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MINIREVIEW

CEREBRAL METABOLIC EFFECTS OF SEROTONIN DRUGS AND NEUROTOXINS

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Summary

The functional effects of serotonin (5-HT) drugs and toxins on regional cerebral metabolic rates for glucose (rCMRglc) have been determined in rats with the in vivo, quantitative, autoradiographic [$_{14}$C]2-deoxyglucose technique. Serotonin agents produced rCMRglc patterns different and more specific that one would predict from binding studies. At low doses 5-HT$_1$ agonists reduced rCMRglc in limbic areas and at high doses increased rCMRglc in brain motor regions. The 5-HT$_2$ agonists dose-dependently decreased rCMRglc in proencephalic areas and increased it in thalamic nuclei. 5-HT$_3$ receptor antagonism resulted in rCMRglc decreases in limbic, auditory and visual areas and agents with 5-HT$_3$ receptor activity increased rCMRglc in brain regions with high 5-HT$_3$ receptor densities. Serotonin anxiolytics (e.g. azapirones) and antidepressants (e.g. tryciclic and non-tryciclic 5-HT reuptake inhibitors) reduced rCMRglc selectively in limbic areas and in brainstem monoaminergic nuclei. Dose, time from administration, receptor affinity, behavioral and neurochemical correlates, 5-HT system lesion and circulating glucocorticoid were all relevant factors in determining the rCMRglc effects of 5-HT drugs. Acutely neurotoxic amphetamines markedly increased rCMRglc in brain regions such as the nucleus accumbens that are thought to mediate amphetamine reinforcing properties; on the long term, toxic or electrolytic lesions or chronic treatment with 5-HT agonists produced minimal rCMRglc alterations in spite of marked and persistent changes in 5-HT function. In lesioned or chronically treated rats, acute challanges with 5-HT and non 5-HT agonists demonstrated specific deficits that were not detected in a resting state. Serotonin neuromodulation has been studied in humans by using positron emission tomography with ^{15}O-water. Sequential measurements of regional cerebral blood flow (rCBF) were obtained during combined pharmacological challange with the 5-HT$_{1A}$ agonist buspirone and cognitive activation. Buspirone increased a memory related rCBF activation in task specific regions. This technique can provide a strong theoretical basis for the understanding of 5-HT drug mode of action in normal human brain and in neuropsychiatric diseases. Brain metabolism studies in animals will still be needed to elucidate the factors (e.g. pharmacokinetic and pharmacodynamic) relevant to the cerebral response to 5-HT drugs in humans.

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Serotonin (5-HT) mediates several organic functions (e.g. cardiovascular and respiratory activities, sleep, aggression, sexual behavior, food intake, mood, motor output, neuroendocrine secretion, learning and memory) (1, 2, 3). Most of the 5-HT is synthetized in the large neurons of the brainstem raphe nuclei that give rise to the most expansive efferent system of the neuraxis (4). In the forebrain, limbic regions are innervated by the dorsal raphe, the basal ganglia by the median raphe and the neocortex by both nuclei (4). Although a primary 5-HT dysfunction has yet been definitely proven, 5-HT has been implicated in pathological changes of different neuropsychiatric conditions (e.g. depression, obsessive-compulsive and eating disorders, Alzheimer's disease and schizophrenia, psychadelic and toxic properties of certain amphetamines) (1, 2, 3). Treatments that alter 5-HT functions are known to produce therapeutic effects. Serotonin drugs are classified (and reclassified) primarily according to their affinities for and activities at the different 5-HT pharmacological targets (e.g. 5-HT receptors, 5-HT release and reuptake sites) (5); the latter are determined using biochemical, electrophysiological, endocrinological and behavioral methods. Recently, molecular biology techniques allowed the identification and pharmacological characterization of several 5-HT receptor clones (6).

