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Invited review

Neurobehavioral consequences of small molecule-drug immunosuppression

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ABSTRACT

60 years after the first successful kidney transplantation in humans, transplant patients have decent survival rates owing to a broad spectrum of immunosuppressive medication available today. Not only transplant patients, but also patients with inflammatory autoimmune diseases or cancer benefit from these life-saving immunosuppressive and anti-proliferative medications. However, this success is gained with the disadvantage of neuropsychological disturbances and mental health problems such as depression, anxiety and impaired quality of life after long-term treatment with immunosuppressive drugs. So far, surprisingly little is known about unwanted neuropsychological side effects of immunosuppressants and anti-proliferative drugs from the group of so called small molecule-drugs. This is partly due to the fact that it is difficult to disentangle whether and to what extent the observed neuropsychiatric disturbances are a direct result of the patient's medical history or of the immunosuppressive treatment. Thus, here we summarize experimental as well as clinical data of mammalian and human studies, with the focus on selected small-molecule drugs that are frequently employed in solid organ transplantation, autoimmune disorders or cancer therapy and their effects on neuropsychological functions, mood, and behavior. These data reveal the necessity to develop immunosuppressive and anti-proliferative drugs inducing fewer or no unwanted neuropsychological side effects, thereby increasing the quality of life in patients requiring long term immunosuppressive treatment.

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1. Introduction

Since the first renal transplantation in 1954 between identical twins (Merill, 1956), immunosuppressive drugs have been widely employed to prevent graft rejection. The continuous treatment with immunosuppressive drugs is an inevitable prerequisite for long term transplant survival (Halloran, 2004; Miller, 1996). However, the dark side of this success is the fact that all immunosuppressive drugs induce unwanted toxic side effects including impaired functions of the central nervous system (CNS). These partially severe neurological manifestations (Hotson and Pedley, 1976; Palmer and Toto, 1991) include seizures, disturbances of consciousness, neurocognitive dysfunctions such as learning and memory deficiencies, depression, or psychotic disorders (Bronster et al., 1994; Saner et al., 2007).

Neurological complications commonly follow liver transplantation and are a significant source of morbidity and mortality in transplant recipients (Saner et al., 2007; Stein et al., 1992). Encephalopathy is the most common CNS complication after liver transplantation, with multiple causes: anoxia, primary graft nonfunctioning, renal failure, rejection, sepsis, and drugs (Bronster et al., 2000, 1994). In adult lung transplantation patients, neurological complications affect 92% of patients within 10 years, severe in 31% of cases. Most common are perioperative stroke and encephalopathy (Mateen et al., 2010). These previously described

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Table 1
Overview of drug description, mechanism of action, therapeutic use and influences on CNS/behavior.

Drug	Description	Mechanism of action	Therapeutic use	Influences on the CNS/behavior of experimental animals	Influences on the CNS/behavior of humans
Cyclosporine A (CsA)	Calcineurin Inhibitor (CNI)	CsA acts as an inhibitor of calcineurin preventing the dephosphorylation of NFAT and its transfer to the nucleus (Tedesco and Haragsim, 2012)	Prevention of graft rejection in kidney, liver and heart transplantation Rheumatoid Arthritis (RA) Psoriasis	Induced anxiety- and depression-like behaviors in rats through diminished calcineurin activity in the amygdala (Mineur et al., 2014) Induced depressive-like behavior in rats by blocking of the mTOR signaling pathway (Yu et al., 2013)	Increased incidence rate of developing affective or anxiety symptoms such as disorientation, depression, aggression, paranoia, and apathy (Chang et al., 2001; de Groen et al., 1987; Kahan, 1994; Kahan et al., 1987; Lang et al., 2009; Lindenfeld et al., 2004b)
Tacrolimus (TAC, FK506)	CNI	TAC interacts with FKBP12 to form a calcineurin-blocking complex (Halloran, 2004)	Liver- and kidney transplantation	cf. CsA	cf. CsA
Sirolimus (rapamycin) Everolimus Temsirolimus	Mammalian target of rapamycin (mTOR) inhibitor	Sirolimus forms a complex with the FK binding protein 12 (FKBP12) that in turn inhibits mTOR and interleukin-2-driven T-cell proliferation (Guertin and Sabatini, 2009)	Widely used as an immunosuppressant in organ transplantation Cancer therapy	Elevated EEG and cFOS expression in the amygdala and increased anxiety-like behavior in rats (Hadamitzky et al., 2014) In mice, sirolimus can result in abnormal sensorimotor milestones, motor abnormalities and increased anxiety-related behaviors, both in early postnatal development and during adult stages (Tsai et al., 2013; Yu et al., 2013)	Temsirolimus (CCI-779) in tumor therapy induced symptoms of bipolar disorder patients without a medical history of neuropsychiatric complications (Raymond et al., 2004)
Mycophenolate mofetil (MMF)	MMF is the morpholinoethylester of mycophenolic acid (MPA)	MPA inhibits the proliferation and clonal expansion of both B and T cells (Mele and Halloran, 2000)	MMF is usually given in combination with cyclosporine or corticosteroids after kidney, heart or liver transplantation		The prescribing information for MMF reports depression as an adverse event Case report: 64-year-old woman developed a severe depressive disorder after the start of therapy (Draper, 2008)
Leflunomide	Disease-modifying anti-rheumatic drug (DMARD) Pyrimidine synthesis inhibitor	Two possible mechanisms of action (Ruckemann et al., 1998) - reversible inhibition of dihydroorotate dehydrogenase[a] - inhibition of tyrosine kinases	RA Off-label use as an immunosuppressant		Less mental health impairment than otherwise treated groups (Pinho de Oliveira Ribeiro et al., 2013)
Azathioprine	DMARD	Inhibits purine synthesis through its metabolite, 6-mercaptopurine; Inhibits the proliferation of B and T lymphocytes; Reduces antibody production (Lindenfeld et al., 2004b)	RA Used in renal homo-transplantation to prevent graft rejection		*Normal (age-appropriate) mental development in babies exposed to azathioprine in utero and via breastfeeding in a long-term follow-up study* (Angelberger et al., 2011) DMARDs in general: prevalence of depressive and anxiety disorders (14–47 % compared to general population) (Pinho de Oliveira Ribeiro et al., 2013)
Methotrexate (MTX)	Anti-folate, anti-neoplastic drug	Interruption of DNA synthesis (Barnhart et al., 2001)	Used in low doses for the treatment of immune-mediated disorders such as RA Combination therapy (CMF; cyclophosphamide, MTX, and 5-Fluorouracil) in cancer patients	Long-lasting cognitive dysfunctions in rats (Fardell et al., 2010; Seigers and Fardell, 2011; Seigers et al., 2008, 2009, 2010) Decreased hippocampal cell proliferation and white matter density (Seigers et al., 2009) Increased freezing during test of fear conditioning (Gandal et al., 2008)	Mild or even major CNS symptoms (Gonzalez-Suarez et al., 2014; Kivity et al., 2014; Wernick and Smith, 1989) CMF has been shown to be associated with severe, long lasting cognitive impairment (Kreukels et al., 2005; Schagen et al., 1999)

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