of sertraline (plasma concentrations and half-life) is similar in the elderly to that observed in younger patients and therefore no dose adjustment is necessary in this patient group. Furthermore, in contrast to the TCAs and other SSRIs, sertraline, and possibly also citalopram, have a low inhibitory potential for cytochrome P450 isoenzymes with resulting low potential for drug interactions.

Consideration of pharmacokinetic parameters, and in particular the impact of age on drug disposition, is essential when making the choice of antidepressant treatment for late-life depression. In view of the often high level of concurrent medication in these patients, the potential for drug interactions should also be considered in the choice of treatment.

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3. Cytokines in psychiatry – Interaction with pharmacology

3-1 Effects of cytokines on brain catecholamines and indolamines

A.J. Dunn, J.-P. Wang, T. Ando. *Department of Pharmacology and Therapeutics, Louisiana State University Medical Center, Shreveport, Louisiana, USA*

Certain cytokines, most notably interleukin-1 (IL-1), are potent activators of the hypothalamopituitary-adrenocortical (HPA) axis. Associated with the IL-1-induced HPA activation is an increase of noradrenergic catabolites, which is most pronounced in the medial hypothalamus (Dunn, 1988). This suggests an activation of the ventral ascending noradrenergic neurons originating from the A1 and A2 regions of the brain stem. That this increase in NA metabolism reflects synaptic release is suggested because microdialysis studies have indicated increases in extracellular concentrations of noradrenaline (NA: Smagin et al., 1996). This catecholaminergic activation appears to be specific to NA; although we have occasionally observed increases in dopamine catabolites, the effects have been small and not consistent. IL-1 also increases free tryptophan and the serotonin (5-HT) catabolite, 5-hydroxyindoleacetic acid (5-HIAA), although this effect occurs somewhat later than the NA response. Both interleukin-6 (IL-6) and tumour necrosis factor α (TNFα) can also activate the HPA axis, but both are significantly less potent than IL-1, and the effects are shorter lived. We have not observed any activation of brain catecholamine metabolism by either IL-6 or TNFα. However, IL-6 also appears to increase brain tryptophan and 5-HIAA (Dunn & Wang, 1996), and TNFα may have a similar effect.

An important question is whether or not these neurochemical changes underlie the activation of the HPA axis. There is an excellent correlation between the IL-1-induced activation of NA and the HPA axis. Moreover, lesion studies suggest that NA may indeed mediate the HPA activation, but studies with adrenergic receptor antagonists suggest that this is probably not the only mechanism. There is little evidence for a serotonergic mediation of the HPA activation. The temporal correlations are not good, especially with IL-6 which elicits a rapid and short-lived HPA activation, but a slow and prolonged increase in tryptophan and 5-HIAA.

An interesting question is whether cytokines mediate the neurochemical responses to endotoxin (lipopolysaccharide, LPS). The NA response to LPS resembles that to IL-1, but is not impaired by treatment with the IL-1-receptor antagonist. However, an antibody to IL-6 attenuated the indolaminergic responses to LPS, but not to IL-1. This suggests that IL-6 may contribute to the serotonergic response to LPS (as well as the HPA response at later times).

It is concluded that cytokines can alter neurotransmission in the brain. IL-1 has potent effects on NA, whereas IL-6 and TNFα do not. IL-1, IL-6 and, possibly TNFα, all appear to increase brain tryptophan and 5-HT metabolism. IL-6 may mediate in part the indolaminergic response to endotoxin.

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3-2 Cytokines and sickness behavior

R. Dantzer. *INSERM U394, Bordeaux, France*

Non specific symptoms of infection include fever and profound psychological and behavioural changes. Sick individuals experience fatigue, malaise, listlessness and inability to concentrate. They also show hypersomnia, anorexia, depressed activity and loss of interest in their surroundings and social environment. These non specific changes are collectively termed "sickness behaviour".

Peripheral or central injections of lipopolysacharide (LPS), a cytokine inducer, or recombinant proinflammatory cytokines such as interleukin-1 (IL-1α, IL-1β) and tumor necrosis factor-α (TNF-α) induce sickness behaviour in mice and rats, in the form of reduced social interest and decreased food-motivated behaviour. Mechanisms of the behavioural effects of cytokines have been the subject of much investigation during the last three years. Receptors for cytokines have been identified in the brain. In general, smaller quantities of recombinant cytokines are necessary to induce sickness behavior when the injection is made directly into the lateral ventricle of the brain (icv) than when it is given systemically. This difference in the range of active doses is usually interpreted in terms of a central site of action for the treatment under investigation. A more direct evidence in favor of a central site of action is the demonstration that icv administration of the specific antagonist of IL-1 receptors, IL-1ra, blocks IL-1 β-induced decrease in social exploration and attenuates IL-1 β-induced reduction in food-motivated behaviour. These findings do not imply that peripherally released cytokines need to enter the brain to induce symptoms of sickness. Cytokines cannot cross the blood-brain barrier and are more suited to act as local communication signals than as hormones. The use of molecular biology techniques and immunocytochemistry has revealed that peripherally released cytokines actually induce the synthesis and release of cytokines in the brain. In the case of IL-1, cellular sources of this cytokine are mainly represented by perivascular macrophages and microglia. Whether brain cytokines act directly on neurons or indirectly, via other glial cells such as astrocytes, remains to be determined. Neural afferent pathways are reponsible for the tranmission of immune information from the periphery to the brain, as demonstrated by experiments using subdiaphragmatic section of the vagus nerve to interrupt nerve conduction between the abdominal cavity and the brain. Vagotomy abrogated both the induction of IL-1 β mRNA in the mouse brain and the occurrence of depressed behaviour in response to intraperitoneal administration of LPS and IL-1 β, without altering the ability of the host to mount a peripheral inflammatory response.

The profound depressing effects of cytokines on spontaneous and learned behavior are not the non specific result of weakness and physical debilitation but the expression of a highly organized motivational state. The best evidence for the existence of motivational effects of proinflammatory cytokines is the demonstration that the nature of the behavioural changes that occur in response to cytokines depends on environmental conditions. This concept of sickness as a motivational state is important in terms of pathophysiology since it implies that the neural circuits which underlie the expression of sickness behavior and are normally activated by immune stimuli might be activated by non immune stimuli. The elucidation of the mechanisms responsible for the active inhibition of this motivational state is also important.

In conclusion, the mechanisms by which peripherally released cytokines affect brain functions and induce sickness behavior begin to be understood. Peripheral immune stimuli are transduced into a neural message which is conveyed to the brain by primary afferent nerves. This message leads to the local synthesis and release of cytokines. The way the specificity of the immune message is maintained during this entire process has still to be deciphered but it opens fascinating perspectives for the understanding of the communication pathways between the immune system and the brain. In addition, the existence of a cytokine system in the brain with potent behavioural and neuroendocrine activities brings up the question of the way this system is regulated and its possible contribution to the alterations in brain functions that occur in infectious (e.g., the AIDS dementia complex) and non infectious (e.g., stress) states.

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