The quantitative, autoradiographic [^{14}C]2-deoxyglucose ([^{14}C]2DG) method, introduced by Sokoloff et al., in 1977, allows the measurement of the effects of 5-HT drugs and toxins on regional cerebral metabolic rates for glucose (rCMRglc). Glucose is almost the exclusive substrate for energy demand and measurement of rCMRglc provides an index of local brain function (7, 8). Increases and decreases in neuronal activity result, respectively, in increased and decreased rCMRglc. The major advantage of the method is the ability to visualize in great anatomical detail (e.g. raphe nuclei, lateral habenula) the cerebral metabolic activity of conscious animals. The method, however, is limited by its time resolution (e.g. 10-15 min) that requires an adequate optimization of the drug administration in relation to [^{14}C]2DG injection. Further, the method does not identify specific neurotransmitter, neuromodulators or distinguish between excitatory and inhibitory processes. Both neural excitation and inhibition depend on the maintenance of ion gradients which have similar energy demand, regardless of the excitatory or inhibitory nature of the neurotransmitters released. The method is also unable to detect the precise receptor target or the primary anatomic site of action of a pharmacological agent; in pharmacologic studies, in fact, the rCMRglc of a brain region reflect the total afferent inputs and not only local changes induced by the drug (7, 8). The lack of specificity, however, makes of the method a powerful tool to investigate pharmacological effects on specific neuronal circuitries; in turn, these can be related to coincident changes in neurochemical and behavioral measures. Despite its several limitations, the [^{14}C]2DG method provides useful information on psychotropic drugs, especially when they are not fully characterized. The paper reviews the findings contributed by the [^{14}C]2DG to the pharmacology of the 5-HT systems. Relatevely few 5-HT agents are selective for specific 5-HT receptor sub-types and fewer are those that have been studied using brain metabolism techniques. Below, 5-HT drugs have been grouped according to their prevalent 5-HT receptor activity in vivo.

5-HT$_1$ Receptor Drugs

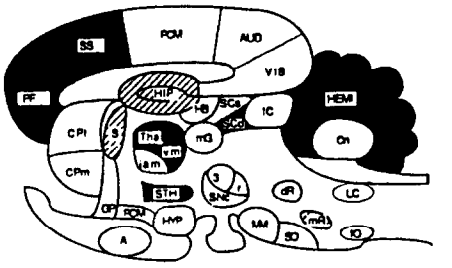
8-hydroxy-2(di-N-propylamino)tetraline (DPAT) is a potent 5-HT$_{1A}$ receptor agonist and has been widely accepted as the prototypical reference compound in studies of 5-HT$_{1A}$ receptor function (5). DPAT has been shown to have a significant affinity for the recently cloned 5-HT7 receptors (9). In rats DPAT had a biphasic dose-dependent effect on rCMRglc. At low doses (0.05 mg/kg), which are almost devoid of behavioral effects (10), DPAT produced only rCMRglc decreases in limbic areas (11); at higher doses (1 mg/kg), that induce the classical 5-HT syndrome (12, 13), DPAT increased the locomotor activity (10) and rCMRglc in motor areas (e.g. somatosensory cortex, extrapyramidal and cerebellar areas)(13, 14). DPAT induced rCMRglc effects in raphe-hippocampal areas are blocked by the 5-HT$_{1A}$ antagonist BMY 7378 (15), suggesting that they are due specifically to 5-HT$_{1A}$ receptor activation. rCMRglc reductions by DPAT likely reflect a decrease in 5-HT release and 5-HT neuron firing (5, 16) resulting from 5-HT$_{1A}$ somatodendritic autoreceptor activation. rCMRglc increases in somatosensory and dopaminergic motor areas by high doses of DPAT coincided with behavioral activation; these changes in rCMRglc are common also to other drugs that produce a motor syndrome (17, 18) and may be related to the catecolamine releasing properties of DPAT.

Buspirone and other azapirones are 5-HT$_{1A}$ agents with anxiolytic and antidepressant activities (19, 20). Buspirone binds with high affinity to 5-HT$_{1A}$ (21) and lesser affinity to dopamine D$_2$ receptors (22). Functionally, buspirone has both agonistic (e.g. nanomolar affinity for 5-HT$_{1A}$ receptors, inhibition of raphe 5-HT neurons and generalization to 5-HT$_{1A}$ stimulus features) (23, 24) and antagonistic 5-HT$_{1A}$ properties (e.g. blockade of the 5-HT syndrome produced by the 5-HT$_{1A}$ agonists DPAT and 5-methoxy-N,N-dimethyltryptamine) (10, 25). At low doses (0.4 mg/kg) buspirone reduced rCMRglc in the raphe-hippocampal regions (26). These were the only rCMRglc effects buspirone had in common with the potent 5-HT$_{1A}$ agonist DPAT and indicate the low doses of buspirone may activate preferentially hippocampal 5-HT$_{1A}$ receptors. High doses of buspirone produced widespread rCMRglc reductions together with rCMRglc increases in the lateral habenula (26), a rCMRglc pattern that resemble closely those of dopaminergic D$_2$ antagonists like haloperidol (27) (Fig. 1). These findings indicate that buspirone, despite its higher affinity for 5-HT$_{1A}$ receptors (21, 22), at high dose may have predominant antidopaminergic effects that can explain the worsening of extrapyramidal symptoms buspirone produces in parkinsonian patients (28). Buspirone rCMRglc effects are similar to those of other azapirones (e.g ipsapirone and gepirone) (29, 30) but not to those of 1-(2pyrimidinyl)-piperazine (31) a metabolite common to the azapirone drugs; difference in rCMRglc effects between buspirone and 1-(2pyrimidinyl)-piperazine, that is a potent α_2-adrenoreceptor blocker (32) suggest that α_2-adrenoreceptor blockade is unlikely involved in buspirone's cerebral metabolic effects.

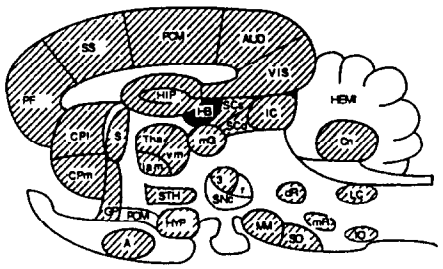
Little other data are available on rCMRglc of agents with 5-HT1 receptor activity. RU-24969, a putative 5-HT$_{1A\text{-}B}$, agonist (33) and high doses of meta-chloro-phenylpiperazine (MCPP), a 5-HT$_{2C}$ agonist (see below) with some affinity for 5-HT$_{1B}$ receptors (34), increased locomotor activity and rCMRglc in brain motor regions (e.g. globus pallidus, striatum and cerebellum) (14, 35) where high densities of 5-HT$_{1B}$ receptors and intense expression ot 5-HT$_{1B}$ receptor mRNA are found (36).

5-HT$_2$ Receptor Drugs

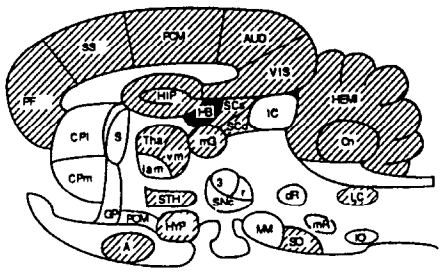
In a recent re-classification of 5-HT receptors, the 5-HT$_2$ receptor family has been expanded to three subtypes on the basis of similarities in molecular structure and signal transduction mechanisms (5). The classical 5-HT$_2$ and 5-HT$_{1C}$ receptors have been renamed 5-HT$_{2A}$ and 5-HT$_{2C}$



DPAT 1 mg/kg



BUSPIRONE 10 mg/kg



HALOPERIDOL 1 mg/kg

FIG. 1.

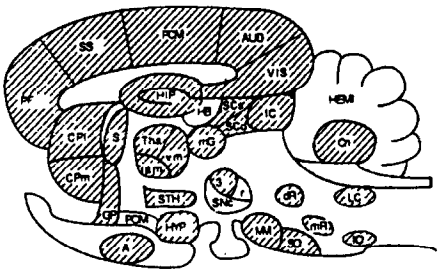
Schematic representation of changes in rCMRglc after DPAT 1 mg/kg (above), buspirone 4 mg/kg (center) or haloperidol 1 mg/kg (bottom). Reproduced from reference 26. Areas of rCMRglc decline compared to control are hatched; areas of increase are solid. List of regions: A, amygdala; AUD, auditory cortex; Cn, cerebellar nuclei; CPl, caudate-putamen, lateral part; CPm, caudate-putamen, medial part; dR, dorsal raphe; GP, globus pallidus; HB, habenular complex; HEMI, cerebellar hemispheres; HIP, hippocampus; HYP, hypothalamus; IC, inferior colliculus; IO, inferior olive; LC, locus coeruleus; mG, medial geniculate; MM, mammillary nuclei; mR, median raphe; PCM, precentral medial cortex; PF: prefrontal cortex; POM, preoptic medial area; r, substantia nigra, pars reticulata; S, medial septum nucleus; SCd, deep layer of the superior colliculus; SCs, superficial layer of superior colliculus; SNc, substantia nigra pars compacta; SO, superior olive; SS, somatosensory cortex; STH, subthalamic nucleus; THa, thalamus, anterior nucleus; vm, thalamus, ventromedial nucleus; vpm, thalamus, ventroposteromedial nucleus; VIS, visual cortex; 3, oculomotor complex.

respectively. Few agonists have been recognized to discriminate between different 5-HT_2 receptor types.

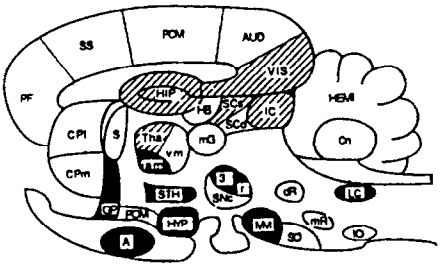
1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) is an hallucinogenic phenylisopropylamine which binds to the different 5-HT_2 receptors but with higher affinity to the 5-HT_{2A} subtype (5). DOI produced a dose-dependent rCMRglc decrease in proencephalic (e.g. neocortices and hippocampus) areas and a simultaneous rCMRglc increases in the interanteromedial nucleus of the thalamus (37). In cortical areas, rCMRglc reductions by DOI may be mediated by either the high 5-HT_{2A} receptor densities (5, 38) or an increased thalamic-cortical inhibitory modulation (39) or both. Whereas in cortical areas rCMRglc effects by DOI peaked at 15 min and tended toward normalization thereafter, in the hippocampus DOI's metabolic effects had a later onset and a longer duration despite the relative paucity of 5-HT_2 receptors found here (37). The peculiar responses to DOI in the hippocampus led us to test the hypothetical role of glucocorticoid. In fact, glucocorticoid receptors are present in a large number and colocalized with 5-HT receptors in hippocampal neurons (40); blood corticosterone levels are under control of the 5-HT systems and, in turn, influence 5-HT neurotransmission (41). Adrenalectomy or adrenal steroid suppression, which enhances many 5-HT mediated behaviors, intensified the metabolic effects of DOI in the thalamus (42). Conversely, adrenalectomy, that disrupts the electrical activity of hippocampal neurons (43) and impairs learning (44), abolished the DOI-induced rCMRglc decreases in the hippocampus (42); these findings suggest that 5-HT_2 receptor function in thalamo-hippocampal pathway is dependent upon the functional state of the hypothalamus-pituitary-adrenal cortex and may be a significant factor in the cognitive impairment observed in clinical conditions of abnormal glucocorticoid function.

MCPP has been extensively employed in human studies to test the involvement of 5-HT_2 receptors in neuropsychiatric diseases (45). MCPP is the major active metabolite of the clinical antidepressants trazodone and etoperidone (46). In vitro MCPP binds to different receptor subtypes (e.g. 5-HT_1, 5-HT_2, α_1- and β-adrenoreceptors and dopamine D_1) (5, 47, 48, 49). Despite the lack of binding specificity, pharmacological studies indicate that MCPP in vivo has a rather specific profile. In fact MCPP endocrine (e.g. increases in plasma concentrations of growth hormone, prolactine and corticosterone), neurovegetative (e.g. hypothermia) and behavioral effects are thought to be due to MCPP's interactions with 5-HT_{2C} and 5-HT_{1B} receptors (50, 51, 52). In our experiments, MCPP had a biphasic dose-dependent effect on behavior and rCMRglc. Low dose MCPP (2.5 mg/kg) reduced locomotor activity and rCMRglc (35). Higher doses of MCPP, induced behavioral activation and both rCMRglc decreases and increases in the interanteromedial thalamic nucleus and basal ganglia (25 mg/kg) or only rCMRglc increases (40 mg/kg) (35). Hypolocomotor effects by low doses of MCPP is due to 5-HT_{2C} (50); 5-HT_{2C} receptor activation may mediate also the widespread rCMRglc reductions in cortical areas where 5-HT_{2C} receptors are found in great number (5). However, rCMRglc effects by low doses of MCPP are reduced in rats with 5-HT fiber destruction, suggesting that presynaptic mechanisms, possibly the 5-HT_{1B} receptors, may contribute to MCPP induced rCMRglc decreases (53). High doses of MCPP produced instead behavioral activation and rCMRglc increases in basal ganglia and in interanteromedial thalamic nucleus. These metabolic effects are enhanced by 5-HT denervation (unpublished data) and resemble, respectively, those of RU-24969 (14) and DOI (37), two agonists of 5-HT_{1B} and 5-HT_{2A} receptors which may be activated also by high dose MCPP (Fig. 2).

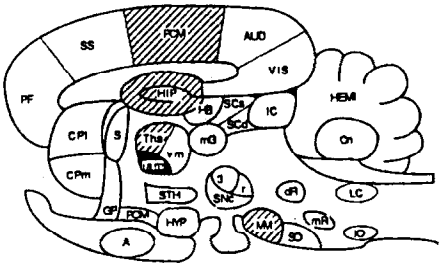
In young rats, two week continous infusion of MCPP (2.5 mg/kg/day) attenuated markedly the behavioral and rCMRglc effects of MCPP but not those of the selective 5-HT_{1A} agonist DPAT. Lack of cross-tolerance between MCPP and DPAT indicates that, in spite of the reported affinity for 5-HT_{1A} receptors (49), MCPP is devoid of significant 5-HT_{1A} activity. During aging 5-HT



MCPP 2.5 mg/kg



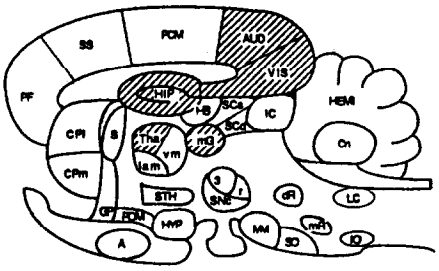
MCPP 25 mg/kg



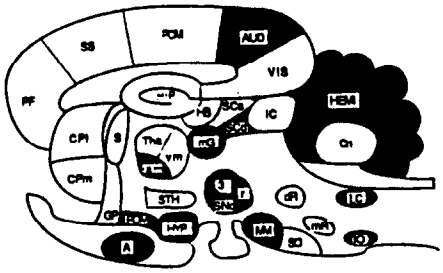
DOI 10 mg/kg

FIG. 2.
Schematic representation of rCMRglc patterns produced by the 5-HT2 agonists MCPP 2.5 mg/kg (above) and 25 mg/kg (center) and DOI 10 mg/kg (bottom). Reproduced from references 35 and 37. Areas of rCMRglc de-cline compared to control are hatched; areas of increase are solid. The list of regions is the same as in figure 1.

markers and functions are reduced (e.g. 5-HT neurons, fibers, receptors densities, 5-HT brain concentrations and 5-HT release) in rodents (54, 55, 56, 57) and in humans (58). We found an age-related reduction of rCMRglc responses to MCPP (59) that correlates well with the reduced MCPP's ability to suppress the 5-HT_{1B} receptor controlled 5-HT release in old rats (60). However, following chronic MCPP administration, behavioral and metabolic responses to acute MCPP decreased at a similar degree in young and old rats (61), suggesting that reduced responses to



ONDANSETRON 0.01 mg/kg



QUIPAZINE 20 mg/kg

FIG. 3.
Schematic representation of rCMRglc patterns produced by ondansetron 0.01 mg/kg (above) and quipazine 20 mg/kg (below). Reproduced from reference 69. Areas of rCMRglc increase compared to control are solid. The list of regions is the same as in figure 1.

MCPP in old rats may be due to an adaptive downregulation of presynaptic 5-HT autoreceptor compensating for 5-HT terminal loss (57).

5-HT$_3$ Receptor Drugs

Ondansetron is a 5-HT$_3$ antagonist well characterized and clinically used for its marked antiemetic properties (62); other potential applications (e.g anxiolytic, promnesic) are under investigation (63). Mitchell and Pratt studied the effects on rCMRglc of three doses (0.01, 0.1 and 1 mg/kg) (64). The higher doses of ondansetron significantly increased rCMRglc only in the raphe nuclei. The lowest dose reduced rCMRglc in 13 of the 66 brain regions studied including the visual and auditory systems, the lateral habenula and, more markedly, the limbic system; the latter metabolic effects are common to other 5-HT (see in this paper buspirone) (26) and non 5-HT (e.g. benzodiazepine) (65) agents which possess, as ondansetron does (65), anxiolytic activity (63) and are related possibly to the high 5-HT$_3$ receptor densities in the hippocampus (66, 67). Overall, rCMRglc effects of ondasetron did not correspond to the known distribution of 5-HT3 receptors

(66, 67). Discrepancy between receptor distribution and topography of rCMRglc effects have been reported for several other 5-HT and non- 5-HT drugs and could be explained by a variety of events (e.g. propagation of activity through neural network, regional variability in the receptor/function relation etc.) (68). 5-HT_3 receptors which are found in high concentrations in brainstem (e.g. area postrema and nucleus of tractus solitarius), limbic and dopaminergic regions (66, 67) and function as modulatory heteroreceptor (5, 72, 73). Hence, ondansetron, which is a 5-HT_3 antagonist, may alter rCMRglc by modulating multiple neurotransmitter release.

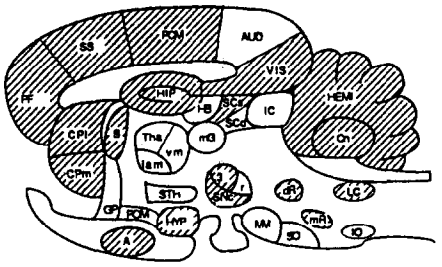
We studied the rCMRglc effects of two doses (5 and 20 mg/kg) of quipazine (69) that has been used as a 5-HT_3 receptor ligand (67). Quipazine increased rCMRglc in brain regions with high densities of 5-HT_3 receptors (area postrema, olfactory bulb, amygdala), in dopaminergic nuclei (substantia nigra pars compacta and pars reticulata) and in terminal fields of their projections (zona incerta, subthalamic nucleus) (Fig. 3). Quipazine neurovegetative, neuroendocrine and behavioral effects can be counteracted by 5-HT_2 but also by dopamine antagonists (70, 71). Furthermore, quipazine's rCMRglc effects are not mediated by 5-HT terminals (53) and quipazine neurochemical and behavioral actions (e.g. increases in dopamine release in basal ganglia and phoshoinositide turnover in cortical region and reduction in dopamine turnover and in haloperodol induced catalepsy) (71, 72) resemble those of 5-HT3 agonists (73, 74). The topographic distribution and direction of rCMRglc changes induced by quipazine are different from those produced by 5-HT_2 agonists and, consistently with quipazine binding properties, are best explained by a preferential activation of 5-HT_3 receptors.

5-HT Reuptake Inhibitors

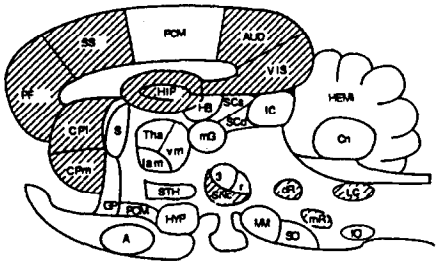
The serotonin reuptake inhibitors represent a class of structurally heterogeous compounds that share a similar ability of inhibiting 5-HT reuptake (75). Clinically, serotonin-reuptake inhibitors are first line antidepressants (76) and uniquely effective in obsessive-compulsive disorders (77). We studied tryciclic (e.g.clomipramine) (78) and non tryciclic 5-HT reupake blockers (79, 80) (e.g. fluoxetine, fluvoxamine) (Fig. 4). Clomipramine (2-50 mg/kg) dose-dependently reduced rCMRglc in areas with high densities of 5-HT reuptake sites (e.g. raphe and hippocampus) (81). Clomipramine decreased rCMRglc and increased 5-HT brain concentrations with similar time-courses (78, 82). Theoretically, the noradrenergic system could contribute to rCMRglc reductions produced by clomipramine in raphe-hippocampal areas. However, noradrenergic antidepressants do not alter rCMRglc in these brain regions (84, 85); further, selective 5-HT reuptake inhibitors decreased rCMRglc in raphe-hippocampal regions (79, 80) and clomipramine rCMRglc effects were greatly reduced by 5-HT fiber ablation (81). These findings demonstrate that, despite the affinity for several receptor subtype and the norepinephrine reuptake sites (83), the primary effectors of clomipramine are the 5-HT reuptake sites.

5-HT Toxins

Amphetamines represent a social health problem because they are abused as psychostimulants. Acute administration of methamphetamine (0.5-2.5 mg/kg) increased rCMRglc in dopaminergic motor regions (e.g. subthalamic, ventromedial thalamic and caudate nuclei and globus pallidus) and mesolimbocortical areas (e.g. nucleus accumbens) which are thought to mediate the motor activating and reinforcing actions of amphetamines (87). Further, methamphetamine markedly increased rCMRglc in regions containing dopaminergic and 5-HT cell bodies, as other amphetamine-like psychostimulants do (88). However, rCMRglc increases in these brain regions were not observed following non-amphetamine psychostimulants and suggest that may be related



CLOMIPRAMINE 50 mg/kg



FLUOXETINE 40 mg/kg

FIG. 4.
Schematic representation of rCMRglc patterns produced by the 5-HT reuptake inhibitor clomipramine 50 mg/kg (above) or fluoxetine 40 mg/kg (below). Reproduced from references 78 and 80. Areas of rCMRglc decline compared to control are hatched. The list of regions is the same as in figure 1.

to the unique toxic properties of amphetamine psychostimulants on dopaminergic and 5-HT neurons (89, 90).

Amphetamine neurotoxic effects (e.g. decrease of 5-HT concentrations, 5-HT reuptake sites and fibers) are long lasting (53, 91) but rCMRglc changes attenuate over time. Days after repeated administration (20 mg/kg/day for 4 days) of methylenedioxy- methamphetamine ("ecstasy"), a psychostimulant and psychomimetic agent (92), rCMRglc was increased only in the hippocampus in spite of a widespread and severe 5-HT terminal loss [e.g. 89% decrease in (3H)paroxetine binding] (93). Weeks after methamphetamine treatment, rCMRglc was significantly elevated in few brain areas (94) (e.g. cingulate and auditory cortices, globus pallidus and hippocampus) and, in a different study, only in a subgroup of rats which developed "sensitization" to methamphetamine (95). We studied the long term effect p-chloroamphetamine (PCA), an halogenated amphetamine which, much alike abuse amphetamines, produces a long lasting 5-HT fiber loss (96). Weeks after PCA rCMRglc increases in visual areas were the only significant findings, in spite of a loss of more than 75% of brain 5-HT (53). Other toxic (e.g. 5,7-dihydrotryptamine and p-chlorophenylalanine) or electrolytic lesion of the 5-HT systems resulted in minimal rCMRglc changes as well (97, 98). It has been speculated that lack of significant rCMRglc changes in 5-HT denervated rats indicates a tonic inactivity of the 5-HT systems (97). However, 5-HT antagonism by methiothepin resulted in large rCMRglc decreases (99) suggesting that 5-HT systems may actually be tonically active. Unfortunately, no firm conclusion can be

drawn in this regard because of the substantial antidopaminergic activity of methiothepin (100). No rCMRglc change has been reported also after lesions of other brain structures such as the lateral habenula (101) or the nucleus basalis of Meynert (102) and it has been suggested that compensatory mechanisms (e.g. receptor regulation, interneural circuitry) restore resting rCMRglc (102). For this reason, the interpretation of cerebral metabolic data remains an important methodological issue in animal and human studies of chronic changes in neurotransmitter systems. Using drugs as probes in PCA lesioned rats, we found that metabolic responses to MCPP and clomipramine were decreased whereas those to quipazine or to the muscarinic agonist arecoline or the dopaminergic agonist bromocriptine were maintained (53). Thus, this approach enabled us to reveal specific presynaptic (e.g. autoreceptors, 5-HT reuptake sites) deficits that were not evident in a resting condition and has important implications also for human studies.

Human PET Studies

The sensitivity.of techniques that measure cerebral metabolism can be greatly enhanced by the use of pharmacological probes and this consideration becomes particularly important with regard to neuropsychiatric pathologies. Serotonin function has been studied in humans with positron emission tomography (PET) and ^{18}F-fluorodeoxyglucose or ^{15}O-water which measure, respectively, rCMRglc and regional cerebral blood flow (rCBF), another sensitive index of brain function (103). In healthy subjects the 5-HT reuptake blocker fluoxetine reduced rCMRglc in the limbic areas (104) as it did in rats (78). In patients suffering from obsessive-compulsive disorders, chronic administration of the 5-HT reuptake blockers fluoxetine or clomipramine ameliorated the obsessive symptomatology and normalized abnormally elevated rCMRglc in regions (e.g. the right head of the caudate or orbitofrontal regions) that are thought to mediate obsessive-compulsive symptoms (105, 106). Fenfluramine, a 5-HT anorectic, increased rCMRglc (107) and rCBF (108) in the prefrontal cortex and a decrease in the occipital areas.

The short lived ^{15}O-water radiotracer allows serial measurements of rCBF, (106) during a variety of pharmacological and/or neuropsychological challenges. Administered to healthy subjects performing a memory task, buspirone increased the task related rCBF activation in the left prefrontal and in the retrosplenial/parahippocampal cortex. The latter is a brain region with a high 5-HT_{1A} receptor density and has been implicated in memory functions in humans (109).

Conclusions

The number of human pathologies ascribed to 5-HT dysfunctions, along with the numbers of 5-HT receptors and of 5-HT drugs entering in clinical practice, are continously increasing. The identification of newer 5-HT receptors eventually will help our comprehension of the 5-HT system pathophysiology and provide a rationale for developing new therapeutics. Pharmacological studies suggest that PET techniques have great potentials in exploring 5-HT modulatory function in the normal brain and neuropsychiatric pathology. At present, we are limited by the scarce availability of selective 5-HT agents (see below table 1). As they will become available, results from brain metabolism studies in animals can provide infomation useful for the assessment of factors (e.g. pharmacokinetic and pharmacodynamic) that govern the human brain response to new 5-HT drugs. When applied to specific human pathologies, pharmacological brain metabolism studies may identify specific functional alterations that may be readily susceptible of therapeutic interventions.

TABLE I
Brain Metabolism Studies on 5-HT Drugs.

Name	Drug Target			Animal studies			Human studies	
	Binding selectivity	Activity	[1]Topography	Relation to dose	[2]Behavioral effects	rCMRglc effects	Pharmacological activities	PET human studies
DPAT	5-$HT_{1A/7}$	A	raphe nuclei limbic areas	LD HD	 5-HT syndrome	decrease in limbic areas increase in extrapyramidal areas		
buspirone gepirone ipsapirone	5-HT_{1A} D_2	A/AA AA		LD HD	no effect	decrease in limbic areas decrease in basal ganglia increase in lateral habenula	anxiolytic antidepressant	increase of memory-related rCBF activation in frontal cortex
RU-24969	5-HT_{1A-B}	A	basal ganglia		hyperlocomotion	increase in basal ganglia		
DOI	5-HT_{2A-C}	A	cortex hippocampus	DD	wet dog shakes	decrease in limbic and cortical areas increase in thalamus	hallucinogenic (?)	
MCPP	5-$HT_{1D/2A-C}$ α, β	A		LD HD	hypolocomotion 5-HT syndrome	decrease limbic and cortical areas increase in basal ganglia and thalamus	anxiogenic	
ondansetron	5-HT_3	AA	limbic brainstem	LD HD	no effect	decrease limbic and cortical areas increase in raphe nuclei	antiemetic anxiolytic (?)	
quipazine	5-HT_3 5-HT_2	A		DD	 wet dog shakes	increase in dopaminergic and 5-HT_3 areas		
clomipramine	5-HT/NE reuptake D_2, H_1	blocker	hippocampus raphe	LD HD	no effect	decrease in raphe and hippocampus widespread decrease	antidepressant antiobsessional	
fluoxetine fluvoxamine	5-HT reuptake	blocker			no effect	widespread decrease antiobsessional	antidepressant	decrease of rCBF in limbic areas
fenfluramine	5-HT release	enhancer					anorexic	increase of rCBF in frontal cortex decrease of rCBF in occipital cortex

[1]Limited to 5-HT receptor target. [2]Concurrent with rCMRglc measurement.
Abbreviations: A, agonist; AA, antagonist; DD, dose-dependent; HD, high dose; LD, low dose. For references see text.

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